ABSTRACT

The leading cause of death in patients with diabetes is cardiovascular disease. This fact has prompted the National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) to elevate diabetes to the status of a coronary heart disease risk equivalent. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate, either immediately or in the long term, ATP III calls for a more intensive prevention strategy. Several studies have demonstrated that people with diabetes and insulin resistance are more likely to experience dyslipidemia than nondiabetics. The focus of this article will be on the management of dyslipidemia and the metabolic syndrome in preventing coronary heart disease in patients with diabetes.


Although medical advances have curbed the rise in most chronic diseases, the incidence of diabetes continues to double every 20 years. The National Institute of Diabetes, Digestive, and Kidney Diseases estimates that 16 million Americans have diabetes, one third of whom are undiagnosed. The chronic complications of diabetes include accelerated development of cardiovascular disease (CVD), end-stage renal disease (ESRD), loss of visual acuity, and limb amputations, all of which contribute to the excess morbidity and mortality found in this patient group. Moreover, diabetes is a major cost driver in health care in the United States. In 1997, medical expenditures directly attributable to diabetes totaled $44.1 billion and comprised $7.7 billion for diabetes and acute glycemic care, $11.8 billion due to the excess prevalence of related chronic complications, and $24.6 billion due to the excess prevalence of general medical conditions. These figures represent the percentage of individuals who have been diagnosed and are currently receiving treatment. Based on the recent trends seen in this population, however, this number has been projected to increase to 29 million by 2050. The potential scope of these projected increases is compounded by the fact that many people, in fact, a greater number than the number with diabetes, have above-normal blood glucose levels that do not meet the diagnostic criteria for diabetes. These conditions, impaired glucose homeostasis, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG), are significant because they often progress to type 2 diabetes.

*This article is based on a presentation given by Dr Golden at a roundtable symposium in Baltimore, Maryland.

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Since the leading cause of death in patients with diabetes is CVD, the newest guidelines issued by the National Cholesterol Education Program Adult Treatment Panel III (ATP III) have elevated diabetes to the status of a coronary heart disease (CHD) risk equivalent. Further, because persons with diabetes who experience a myocardial infarction (MI) have an unusually high death rate, either immediately or in the long term, ATP III calls for a more intensive prevention strategy for such patients, setting a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL. The importance of glycemic control in the prevention of microvascular complications in patients with diabetes has been conclusively demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS) as well as the Diabetes Control and Complications Trial (DCCT). This article expands on efforts to prevent CHD in this population by focusing on the management of dyslipidemia and the metabolic syndrome. It is important to note that aggressive management of hypertension, smoking cessation, and aspirin prophylaxis, which are not discussed in this article, are also extremely important in CHD prevention in diabetes.

**The Insulin Resistance Syndrome**

Type 2 diabetes and atherosclerotic cardiovascular disease share common metabolic antecedents: IGT, hypertension, dyslipidemia, and abdominal obesity. The insulin resistance syndrome, referred to as Syndrome X in a landmark presentation by Gerald Reaven at the 1988 American Diabetes Meeting Ban ting Lecture, has been proposed as the common soil from which these 2 diseases are derived.

Dr. Reaven defined Syndrome X in terms of the following characteristics:

- Resistance to insulin-stimulated glucose uptake
- Hyperinsulinemia
- IGT
- Hyperglycemia
- Hypertension
- Elevated triglycerides
- Decreased high-density lipoprotein cholesterol (HDL-C)

Interestingly, abdominal and visceral obesity were not included in the description of Syndrome X, yet today they are thought to be central features of insulin resistance. Other recently defined features of the syndrome include increased plasma free fatty acids, increased hemostatic markers, including plasminogen activator inhibitor-1 (PAI-1), and increased amounts of small, dense LDL particles. These new features, combined with those previously identified, have been redefined as “the metabolic syndrome,” a key area of emphasis in the ATP III guidelines.

Most of the metabolic consequences of insulin resistance are cardiovascular in nature. To compensate for tissue insulin resistance, the pancreas increases its production of insulin. If this hyperinsulinemia is accompanied by progressive beta-cell failure, the resulting hyperglycemia will ultimately lead to type 2 diabetes.

