

Hyperlipidemia and Cardiovascular Risk Factors in Patients With Type 2 Diabetes

Based on a presentation by Ronald B. Goldberg, MD

Presentation Summary

Atherosclerosis accounts for approximately 80% of all mortality caused by diabetes and for most hospitalizations necessitated by the complications of diabetes. Overall, individuals with diabetes have a 2- to 3-fold increased risk of cardiovascular disease compared with that in individuals without diabetes. The major risk factors contributing to the excess of cardiovascular disease caused by diabetes include: hyperglycemia, insulin resistance, dyslipidemia, hypertension, smoking, albuminuria, and the procoagulant state. Although the low-density lipoprotein (LDL) and total cholesterol levels of patients with diabetes are similar to those of the nondiabetic population, triglyceride levels are usually higher in

those with diabetes. Evaluation of results in the subsets of the large Scandinavian Simvastatin Survival Study (4S) and the Cholesterol and Recurrent Events (CARE) trials that include subjects with diabetes indicates that cholesterol-lowering drugs can significantly reduce the cardiovascular event rate in patients with diabetes. Current options for the management of cardiovascular risk factors in those with diabetes include lowering the LDL cholesterol level below 100 mg/dL, lowering blood pressure below 130/85 mm Hg, improving hyperglycemia and the atherogenic lipid profile (ie, triglyceride and high-density lipoprotein [HDL] levels), treating microalbuminuria, reducing insulin resistance, and using aspirin to reduce the clotting risk.

The risk of cardiovascular events associated with diabetes has been recognized for decades.¹ Atherosclerosis accounts for approximately 80% of mortality associated with diabetes, three fourths of which is due to coronary disease and approximately one fourth of which is attributable to cerebral or peripheral vascular disease. Atherosclerosis also contributes significantly to diabetes-related treatment costs, as indicated by its presence in more than 75% of hospital-

izations related to complications resulting from diabetes.²

Clinicians and researchers must understand the mechanisms of cardiovascular risk in diabetes before they attempt evidence-based prevention. More than half of all patients with newly diagnosed type 2 diabetes exhibit signs of cardiovascular disease.

The chair of this AJMC symposium, Dr. Saudek, once commented on a seminal article by Haffner³ by posing the question, "When does the

clock start ticking in diabetes?"⁴ The answer, unfortunately, is years or even decades before diagnosis.³

Because of the correlation between insulin resistance and the development of atherosclerosis,⁵ clinicians are naturally intrigued by the prospect that insulin resistance that predates diabetes can serve as an early and potentially treatable warning. However, whether insulin resistance itself accelerates atherosclerosis or is simply a marker for disease is unclear. This is just 1 of many potential pathophysiologic mechanisms requiring study. The effects of lifestyle modification and pharmaceutical treatment on the prevention of progression from impaired glucose tolerance to diabetes are now being tested in the Diabetes Prevention Program (DPP).⁶

In this review, studies related to major cardiovascular risk factors for diabetes are summarized. Evidence from both interventional and observational trials, especially data related to hyperlipidemia, are included.

Overview of Risks

The Framingham data⁷ established that persons with diabetes have a risk of specific cardiovascular events that is anywhere from 2 to 10 times greater than that seen in individuals who do not have diabetes. That classic observational study documented that the excess risk at 30 years of follow-up (patient age range, 30 to 64 years) was greatest in diabetic women, who had, for example, a risk ratio of approximately 10 times for cardiac failure and 9 times for intermittent claudication compared with their nondiabetic counterparts. The overall age-adjusted annual rate of total cardiovascular disease in patients with diabetes was 38 per 1000 in men and 30 per 1000 in women, rates that were approximately 3 to 4 times greater than those observed in the group of subjects without diabetes.

Specific factors implicated in this excess risk (Table 1) were studied in a

large survey in which cardiovascular mortality in 6000 men with diabetes was tracked over a 12-year period.⁸ The results of the Multiple Risk Factor Intervention Trial (MRFIT) indicated that cardiovascular mortality increased progressively in subjects with diabetes who had from 1 to 3 of the following risk factors: a total serum cholesterol level of more than 200 mg/dL, systolic blood pressure more than 120 mm Hg, and cigarette smoking. The mortality rate also increased in subjects without diabetes who had those risk factors, but much less so. Even in the small group of subjects without risk factors, the excess risk in those with diabetes was approximately 4 times greater, which suggests that other unmeasured factors, such as the level of high-density lipoprotein (HDL) cholesterol or triglycerides or the state of the arterial wall, contribute to cardiovascular risk.

