

Management of Dyslipidemia in Adults With Diabetes

AMERICAN DIABETES ASSOCIATION

RATIONALE FOR TREATMENT OF DYSLIPIDEMIA

— The rationale for the treatment of diabetic dyslipidemia is discussed in detail in the American Diabetes Association (ADA) technical review “Management of Dyslipidemia in Adults With Diabetes” (1). Type 2 diabetes is associated with a two- to fourfold excess risk of coronary heart disease (CHD). Although the degree of glycemia in diabetic patients is strongly related to the risk of microvascular complications (retinopathy and renal disease), the relation of glycemia to macrovascular disease in type 2 diabetes is more modest. The finding of increased cardiovascular risk factors before the onset of type 2 diabetes also suggests that aggressive screening for diabetes combined with improved glyce- mic control alone will not be likely to completely eliminate excess risk of CHD in type 2 diabetic patients. Clearly, a multifactorial approach to prevention of CHD in type 2 diabetes will be necessary.

PREVALENCE OF DYSLIPIDEMIA IN TYPE 2 DIABETES

— The most common pattern of dyslipidemia in type 2 diabetic patients is elevated triglyceride levels and decreased HDL cholesterol levels. The concentration of LDL cholesterol in type 2 diabetic patients is usually not significantly different from nondiabetic individuals. Diabetic patients may have elevated levels of non-HDL cholesterol (LDL plus VLDL). However, type 2 diabetic patients typically have a preponderance of smaller, denser LDL particles, which possibly increases atherogenicity even if the absolute concentration of LDL

cholesterol is not significantly increased. Lastly, as shown in the technical review (1), the median triglyceride level in type 2 diabetic patients is <200 mg/dl (2.30 mmol/l), and 85–95% of patients have triglyceride levels below 400 mg/dl (4.5 mmol/l).

As in nondiabetic individuals, lipid levels may be affected by factors unrelated to glycemia or insulin resistance, such as renal disease, hypothyroidism, and the frequent occurrence of genetically determined lipoprotein disorders (e.g., familial combined hyperlipidemia and familial hypertriglyceridemia). These genetic disorders may contribute to the severe hypertriglyceridemia seen in some patients with diabetes. Furthermore, use of alcohol and estrogen may also contribute to hypertriglyceridemia.

LIPOPROTEIN RISK FACTORS FOR CHD

— Relatively few prospective studies of lipids and lipoproteins as predictors of CHD have been reported in type 2 diabetic subjects, and the results have been somewhat contradictory. In the large Multiple Risk Factor Intervention Trial (MRFIT), total cholesterol as well as cigarette smoking and blood pressure predicted the development of cardiovascular disease in diabetic and nondiabetic subjects, suggesting that risk factors may be predictive in both groups. In a Finnish study, increased triglyceride levels and decreased HDL cholesterol levels (but neither LDL nor non-HDL cholesterol) predicted CHD in well-characterized type 2 diabetes subjects. However, after adjustment for HDL cholesterol, neither to-

tal nor VLDL triglyceride predicted CHD. Baseline data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that both decreased HDL and elevated LDL predicted CHD (3). In observational studies, HDL may be the most consistent predictor of CHD in type 2 diabetes subjects, followed by triglyceride and total cholesterol.

CLINICAL TRIALS OF LIPID LOWERING IN DIABETIC SUBJECTS

— No clinical trial has been done on the effects of lipid-lowering agents on subsequent CHD specifically in diabetic subjects. However, a number of clinical trials have included small numbers of adult type 2 diabetic subjects. In the Scandinavian Simvastatin Survival Study (4S) trial, simvastatin (HMG CoA reductase inhibitor or “statin”) significantly reduced CHD incidence and total mortality (borderline significantly) in diabetic subjects with high LDL cholesterol and with previous clinical CHD. In the Cholesterol and Recurrent Events (CARE) study, pravastatin reduced CHD incidence significantly in diabetic subjects with average LDL levels and with previous clinical CHD. In the Helsinki Heart Study, gemfibrozil (fibrin acid derivative) was associated with a reduction in CHD in diabetic subjects without prior CHD (although this result was not statistically significant). In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), gemfibrozil was associated with a 24% decrease in cardiovascular events in diabetic subjects with prior cardiovascular disease (4).