Insulin resistance also results in dyslipidemia, manifesting primarily as high triglyceride levels and low HDL-C. Hypertension is also exacerbated as a result of a hyperadrenergic state that accompanies insulin resistance, as well as increased renal sodium absorption induced by hyperinsulinemia. At the same time, a hypercoagulable state occurs, due to increased PAI-1, leading to a state of impaired fibrinolysis. These combined factors lead to atherosclerosis, and finally, to the development of CVD.

**Atherosclerosis and Heart Disease in Diabetes**

Atherosclerosis is the primary cause of mortality in people with diabetes, primarily as a consequence of coronary atherosclerosis, with cerebral or peripheral vascular disease accounting for 25% of such deaths. More than 75% of all hospitalizations for diabetic complications are related to atherosclerosis, and more than 50% of patients with newly diagnosed type 2 diabetes show evidence of CVD. This is consistent with the findings of many epidemiological studies, which have shown the presence of cardiovascular risk factors in the prediabetic state, including increased blood pressure and body mass index; elevated triglycerides, glucose, and insulin; and reduced HDL-C.

Potential mechanisms of atherogenesis in diabetes are as follows:

- Abnormalities in apoprotein and lipoprotein particle distribution
- Advanced glycation of proteins in plasma and arterial wall
- Accelerated oxidation of LDL-C
• Procoagulant state: impaired fibrinolysis
• Insulin resistance and hyperinsulinemia
• Enhanced smooth muscle cell proliferation and foam cell formation
• Endothelial dysfunction

Not surprisingly, mortality rates for ischemic heart disease are much higher among men and women who have diabetes compared to nondiabetics (Figure 1). And whereas men who have diabetes have nearly twice the risk of death from CHD, women with diabetes have as much as a 4-fold increase in the risk of death when compared to nondiabetic women, suggesting that women with diabetes appear to be at greater risk relative to their male counterparts.

The argument for making diabetes a CHD risk equivalent is supported by a landmark study published by Steven Haffner, MD, in 1998. The study showed that patients with diabetes who had never experienced MI had a risk of cardiovascular disease mortality comparable to nondiabetic individuals who had experienced MI. This study formed the basis for the decision by the American Diabetes Association (ADA) to lower LDL-C targets for patients with diabetes that preceded the 2001 release of the ATP III guidelines.

MANAGEMENT OF DYSLIPIDEMIA IN PATIENTS WITH DIABETES

Several studies have demonstrated that people with diabetes and insulin resistance are more likely to experience dyslipidemia than nondiabetics. Typically, patients with diabetes have elevated triglycerides, elevated small, dense LDL particles, and low HDL-C (<31 mg/dL) compared to nondiabetics. The Strong Heart Study also demonstrated lower HDL-C levels in diabetics as compared to nondiabetics, as well as the presence of smaller LDL particles.

Two underlying physiological mechanisms have been identified to account for hypertriglyceridemia in diabetes. The first is decreased triglyceride clearance. Whereas lipoprotein lipase (LPL) is the enzyme that normally degrades triglycerides in very low-density lipoprotein (VLDL) particles, in the setting of diabetes and insulin resistance, LPL is resistant to activation by insulin (Figure 2). Further, VLDL particles present in diabetics and individuals with insulin resistance have a higher proportion of apolipoprotein (apo) CIII, which inhibits LPL. The result is decreased triglyceride clearance.

Figure 1. Mortality Rates for Ischemic Heart Disease in Patients With and Without Diabetes*

*In national sample of adults in NHANES I (1971-75).

Figure 2. Decreased Triglyceride Clearance

Very low-density lipoprotein
- Lipoprotein lipase (LPL) resistant to activation by insulin
- Increased ratio of apolipoprotein CIII:CII

Intermediate-density lipoprotein
- More atherogenic

Small, triglyceride-enriched, dense LDL
- More atherogenic
- More easily oxidized
- Decreased binding to LDL receptors
clearance of VLDL as well as intermediate-density lipoproteins, which are more atherogenic and present in the circulation for a longer period of time.

