Dyslipidemia Management 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 cardiovascular disease (CVD).

PREVALENCE OF DYSLIPIDEMIA IN TYPE 2 DIABETES

— The most common pattern of dyslipidemia in patients with type 2 diabetes patients is elevated triglyceride levels and decreased HDL cholesterol levels. The mean concentration of LDL cholesterol in those with type 2 diabetes is not significantly different from that in those individuals who do not have diabetes. However, qualitative changes in LDL cholesterol may be present. In particular, patients with diabetes tend to have a higher proportion of smaller and denser LDL particles, which are more susceptible to oxidation and may thereby increase the risk of cardiovascular events. Insufficient data are available to make recommendations on the measurement of particle size in clinical practice.

As in those who do not have diabetes, lipid levels may be affected by factors unrelated to glycemia or insulin resistance, such as renal disease, hypothyroidism, and 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 or estrogen may also contribute to hypertriglyceridemia.

LIPOPROTEIN RISK FACTORS FOR CVD

— Available prospective cohort studies suggest that lipid abnormalities are associated with increased risk of cardiovascular events in patients both with and without diabetes. Various studies have demonstrated that LDL, HDL, and triglycerides are independent predictors of CVD (2).

CLINICAL TRIALS OF LIPID LOWERING IN DIABETIC SUBJECTS

— The recently completed Heart Protection Study has been the largest study to date, enrolling and randomizing 5,963 patients age >40 years with diabetes and total cholesterol >135 mg/dl. In this trial, patients with diabetes assigned to simvastatin had a 22% reduction (95% CI 13–30) in the event rate for major CVD events. This risk reduction was similar across all LDL subcategories examined, including patients with lower pretreatment LDL cholesterol levels (<116 mg/dl) and those without identified vascular disease (3). Numerous other statin trials have included much smaller numbers of patients with diabetes but have demonstrated similar reductions in CVD events.

Two outcomes studies have been conducted with the fibric acid derivative gemfibrozil. 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, low HDL (<40 mg/dl), and modestly elevated triglycerides (4).

MODIFICATION OF LIPOPROTEINS BY MEDICAL NUTRITION THERAPY AND PHYSICAL ACTIVITY

— There is little evidence from clinical trials to determine the effect of different dietary interventions on the incidence of cardiovascular events. Observational studies suggest that patients who report healthier diets and greater physical activity have fewer cardiovascular events (5,6). 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 decreased triglycerides and increased HDL cholesterol levels and also to modest lowering of LDL cholesterol levels. Patients with diabetes 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 patients with diabetes.

Recommendations of the American Heart Association for patients with CVD (7) have suggested that the maximal MNT typically reduces LDL cholesterol 15–25 mg/dl (0.40–0.65 mmol/l). Lifestyle intervention may be evaluated at regular 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 modestly. In general, glucose-lowering agents do not change or have only a minimal effect on HDL levels. Thiazo-

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, 2003.

Abbreviations: ADA, American Diabetes Association; CHD, coronary heart disease: CVD, cardiovascular disease; MNT, medical nutrition therapy; NCEP, National Cholesterol Education Program.

lidinediones may increase HDL and LDL levels, but the long-term effect of such changes is not known

TREATMENT GOALS FOR LIPOPROTEIN THERAPY — No completed clinical trials have examined the effect of implementing different lipid treatment goals, including the question of what LDL cholesterol goal should be used and whether the use of multi-drug therapy is more effective than monotherapy for patients with complex lipid abnormalities. Current trials are examining these questions.

Because of frequent changes in glycemic control in patients with diabetes and the effects on levels of LDL, HDL, total cholesterol, and triglyceride, levels should be measured every year in adult patients. If values are at low-risk levels (LDL <100 mg/dl, triglycerides <150 mg/dl, and HDL >50 mg/dl), assessment may be repeated every 2 years.