MODIFICATION OF LIPOPROTEINS BY MEDICAL NUTRITION THERAPY AND PHYSICAL ACTIVITY

— The ADA has made recommendations for both medical nutrition therapy (MNT) (5) and physical activity (6). Weight loss and increased physical activity will lead to de-

The recommendations in this paper are based on the evidence reviewed in the following publication: Management of dyslipidemia in adults with diabetes (Technical Review). *Diabetes Care* 21:160–178, 1998.

The initial draft of this paper was prepared by Steven M. Haffner, MD. This paper was peer-reviewed, modified, and approved by the Professional Practice Committee and the Executive Committee, November 1997. Most recent review/revision, 2000.

Abbreviations: ADA, American Diabetes Association; CARE, Cholesterol and Recurrent Events Study; CHD, coronary heart disease; CVD, cerebrovascular disease; MNT, medical nutrition therapy; NCEP, National Cholesterol Education Program; 4S, Scandinavian Simvastatin Survival Study.

Table 1—Category of risk based on lipoprotein levels in adults with diabetes

Risk	LDL	HDL	Triglyceride
	cholesterol	cholesterol*	
High	≥130	<40	≥400
Borderline	100–129	40–59	150–399
Low	<100	≥60	<150

Data are given in milligrams per deciliter. *For women, the HDL cholesterol values should be increased by 10 mg/dl.

creased triglyceride and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Diabetic patients who are overweight should be given a prescription for MNT and for increased physical activity. The proportion of saturated fat in the meal plan should be reduced. The ADA suggests an increase in either carbohydrate or monounsaturated fat to compensate for the reduction in saturated fat. Some (but not all) studies suggest that a high-monounsaturated fat diet may have better metabolic effects than a high-carbohydrate diet, although other experts have suggested that such a dietary modification may make weight loss more difficult in obese diabetic patients.

Recommendations of the American Heart Association for patients with CHD (7) have suggested that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl (0.40–0.65 mmol/l). Thus, if the LDL cholesterol exceeds the goal by >25 mg/dl (0.65 mmol/l), the physician may decide to institute pharmacological therapy at the same time as behavioral therapy for high-risk patients (i.e., diabetic patients with a prior myocardial infarction and/or other CHD risk factors). In other patients, behavioral interventions may be evaluated at 6-week intervals, with consideration of pharmacological therapy between 3 and 6 months.

MODIFICATION OF LIPOPROTEINS BY GLUCOSE-LOWERING AGENTS

Interventions to improve glycemia usually lower triglyceride levels. In general, glucose-lowering agents do not change or have only a modest effect on raising HDL levels. However, the HDL composition may change in a direction thought to be antiatherogenic. Thiazolidinediones may increase HDL and LDL levels, but the long-term effect of such changes is not known. LDL cholesterol may decrease modestly (up to 10–15%) with

Table 2—Treatment decisions based on LDL cholesterol level in adults with diabetes

	Medical nutrition therapy		Drug therapy	
	Initiation level	LDL goal	Initiation level	LDL goal
With CHD, PVD, or CVD	≥100	<100	≥100	<100
Without CHD, PVD, and CVD	≥100	<100	≥130*	<100

Data are given in milligrams per deciliter. *For patients with LDL between 100 and 129 mg/dl, a variety of treatment strategies are available, including more aggressive MNT and pharmacological treatment with a statin; in addition, if the HDL is <40 mg/dl, a fibric acid such as fenofibrate may be used in these patients. MNT should be attempted before starting pharmacological therapy. PVD, peripheral vascular disease.

the achievement of optimal glycemic control. Since improved glycemic control may also lower triglyceride levels, it might also cause a favorable change in LDL composition.

TREATMENT GOALS FOR LIPOPROTEIN THERAPY

The categories of CHD risk by lipoprotein levels in type 2 diabetic patients are shown in Table 1. Because of frequent changes in glycemic control in diabetic patients and their effects on levels of lipoprotein, levels of LDL, HDL, total cholesterol, and triglyceride should be measured every year in adult patients. If values fall in lower-risk levels, assessment may be repeated every 2 years. In children with diabetes, consideration should be given to measuring lipoproteins after age 2 years, as suggested by the National Cholesterol Education Program (NCEP) Report of the Expert Panel on Blood Cholesterol in Children and Adolescents (8).

Optimal LDL cholesterol levels for adults with diabetes are <100 mg/dl (2.60 mmol/l), optimal HDL cholesterol levels are >40 mg/dl (1.02 mmol/l), and desirable triglyceride levels are <150 mg/dl (1.7 mmol/l). (In women who, at least when nondiabetic, tend to have higher HDL cholesterol levels than men, it may be desirable to have even higher HDL cholesterol levels [>50 mg/dl (1.28 mmol/l)].) However, raising HDL cholesterol levels pharmacologically in diabetic patients is very difficult since the most effective agent raising HDL cholesterol levels is nicotinic acid, which is relatively contraindicated in diabetic patients. Fibrates can raise HDL cholesterol levels significantly without affecting glycemic control.