Although hyperglycemia correlates strongly with the risk and severity of microvascular complications in diabetic patients, the relation between blood glucose and coronary risk is less clear. In 1 observational study, for example, a 1% reduction in hemoglobin A1c (HbA1c) was associated with a 50% reduction in

Table 1. Established Cardiovascular Risk Factors in Individuals With Diabetes

<p>Ranked in the order of decreasing magnitude of risk:</p> <ul style="list-style-type: none"> ■ Dyslipidemia ■ Hypertension ■ Smoking ■ Albuminuria ■ Hyperglycemia ■ Insulin resistance ■ Procoagulant state

retinopathy but with only a 10% decrease in deaths from ischemic heart disease.⁹ Interventional trials reveal a similarly tenuous connection between hyperglycemia and macrovascular disease. Most often cited in this regard is the United Kingdom Prospective Diabetes Study (UKPDS), in which the group treated intensively with sulfonylureas or insulin exhibited a 25% reduction in microvascular endpoints but only a 16% reduction in myocardial infarction (the latter result narrowly missed statistical significance [$P = 0.052$]). The debate about the role of hyperglycemia in cardiovascular disease was thus extended.¹⁰

Focus on Hyperlipidemia

Trends in serum lipid profiles have been confirmed in large surveys, including a Finnish study of age- and

weight-matched men and women newly diagnosed as having diabetes (Figure 1).¹¹ Persons with diabetes tend to have a higher triglyceride level and a lower HDL cholesterol level than do those without diabetes, but here is usually no difference in the low-density lipoprotein (LDL) cholesterol level.

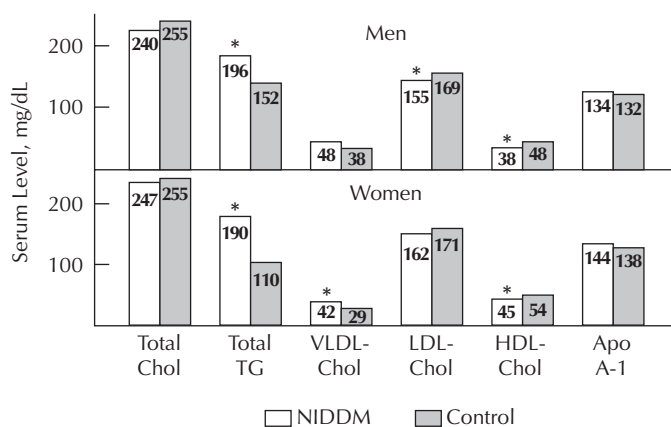
The results of MRFIT indicated that the overall prevalence of hypercholesterolemia was not increased in diabetic subjects but that at every level of serum cholesterol, the risk of cardiovascular mortality in diabetic men was approximately 4 times higher than in nondiabetic men.⁸ Thus, diabetic individuals with a cholesterol level of 200 mg/dL had a greater risk of dying from a heart attack than did nondiabetic individuals with a cholesterol level higher than 280 mg/dL.

After the availability of the statin drug class, researchers had a tool with which to test the effects of cholesterol lowering in hyperlipidemic patients with diabetes. They included 202 subjects with mild type 2 diabetes, coronary disease, and moderately severe hypercholesterolemia (mean LDL cholesterol level, 186 mg/dL).¹²

Over 6 years of follow-up, the LDL cholesterol level in those diabetic patients treated with simvastatin decreased 36%; this was associated with a significant 55% reduction in cardiovascular events ($P = 0.002$) when compared with the LDL cholesterol level in subjects who received placebo. That degree of risk reduction was greater (although not statistically different) than the 32% event rate reduction seen in the much larger subset of subjects without diabetes, which suggests that treating the lipid level may exert a more powerful cardiovascular benefit in persons with diabetes than in those who do not have diabetes.

In 586 diabetic patients with a more typical LDL cholesterol level (136 mg/dL) and a history of coronary artery disease, treatment with pravastatin reduced the coronary event rate

Figure 1. Serum Lipids and Lipoproteins in Patients With Newly Diagnosed Type 2 Diabetes



Source: Adapted from Reference 11.
 Chol = Cholesterol; TG = triglycerides; VLDL = very low-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein; Apo A-1 = apolipoprotein A-1.

over 6 years by 27%, compared with the result of placebo treatment ($P = 0.001$).¹³ In the population without diabetes, the pravastatin-related event reduction was 22%.

Although both of those studies involved data extrapolation from general populations (ie, they were not designed a priori to evaluate lipid lowering in subjects with diabetes), the results are important. The absolute cardiovascular risk is approximately 4 times greater in those with diabetes, and these 2 studies document the need for aggressive cholesterol lowering in diabetic patients with preexisting coronary heart disease. In a small number of individuals with diabetes but without coronary artery disease in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), therapy with lovastatin reduced coronary events, but this did not reach statistical significance. Well-designed clinical trials to answer these questions in diabetic subjects both with and without coronary heart disease have not yet been completed.