The second mechanism is a function of increased triglyceride synthesis and overproduction of VLDL, primarily in the liver. Insulin resistance in diabetes represents a hyperadrenergic state with increased catecholamines, enhancing the release of free fatty acids from adipose tissue via activation of hormone-sensitive lipase. The free fatty acids are then absorbed by the liver, ultimately resulting in increased synthesis of VLDL cholesterol (VLDL-C). Ultimately, the LDL that results from the overproduction of VLDL is smaller, and denser, both contributing to increased atherogenic qualities. They are more easily oxidized and exhibit a decreased binding affinity for the LDL receptor.8 The etiology of the low HDL-C is not as well understood, but probably results from enhanced transfer of cholesterol esters from HDL in exchange for triglycerides from VLDL. The cholesterol ester poor, triglyceride-enriched HDL and apo A1, the primary lipoprotein within HDL, are subject to enhanced degradation in the kidney. Thus, both small, dense LDL and low HDL are secondary to VLDL overproduction.

BENEFITS OF LIPID LOWERING IN TYPE 2 DIABETES

Several subgroup analyses of many of the CHD prevention randomized trials have reported the benefits of lipid-lowering therapy in type 2 diabetes. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a statin trial, has demonstrated the value of primary prevention.19 Among the 2% to 3% of study subjects with diabetes, the aggregate fatal and nonfatal CHD risk reduction achieved through the use of statin therapy was 55%, clearly a significant reduction.20 Of the 4 secondary prevention trials that included a significant number of subjects with diabetes, a CHD risk reduction among those subjects was approximately 23%.24 A subgroup analysis of diabetics within the Scandinavian Simvastatin Survival Study (4S) also found that lipid-lowering therapy resulted in a significant reduction in CHD and atherosclerotic events. The probability of not having a major CHD event in the 4S among patients without diabetes was 71% in the placebo group and 80% in the treated group; in patients with diabetes, it was 51% in the placebo group and 75% in the treated group. The reduction in risk in treated diabetic patients was 55% compared with 32% in treated nondiabetic patients. Despite being a retrospective subgroup analysis, these data strongly suggest that cholesterol lowering improves the prognosis of diabetic patients with CHD. Moreover, the study suggests that diabetics may benefit more from lipid-lowering therapy than nondiabetic patients.21

The 4S study was large enough to also evaluate individuals with IFG. Of 4S subjects with known baseline fasting glucose (FG) (4398 of 4444), 678 subjects met criteria for IFG, defined as FG from 110 mg/dL to 125 mg/dL. Compared with the 335 placebo-treated IFG subjects, the 343 simvastatin-treated IFG subjects had significantly reduced total mortality, coronary mortality, major coronary events, and need for revascularizations.22 IFG is considered a risk factor for future diabetes and likely reflects early beta-cell dysfunction. A subgroup analysis of 976 patients with diabetes or IGT who participated in the Cholesterol and Recurrent Events (CARE) study revealed that the risk reduction for coronary events (CHD death, nonfatal MI, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty) in the treated diabetic group was 27%, which was similar to a risk reduction of 22% in the treated nondiabetic population.23 Thus, studies that evaluate the benefits of statin therapy suggest that diabetics have at least the same benefits from lipid-lowering therapy as nondiabetics, with the 4S study suggesting that diabetics may experience greater benefit.

FIBRATE TRIALS

The Helsinki Heart Study is to date the only published analysis of the benefits of primary prevention with fibrate therapy that included patients with diabetes. The 2% to 3% of diabetic subjects who participated in the study experienced a 33% reduction in relative risk for a CHD event. While the result, based upon a small sample size (only 135 patients had diabetes at study entry), did not achieve statistical significance, the findings do suggest possible therapeutic benefit.24 The major secondary prevention trial to analyze this issue was the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), which targeted patients with primarily isolated low HDL-C and normal triglycerides.25 The 25% of study participants with diabetes experienced a 24% reduction in relative risk for CVD events.
Clinical Practice Recommendations

The ADA clinical practice guidelines for patients with diabetes who have CVD recommend the institution of both nutritional and drug therapy when LDL-C is >100 mg/dL (Table 1). For diabetics without evidence of CVD, the recommendation is for the initiation of pharmacologic therapy when the LDL-C is ≥130 mg/dL. However, many experts recommend starting pharmacologic therapy when LDL-C is between 100 and 130 mg/dL, so the ADA may change this recommendation in the future when their clinical committee reassesses its clinical practice guidelines.