The recommendations for treatment of elevated LDL cholesterol (Table 2) generally follow the guidelines of both the NCEP (9) and a recent ADA consensus development conference (1993) (10), with the following caveats. Pharmacological therapy should be initiated after behavioral interventions are

used. However, in patients with clinical cardiovascular disease or very high LDL cholesterol levels (i.e., ≥200 mg/dl [5.15 mmol/l]), pharmacological therapy should be initiated at the same time that behavioral therapy is started.

In the context of the NCEP report, it is suggested that diabetic subjects with clinical CHD and an LDL cholesterol level of ≥100 mg/dl (2.60 mmol/l) after MNT and glucose interventions be treated with pharmacological agents. For diabetic patients without pre-existing CHD, the current ADA recommendations for starting pharmacological therapy are 1) an LDL cholesterol level of ≥130 mg/dl (3.35 mmol/l) and 2) a goal of <100 mg/dl (2.60 mmol/l) for LDL cholesterol. These recommendations are based not only on the high incidence of CHD in patients with diabetes, but also on their higher case fatality rate once they have CHD. Since a large proportion of diabetic patients die before they reach the hospital, a preventive strategy based solely on secondary prevention would not be able to “save” large numbers of these diabetic patients. In patients with LDL between 100 mg/dl (2.60 mmol/l) and 129 mg/dl (3.30 mmol/l), a variety of treatment strategies are available, including more aggressive MNT and pharmacological treatment with a statin (11). MNT should be attempted before starting pharmacological therapy. In addition, if the HDL is <40 mg/dl, a fibric acid such as fenofibrate might be used in patients with LDL between 100 and 129 mg/dl.

In agreement with the earlier ADA consensus panel (10), increased triglyceride levels are recognized as a target for intervention. Since recommended LDL levels are considered to be <100 mg/dl (2.60 mmol/l), and since many diabetic patients have increased triglyceride levels, a large proportion of diabetic patients will have elevated levels of both LDL cholesterol and triglycerides. As such, there is likely to be an increase of diabetic patients on pharmacological therapy and thus an increase in expendi-

Table 3—Order of priorities for treatment of diabetic dyslipidemia in adults*

I. LDL cholesterol lowering*
First choice
HMG CoA reductase inhibitor (statin)
Second choice
Bile acid binding resin (resin) or fenofibrate
II. HDL cholesterol raising
Behavioral interventions such as weight loss, increased physical activity, and smoking cessation may be useful
Difficult except with nicotinic acid, which should be used with caution, or fibrates
III. Triglyceride lowering
Glycemic control first priority
Fibric acid derivative (gemfibrozil, fenofibrate)
Statins are moderately effective at high dose in hypertriglyceridemic subjects who also have high LDL cholesterol
IV. Combined hyperlipidemia
First choice
Improved glycemic control plus high-dose statin
Second choice
Improved glycemic control plus statin† plus fibric acid derivative† (gemfibrozil, fenofibrate)
Third choice
Improved glycemic control plus resin plus fibric acid derivative (gemfibrozil, fenofibrate)
Improved glycemic control plus statin† plus nicotinic acid† (glycemic control must be monitored carefully)

*Decision for treatment of high LDL before elevated triglyceride is based on clinical trial data indicating safety as well as efficacy of the available agents. †The combination of statins with nicotinic acid and especially with gemfibrozil or fenofibrate may carry an increased risk of myositis. See text for recommendations for patients with triglyceride levels >400 mg/dl.

tures on pharmacological therapy. However, the clinical trial data suggest that reduction of LDL cholesterol is associated with reduction in CHD and perhaps overall mortality.

Economic analyses, based on the 4S study, suggest that pharmacological therapy may be cost-effective once indirect costs of CHD are taken into account (12).

Table 3 shows the order of priorities for treatment of dyslipidemia. Treatment of LDL cholesterol is considered as the first priority for pharmacological therapy of dyslipidemia for a number of reasons (1). Clinical trials (4S and CARE) showing the effectiveness of statins in reducing CHD in diabetic subjects show greater risk reductions with narrower confidence intervals than the Helsinki Study with gemfibrozil.