The treatment of individuals who have diabetes without coronary disease or those with diabetes and a lower than average cholesterol level is also of interest. Although some data demonstrate the benefit of treatment with statins in diabetic persons without coronary disease and with an LDL cholesterol level of approximately 150 mg/dL,¹⁴ the answers to those important questions are not yet clear.

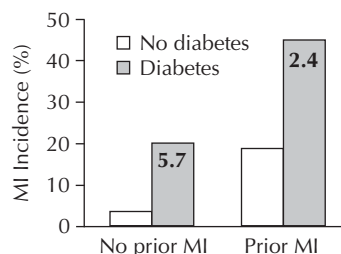
Lacking the interventional data needed to design true evidence-based lipid treatment protocols for persons with diabetes, the American Diabetes Association (ADA) was heavily influenced by the results of the recent 7-year East-West Finnish study of myocardial infarction [MI], fatal and nonfatal) incidence.¹⁵ The event rate in diabetic patients *without* prior MI was as high as the event rate in nondiabetic subjects *with* prior MI

(Figure 2). This suggests that diabetic subjects have as much risk of a cardiovascular event as nondiabetic subjects who have a history of MI.

Although that Finnish population was elderly and at extremely high risk (most were undergoing treatment for hypertension, and the average cholesterol level was approximately 280 mg/dL), the ADA was sufficiently motivated by the results to recommend (with only minor qualifications) treating all patients with diabetes as if they had cardiovascular disease. Thus in individuals with diabetes and without a history of cardiovascular disease, current ADA recommendations call for initiating nutritional therapy at an LDL cholesterol level of 100 mg/dL and drug therapy at an LDL cholesterol level of 130 mg/dL. The LDL cholesterol treatment target is ≤ 100 mg/dL.¹⁶

The ADA recommendations essentially mirror those of the National Cholesterol Education Program (NCEP) for patients with coronary heart disease. The ADA recommendations, however, go even further. In a footnote that reflects equal parts concern (about the risk of hyperlipidemia) and uncertainty (about the

Figure 2. Diabetes and Myocardial Infarction: Risk Factors



Source: Adapted from Reference 15.
MI = Myocardial infarction.

exact level at which treatment should begin), the ADA states that in individuals with multiple risk factors “some authorities recommend drug initiation between 100 and 130 mg/dL.”¹⁶

Others have interpreted the Finnish results by defining patients with diabetes as “coronary heart disease risk equivalents” and by encouraging managed care organizations to consider them good candidates for aggressive cholesterol management.¹⁷

Current clinical trials evaluating statin therapy in diabetic subjects should eventually clarify these issues.

Hypertriglyceridemia

The relationship between hypertriglyceridemia and coronary heart disease is multifaceted. The overall risk may relate less to the fasting lipid profile than it does to the prolonged periods of lipemia that occur after meals. In this critical postprandial period, the arterial wall of the patient with hypertriglyceridemia may be exposed to an accumulation of highly atherogenic triglyceride-rich particles.

Hypertriglyceridemia may also be a driving force behind the generation of smaller and more dense forms of LDL cholesterol (the oxidation-prone phenotype B), which enters the arterial wall more easily.¹⁸ In addition, hypertriglyceridemia is strongly associated with a low HDL cholesterol level in persons with diabetes and has also been linked to an increased propensity to coagulability, possibly via elevated plasminogen activator inhibitor or factor VIIc levels or from activation of prothrombin to thrombin.

The current ADA recommendation is to treat individuals who have both diabetes and a triglyceride level higher than 200 mg/dL. Although definitive clinical study support is lacking, fibrates are often the first choice after lifestyle modification for the treatment of hypertriglyceridemia. In the Helsinki Heart Study,¹⁹ a reduced risk of cardiac events was documented in men taking gemfibrozil, a risk reduc-

tion that was limited primarily to the subgroup of patients with hypertriglyceridemia (> 200 mg/dL) and a high LDL/HDL ratio (> 5.0).

Although it included only approximately 100 patients with diabetes, the Helsinki Heart Study was significant in encouraging clinicians to consider the combination of lipid risks—both triglycerides and LDL/HDL ratio—before making their treatment decision. Recent studies²⁰ with statins have confirmed that theory and have indicated that the HDL cholesterol level can be used to determine which patients are more likely to benefit from LDL-lowering drug therapy.