According to the ATP III guidelines, the primary target for therapy is reduction of LDL-C, with a goal of <100 mg/dL for patients with diabetes (Table 2). Intensified therapeutic lifestyle changes (TLC), such as weight reduction, dietary changes, and increased physical activity, are recommended for patients with LDL-C between 100 and 129 mg/dL. For such patients, ATP III also recommends the use of pharmacologic therapy, usually a fibrate or a nicotinic acid, to treat low HDL-C, high triglycerides, and small, dense LDL in order to modify atherogenic dyslipidemia. Management of other risk factors, such as hypertension, is also strongly recommended.

In patients with LDL-C ≥130 mg/dL, both TLC and cholesterol-lowering drug therapy are recommended. Yet as with the ADA recommendations, this cut-off point may change with the issue of ATP IV, depending upon emerging medical evidence. When triglycerides rise to levels >200 mg/dL, non-HDL-C becomes a secondary therapeutic target, with the goal of lowering non-HDL-C to <130 mg/dL.

Order of Priorities for Treatment of Diabetic Dyslipidemia: LDL-Cholesterol

In treating dyslipidemia in patients with diabetes, LDL-C is considered the first priority for drug therapy. Statins are the first choice for lowering of LDL-C, based on recent clinical trial evidence (4S, CARE). Second-line therapy includes bile acid binding resins or fenofibrate.

HDL-Cholesterol

The second priority for drug therapy is to increase HDL-C. Behavioral interventions and glycemic con-
trol may increase HDL-C levels, but significant elevations cannot be achieved without the use of drugs, such as niacin (which may be contraindicated in some diabetic patients) or fibrates. An important consideration in striving toward higher HDL-C goals is improving glycemic control, which will be discussed in the section on triglycerides.

Niacin has been shown to be effective in elevating HDL-C, but has primarily been contraindicated in diabetes. Yet there is evidence from the Arterial Disease Multiple Intervention Trial (ADMIT)\(^3\) that niacin, at a dose gradually titrated to 3 g/day, reduced LDL-C and triglycerides and increased HDL-C in diabetic patients, who experienced a small, but significant increase in fasting blood sugar (from 165 mg/dL at baseline to 173 mg/dL at follow-up visit), without an accompanying increase in hemoglobin A1C \((HbA1C)\). By study end, blood glucose levels returned to baseline, suggesting a transient hyperglycemic effect that is likely to resolve.

Fibrates are also effective in raising HDL-C, and the VA-HIT trial has shown that raising HDL-C has been associated with reduced CVD events.

### Triglycerides

Glycemic control is the first priority in lowering triglycerides. Patients who are hyperglycemic and who have poorly controlled diabetes are more insulin resistant. In such cases, LPL is resistant to the effects of insulin, with an inverse relationship between the degree of hypoglycemia and the sensitivity of LPL to insulin. As a result, triglycerides are elevated and HDL-C is diminished. In fact, in my practice I have seen as much as a 400 to 500 mg/dL decline in triglycerides when hyperglycemia is treated aggressively to achieve an HbA1C as close to 7% as possible.

Once blood sugar is controlled, fibric acid derivatives are effective and should be used as first-line agents if the triglycerides are >400 mg/dL. The statins are usually more effective when the triglycerides are below that level. Once the triglyceride level is reduced to approximately 200 mg/dL, the LDL-C should be reassessed, and frequently patients will require the addition of a statin, considered to be the third-line therapy for hypertriglyceridemia. For patients with elevated triglycerides in combination with elevated LDL-C, high doses of the more potent statins can be very effective in lowering triglycerides. Some clinicians also use high doses of omega-3 fatty acids (up to 6 to 8 g/day of eicosapentanoic acid) in addition to other pharmacologic therapies. According to ATP III guidelines, the treatment goal for triglycerides is <150 mg/dL.