The initial therapy for hypertriglyceridemia is behavioral modification with weight loss, increased physical activity, and moderation of alcohol consumption. In the case of severe hypertriglyceridemia ($\geq 1,000$ mg/dl [11.3 mmol/l]), severe dietary fat restriction (<10% of calories) (in addition to pharmacological therapy) is necessary to reduce the risk of pancreatitis. Improved glycemic control (which has been facilitated by the introduction of new glucose-lowering agents and more frequent

use of combination therapy) is also very effective for reducing triglyceride levels and should be aggressively used before the introduction of fibric acids. After the achievement of optimal glycemic control (or at least after the achievement of as much improvement as likely to be possible), the physician may consider adding a fibric acid. In Table 1, the decision to start pharmacological therapy treatment is dependent on the clinician's judgment between triglyceride levels of 200 mg/dl (2.30 mmol/l) and 400 mg/dl (4.50 mmol/l). Above 400 mg/dl (4.50 mmol/l), strong consideration should be given to pharmacological treatment of triglyceridemia. In contrast, improved glycemic control will only modestly reduce LDL cholesterol levels, and therefore in diabetic patients with both high LDL cholesterol and high glucose levels, one might simultaneously initiate glucose lowering and statin therapy. In some studies, higher-dose statins are moderately effective in reducing triglyceride levels in markedly hypertriglyceridemic subjects (triglyceride ≥ 300 mg/dl [3.40 mmol/l]). The critical issue is that gemfibrozil should not be initiated alone in diabetic patients who have undesirable levels of both triglyceride and LDL cholesterol. Fenofibrate, a recently approved fibric acid derivative, may have

greater LDL-lowering effects and may be useful in diabetic patients with combined hyperlipidemia. Although HDL cholesterol, as noted above, is a powerful predictor of CHD in diabetic patients, it is difficult to raise HDL cholesterol levels without pharmacological intervention. Nicotinic acid, which should be used with caution in diabetic patients, and fibrates can effectively increase HDL cholesterol levels. Behavioral interventions (weight loss, smoking cessation, increased physical activity) may increase HDL cholesterol.

In some cases, combined lipid therapy may be initiated. Several options are shown in Table 3. The combination of statins with nicotinic acid and especially with gemfibrozil or fenofibrate has been associated with increased risk of myositis, although the risk of clinical myositis (as opposed to elevated creatinine phosphokinase levels) appears to be low. However, the risk of myositis may be increased with the combination of gemfibrozil and cerivastatin or in patients with renal disease. The combination of statins with nicotinic acid is extremely effective in modifying diabetic dyslipidemia (with the largest increases in HDL cholesterol levels), but the combination may significantly worsen hyperglycemia. Thus, this combination should be used with extreme caution: use low doses of nicotinic acid (≤ 2 g of nicotinic acid per day) with frequent monitoring of glucose levels.

LIPID-LOWERING AGENTS — A brief summary of the actions of available agents for lipid lowering in patients with diabetes is shown in Table 4. Generally, one or two agents are available in each class with the exception of the statins, for which there are many. The choice of statin should depend principally on the LDL reduction needed to achieve the target (<100 mg/dl [2.60 mmol/l]), on the initial LDL level, and on the judgment of the treating physician.

It should also be noted that the higher doses of statins may be moderately effective at reducing triglyceride levels (though not necessarily at raising HDL levels) and thus may reduce the need for combination therapy. With the use of high doses of statins, the LDL levels may be reduced to 80 mg/dl (2.05 mmol/l) or less, and there is no safety data at such low LDL levels. The use of very high-dose statin therapy (i.e., simvastatin 80 mg or atorvastatin 40 or 80 mg) to treat hypertriglyceridemia should be restricted to patients with both high levels of LDL cho-

Table 4—Pharmacologic agents for treatment of dyslipidemia in adults

	Effect on lipoprotein			Clinical trials in diabetic subjects
	LDL	HDL	Triglyceride	
First-line agents				
LDL lowering				
HMG CoA reductase inhibitor	↓ ↓	↔ ↑	↔ ↓	4S (simvastatin) CARE (pravastatin)
Triglyceride lowering				
Fibric acid derivative	↓ ↔ ↑	↑	↓ ↓	Helsinki (gemfibrozil)
Second-line agents				
LDL lowering				
Bile acid binding resins	↓	↔	↑	None
LDL and triglyceride lowering				
Nicotinic acid	↓	↑ ↑	↓ ↓	None

In diabetic patients, nicotinic acid should be restricted to ≤ 2 g/day: short-acting nicotinic acid is preferred.

lesterol as well as high triglyceride levels. Changes in therapy should be done at ~4- to 6-week intervals based on laboratory findings.