A recent study has added a new dimension to therapeutic decision-making. This Veterans' Administration (VA) HDL Intervention Trial evaluated the use of gemfibrozil (600 mg bid) in 2531 men (25% of whom had diabetes) with a history of coronary heart disease, a mean LDL cholesterol level of 111 mg/dL, a mean HDL cholesterol level of 32 mg/dL, and a mean triglyceride level of 161 mg/dL.²¹ After 7 years of therapy, the mean HDL cholesterol level had increased by 7.5% ($P < 0.01$), and the mean triglyceride level had decreased by 24.5% ($P < 0.01$) to between 110 and 120 mg/dL. The mean LDL cholesterol level was essentially unchanged. There was a significant reduction in the primary endpoint of nonfatal MI and death from coronary heart disease ($-22%$, $P = 0.006$) as well as from stroke ($-27%$, $P = 0.05$). The results in the subset of diabetic subjects were similar to those in the overall population.

Based in part on those VA results, a new strategy for diabetic patients with a history of coronary heart disease is developing. That strategy, which has been used for select patients in our clinic, involves first using a statin to lower the LDL cholesterol level and then adding a fibrate if the level of HDL cholesterol is less than 35 mg/dL or if the triglyceride is above 200 mg/dL.

Although it is rare, the serious muscle problem of rhabdomyolysis that is associated with the combined use of the fibrate and a statin must be weighed against any potential cardiovascular risk reduction associated with this approach. Again, studies already under way should clarify the clinical benefits and risks of such lipid-lowering approaches in the treatment of patients with diabetes.²²

Hypertension

The prevalence of hypertension in diabetic persons is twice that seen in those who do not have diabetes. The highest rates (~ 50%) of hypertension occur in non-Hispanic whites and in African-Americans.²³ The results of MRFIT have documented a strong relationship between high systolic blood pressure and cardiovascular mortality.⁸ As described earlier with respect to serum cholesterol, the mortality risk increases in a curvilinear fashion with increasing blood pressure, and, at all levels, the absolute level of risk in persons with diabetes remains approximately 3 times higher than that in individuals who do not have diabetes. Thus those with diabetes are at greater risk of (and from) hypertension.

The benefits of lowering blood pressure in diabetic patients with the use of calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or thiazide diuretics have been documented. In the UKPDS, a representative study, 1148 hypertensive patients with diabetes were randomized to either tight control (an ACE inhibitor or a beta-blocker) or to less-tight control (other drugs).²⁴ When compared with patients in the less tightly controlled group (mean treatment blood pressure, 154/87 mm Hg), those in the tightly controlled group (mean blood pressure, 144/82 mm Hg) exhibited risk reductions of 21% in MI ($P = 0.13$), 44% in stroke ($P = 0.013$), and 37% in microvascular disease ($P = 0.002$). There was no difference in the

outcomes of patients treated with an ACE inhibitor or a beta-blocker.

The pathophysiologic mechanisms linking hypertension and vascular disease risk appear to extend beyond simple pressure-related actions. The potential atherogenic mechanisms associated with hypertension suggest that treatments designed solely to reduce systolic pressure may exclude opportunities for cardiovascular risk reduction (Table 2).

This thinking, combined with evidence that certain ACE inhibitors may have nonpressure-related effects on endothelial function, recently prompted a novel study involving the administration of an ACE inhibitor (ramipril), a placebo, or vitamin E to more than 3000 subjects with diabetes without regard to their respective blood pressure level.²⁵ Treatment results 4.5 years after the initiation of the study indicated a significant reduction in cardiovascular disease in all ramipril-treated patient groups, even after adjustment was made for blood pressure levels, which suggests yet another potential avenue of risk reduction for the patient with diabetes and coronary risk factors.

Table 2. Direct and Indirect Relationships Between Hypertension and Vascular Disease in Diabetic Subjects

Atherogenic Mechanisms (Direct)	
■	Increased sympathetic drive
■	Endothelial dysfunction
■	Increased platelet aggregability
■	Atherogenic lipoproteins
■	Left ventricular hypertrophy
Clinical Associations (Indirect)	
■	Insulin resistance
■	Glucose intolerance
■	Dyslipidemia