### Combined Hyperlipidemia

In patients with diabetes and combined hyperlipidemia, all strategies involve improving glycemic control. The first choice is to improve glycemic control, followed by a high-dose statin to reduce LDL-C. A second choice would be combination of a statin with a fibric acid derivative (gemfibrozil or fenofibrate). The risk of myositis with combination therapy increases; therefore, this approach should be undertaken with some caution. For patients who cannot tolerate statins in combination with fibrates, a third choice is the use of a resin with a fibric acid derivative or the use of a statin with niacin. However, when using this combination, the clinician

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**Table 3. ATP III: The Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity(^*) ((\text{Waist circumference}(^{\text{‡}})))</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>TG</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/≥85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dL</td>
</tr>
</tbody>
</table>

\(^{\text{†}}\)Abdominal obesity is more highly correlated with metabolic risk factors than BMI.\n
\(^{\text{‡}}\) Some men develop metabolic risk factors when circumference is only marginally increased.

HDL-C = High Density Lipoprotein Cholesterol; TG = Triglycerides.

*Diagnosis is established when ≥3 of these risk factors are present.

Cardiovascular Risk Management in the Metabolic Syndrome

As mentioned previously, ATP III stresses the role that the metabolic syndrome plays in contributing to CHD risk. This constellation of major risk factors is carefully weighed in the assessment of a patient’s overall risk for CHD. The syndrome, as defined in the current ATP III guidelines, is characterized by abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, low HDL-C), elevated blood pressure, and IFG28 (Table 3). Individuals with ≥ 3 of these factors present are considered to have the metabolic syndrome, which ATP III recognizes as a secondary target of risk-reduction therapy, after the primary target of LDL-C. The metabolic syndrome is closely linked to insulin resistance in which the normal actions of insulin are impaired. While some individuals are genetically predisposed to insulin resistance, excess body fat, abdominal obesity in particular, and physical inactivity promote the development of insulin resistance.

Management of the metabolic syndrome has a 2-fold objective: to reduce underlying causes such as obesity and physical inactivity, and to treat associated nonlipid and lipid risk factors.26 A first step following the acquisition of a fasting lipoprotein profile is to assess the patient’s overall risk for CHD using the Framingham risk scoring assessment provided by ATP III. LDL-C target goals are based upon the individual patient’s 10-year risk of having a cardiovascular event.

The patients at highest risk are those with known coronary artery disease (CAD) or CHD risk equivalents such as diabetes and atherosclerotic disease, and patients with a history of ischemic stroke. Such patients carry a risk for major coronary events of >20% within 10 years and are to be treated aggressively. Also considered at risk are patients who may not have a history of CHD, but who are still at risk for MI or cardiac death in the short term. Using Framingham projections of 10-year absolute CHD risk, major risk factors include cigarette smoking, age, and hypertension.

ATP III sets LDL-C goals that are based upon the degree of patient risk, so that patients with CHD or CHD risk equivalents such as diabetes and atherosclerotic disease have an LDL-C goal of <100 mg/dL.

While not yet recommended by ATP III, emerging medical evidence suggests that a future consideration for management of the metabolic syndrome will be treatment of glucose intolerance. A recently published randomized, controlled clinical trial explored the effects of placebo and lifestyle modification on the incidence of type 2 diabetes in 522 Finnish individuals with IGT over 3 years of follow-up. Subjects in the intensive lifestyle intervention arm demonstrated a reduction in the incidence of type 2 diabetes of approximately 58%.29 A similar result was found for the intensive lifestyle intervention arm in the Diabetes Prevention Program Trial in the United States, which compared lifestyle intervention to metformin therapy and placebo in 3234 glucose-intolerant individuals. This trial suggested that lifestyle modifications were more beneficial than pharmacological therapy, as the incidence of diabetes in the metformin arm was only reduced by approximately 33%. These findings have important ramifications in terms of cardiovascular risk modification with the metabolic syndrome, given that diabetes is such a strong risk factor for CVD.

REFERENCES

5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in