Lipid-associated risk for CVD events is graded and continuous. Target LDL cholesterol levels for adults with diabetes are <100 mg/dl (2.60 mmol/l); HDL cholesterol levels are >40 mg/dl (1.02 mmol/l); and triglyceride levels are <150 mg/dl (1.7 mmol/l). In women, who tend to have higher HDL cholesterol levels than men, an HDL goal 10 mg/dl higher may be appropriate.

The recommendations for treatment of elevated LDL cholesterol generally follow the guidelines of both the NCEP (8) and an ADA consensus development conference (9), with the following caveats. Pharmacological therapy should be initiated after lifestyle intervention has been implemented. However, in patients with clinical cardiovascular disease and LDL >100 mg/dl, pharmacological therapy should be initiated at the same time that lifestyle intervention is started.

For patients with diabetes without preexisting CVD, 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 CVD in patients with diabetes (10), but also on the higher case fatality rate of these patients once they have CVD. 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.

Recent findings from the Heart Protection Study (3), in people with diabetes over the age of 40 years with a total cholesterol ≥135 mg/dl, suggest that statin therapy to achieve an LDL reduction of ~30% regardless of baseline LDL levels may be appropriate.

Table 1 shows the order of priorities for treatment of dyslipidemia. Treatment of LDL cholesterol is considered the first priority for pharmacological therapy of dyslipidemia for a number of reasons (1).

Hypertriglyceridemia may be a risk factor for CVD in people with diabetes. The initial therapy for hypertriglyceridemia is lifestyle intervention with weight loss, increased physical activity, restricted intake of saturated fats, incorporation of monounsaturated fats, reduction of carbohydrate intake, and reduction of alcohol consumption. In the case of severe hypertriglyceridemia (≥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 can be very effective for reducing triglyceride levels and should be aggressively pursued. Insulin therapy (alone or with insulin sensitizers) may also be particularly effective in lowering triglyceride levels. After the achievement of optimal glycemic control (or at least after the achievement of as much improvement as likely to be possible), the physician should consider adding a fibric acid and/or niacin.

The decision to start pharmacological therapy 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 to minimize the risk of pancreatitis. 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]). Gemfibrozil should not be initiated alone in diabetic patients who have undesirable levels of both triglyceride and LDL cholesterol. Fenofibrate has greater LDL-lowering effects, is arguably safer in combination with statin therapy, and may be useful in those patients with diabetes with combined hyperlipidemia.

Although HDL cholesterol is a powerful predictor of CVD in patients with diabetes, it is difficult to raise HDL cholesterol levels without pharmacological intervention. Nicotinic acid, which should be used with caution in patients with diabetes, and fibrates can effectively increase HDL cholesterol levels. Low doses of nicotinic acid (≤2 g nicotinic acid/day) may not have much of a detrimental effect of glycemic control, and any deterioration may be easily remediable by adjustment of hypoglycemic medications. Behavioral interventions (weight loss,

Table 1—*Order of priorities for treatment of diabetic dyslipidemia in adults*

I. LDL cholesterol lowering
Lifestyle interventions
Preferred
HMG CoA reductase inhibitor (statin)
Others
Bile acid binding resin (resin), cholesterol absorption inhibitor, fenofibrate or niacin
II. HDL cholesterol raising
Lifestyle interventions
Nicotinic acid or fibrates
III. Triglyceride lowering
Lifestyle interventions
Glycemic control
Fibric acid derivative (gemfibrozil, fenofibrate)
Niacin
High-dose statins (in those 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
Third choice
Improved glycemic control plus statin plus nicotinic acid

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, fenofibrate, and especially gemfibrozil may carry an increased risk of myositis. See text for recommendations for patients with triglyceride levels >400 mg/dl.

smoking cessation, increased physical activity) may increase HDL cholesterol.

In some cases, combined lipid therapy may be initiated. Several options are shown in Table 1. The combination of statins with nicotinic acid, fenofibrate, and especially gemfibrozil 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 a statin or in patients with renal disease. Combinations of statins with nicotinic acid and fibrates are extremely effective in modifying diabetic dyslipidemia.