CONSIDERATIONS IN THE TREATMENT OF ADULTS WITH TYPE 1 DIABETES

— Type 1 diabetic patients who are in good control tend to have normal (and sometimes better than normal) levels of lipoprotein. Their composition of lipoproteins may be abnormal, but the effects of these compositional abnormalities in relation to CHD are unknown. There is relatively little observational data on lipoproteins and CHD, and there are no clinical trials relating lipoproteins to CHD. It seems reasonable that if type 1 diabetic patients have LDL cholesterol levels that are above the goals recommended for type 2 diabetic patients (Table 2), they should be aggressively treated. Improved glycemic control may be even more important in type 1 diabetic patients than in type 2 diabetic patients for reduction of CHD (e.g., Wisconsin Epidemiologic Study of Diabetic Retinopathy [WESDR]).

CONCLUSIONS— Aggressive therapy of diabetic dyslipidemia will probably reduce the risk of CHD in patients with diabetes. Primary therapy should be directed first at lowering LDL levels. The goal is to reduce LDL concentrations to levels recommended for patients with pre-existing CHD (≤ 100 mg/dl [2.60 mmol/l]). The initiation level for behavioral interventions is also an LDL cholesterol of >100 mg/dl (2.60 mmol/l). The initial therapy should be to use statin therapy with the addition of a resin if necessary to reach the LDL goal.

However, limited data are available from clinical trials, especially in diabetic patients without clinical cardiovascular disease. In the absence of such data, because of the high mortality for diabetic patients with first myocardial infarction, aggressive treatment of dyslipidemia is also indicated. For patients without previous CHD, the goal for LDL cholesterol is ≤ 100 mg/dl (2.60 mmol/l); the initiation level for pharmacological therapy is set at an LDL level ≥ 130 mg/dl (3.35 mmol/l). However, for patients with LDL levels between 100 and 129 mg/dl, a variety of treatment strategies are available, including more aggressive MNT and pharmacological treatment with a statin. MNT should be attempted before starting pharmacological therapy. In addition, if the HDL is <40 mg/dl, a fibric acid such as fenofibrate might be used in patients with LDL cholesterol between 100 and 129 mg/dl.

The initial therapy for hypertriglyceridemia is improved glycemic control. Additional triglyceride lowering can be achieved with very high dose statins (for subjects with both high LDL and triglyceride levels) or fibric acid derivatives (gemfibrozil or fenofibrate).

References

- Haffner SM: Management of dyslipidemia in adults with diabetes (Technical Review). *Diabetes Care* 21:160–178, 1998
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
- Turner RC, Millns H, Neil HA, Stratton IM,

Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus (UKPDS 23). *BMJ* 316:823–828, 1998

- Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J: Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341:410–418, 1999
- American Diabetes Association: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Position Statement). *Diabetes Care* 26 (Suppl. 1):S51–S61, 2003
- American Diabetes Association: Diabetes mellitus and exercise (Position Statement). *Diabetes Care* 24:S51–S55, 2001
- Grundy SM, Balady GJ, Criqui MH, Fletcher G, Greenland P, Hiratzka LF, Houston-Miller N, Kris-Etherton P, Krumholz HM, LaRosa J, Ockene IS, Pearson TA, Reed J, Smith SC, Washington R: When to start cholesterol-lowering therapy in patients with coronary heart disease: a statement for healthcare professionals from the American Heart Association task force on risk reduction. *Circulation* 95:1683–1685, 1997
- Expert Panel on Blood Cholesterol Levels in Children and Adolescents: Treatment recommendations of the National Cholesterol Education Program Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 89 (Suppl.):525–584, 1992
- Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2497, 2001
- American Diabetes Association: Detection and management of lipid disorders in diabetes (Consensus Statement). *Diabetes Care* 16:828–834, 1993
- Haffner SM, Lehto S, Rönkä T, Pyörälä K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 339:229–234, 1998
- Herman WH, Alexander CM, Cook JR, Bocuzzi SJ, Musliner TA, Pederson TR, Kjekshus J, Pyörälä K: Effect of simvastatin treatment on cardiovascular resource utilization in impaired fasting glucose and diabetes: findings from the Scandinavian Simvastatin Survival Study. *Diabetes Care* 22:1771–1778, 1999