LIPID-LOWERING AGENTS —

The choice of statin should depend principally on the LDL reduction needed to achieve the target (<100 mg/dl [2.60 mmol/l]) 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 statins, LDL levels may be reduced to ≤50 mg/dl (1.30 mmol/l). There is no safety data at such low LDL levels. The use of very high-dose statin therapy (e.g., simvastatin 80 mg or atorvastatin 40 or 80 mg) to treat hypertriglyceridemia should be restricted to patients with both high LDL cholesterol levels and high triglyceride levels.

Changes in therapy should be based on laboratory follow-up between 4 and 12 weeks after initiating therapy. Once goals have been achieved, laboratory follow-up every 6–12 months is suggested.

CONSIDERATIONS IN THE TREATMENT OF ADULTS WITH TYPE ONE DIABETES —

Patients with type 1 diabetes who are in good glycemic control tend to have normal levels of lipoproteins, unless they are overweight or obese, in which case they may get a lipid profile very similar to that seen in type 2 diabetes. Their composition of lipoproteins may be abnormal, but the effects of these compositional abnormalities in relation to CVD are unknown. There is relatively little observational data on lipoproteins and CVD, and there are no clinical trials relating lipoproteins to CVD. It seems reasonable that if patients with type 1 diabetes have LDL cholesterol levels that are above the goals recommended for those with type 2 diabetes (<100 mg/dl), they should be aggressively treated. Improved glycemic control may be even more important in those with type 1 diabetes than in those with type 2 diabetes for reduction of CVD (e.g., Wisconsin Epidemiologic Study of Diabetic Retinopathy [WESDR]).

CONCLUSIONS —

Aggressive therapy of diabetic dyslipidemia will reduce the risk of CVD in patients with diabetes. Primary therapy should be directed first at lowering LDL levels. The goal is to reduce LDL concentrations to ≤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 pharmacological therapy should be to use statins. A cholesterol absorption inhibitor, a resin, niacin, or fenofibrate may be added if necessary to reach the LDL goal or in the case of statin intolerance. There are no outcome studies of combination lipid-lowering therapies.

In addition, if the HDL is <40 mg/dl, a fibric acid, such as fenofibrate, or niacin might be used in patients with LDL cholesterol between 100 and 129 mg/dl.

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

RECOMMENDATIONS

Screening

- In adult patients, test for lipid disorders at least annually and more often if needed to achieve goals. In adults with low-risk lipid values (LDL <100 mg/dl, HDL >50 mg/dl, and triglycerides <150 mg/dl), repeat lipid assessments every 2 years. (E)

Treatment recommendations and goals

- Lifestyle modification focusing on the reduction of saturated fat and cholesterol intake, weight loss, increased physical activity, and smoking cessation has been shown to improve the lipid profile in patients with diabetes. (A)
- Patients who do not achieve lipid goals with lifestyle modifications require pharmacological therapy. (A)
- Lower LDL cholesterol to <100 mg/dl (2.6 mmol/l) as the primary goal of therapy for adults. (B)
- Lowering LDL cholesterol with a statin is associated with a reduction in cardiovascular events. (A)
- In people with diabetes over the age of 40 years with a total cholesterol ≥135 mg/dl, statin therapy to achieve an LDL reduction of ~30% regardless of baseline LDL levels may be appropriate. (A)
- In children and adolescents with diabetes, LDL cholesterol should be lowered to <100 mg/dl (2.60 mmol/l) using MNT and medications, based on LDL level and other cardiovascular risk factors in addition to diabetes. (E)
- Lower triglycerides to <150 mg/dl (1.7 mmol/l), and raise HDL cholesterol to >40 mg/dl (1.15 mmol/l). In women, an HDL goal 10 mg/dl higher may be appropriate. (C)
- Lowering triglycerides and increasing HDL cholesterol with a fibrate is associated with a reduction in cardiovascular events in patients with clinical CVD, low HDL, and near-normal levels of LDL. (A)
- Combination therapy using statins and fibrates or niacin may be necessary to achieve lipid targets, but has not been evaluated in outcomes studies for either event reduction or safety. (E)

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