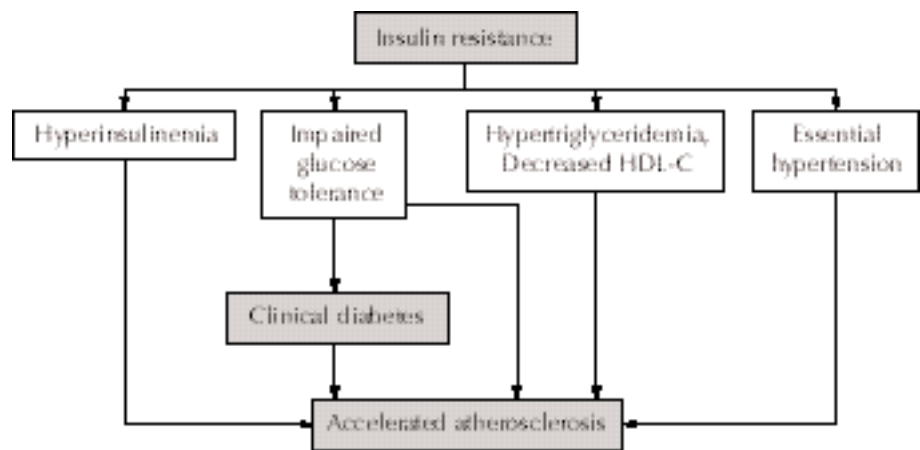
Insulin Resistance, Microalbuminuria, and Coagulation

The mechanisms linking insulin resistance to atherosclerosis are also manifold and complex (Figure 3). Insulin resistance is an early indicator of increased cardiovascular risk, and

the relationship remains even after adjustment for factors such as glucose tolerance, adiposity, insulin levels, and other cardiovascular risk factors.

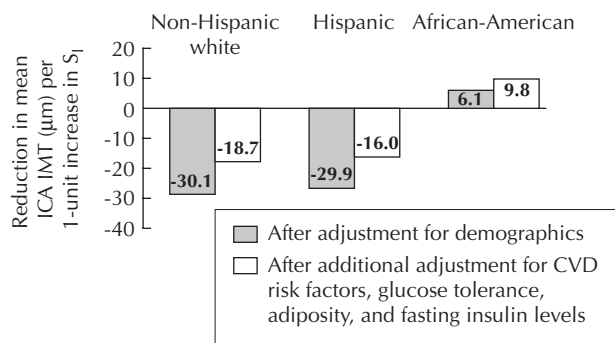
Increases in insulin sensitivity have been associated with sizeable reductions in the thickness of the

Figure 3. Insulin Resistance and Atherosclerosis: Posited Relationships



HDL-C = High-density lipoprotein cholesterol.

Figure 4. Insulin Resistance and Carotid Artery Wall Thickness



Source: Adapted from Reference 5.

ICA = Intimal carotid artery; IMT = intimal-medial thickness; S_1 = insulin sensitivity; CVD = cardiovascular disease.

carotid wall, which is a commonly used research marker for atherosclerosis (Figure 4).⁵ Although the number of patients studied was small and the standard deviation of the measurement error was high, those ultrasonographic results indicated the possibility of an antiproliferative effect related to reduced insulin resistance. Also, because those reductions appeared in both non-Hispanic whites and Hispanics but not in African-Americans, the results should remind clinicians and researchers of ethnic variabilities in the pathogenesis of cardiovascular disease.

Microalbuminuria is another measurable trait that greatly increases the risk of cardiovascular complications in patients with diabetes. In 1 study, for example, the 10-year survival rate in diabetic individuals with microalbuminuria was only 32%.²⁶ Atherosclerotic complications accounted for 58% of the deaths, versus only 7% caused by renal failure.

Finally, although it is accepted that patients with type 2 diabetes have a propensity toward clotting, more remains to be learned about the underlying pathophysiologic factors of that association and its potential prevention. Subjects with diabetes benefit as much from antiplatelet therapy as do those without diabetes,²⁷ but the role of such drug intervention in primary or secondary risk reduction is unclear.

Summary

The current alternatives for improving cardiovascular outcomes in persons with diabetes are varied and in need of further study. Management options range from lifestyle interventions designed to reduce insulin resistance or hyperglycemia to treatment with drugs that lower the LDL cholesterol or triglyceride level, reduce the risk of clotting, or reduce the blood sugar level (Table 3).

Note that the agents commonly used to control diabetes may also act

negatively or positively on atherogenic risk factors. For example, all oral antihyperglycemic agents tend to make the blood less coagulable by lowering the blood sugar level, and the thiazolidinediones and metformin appear to have an additional direct effect of decreasing plasminogen activator inhibitor, which further enhances the anticlotting tendency.

The newer agents also reduce insulin resistance and improve the lipid profile. With the thiazolidinediones, the lowering of insulin resistance and the enlargement of LDL particle size are especially notable and are of potential clinical value. Experimental animal, in vitro, and clinical data regarding endothelial dysfunction also indicate that the thiazolidinediones may improve endothelial function and may decrease smooth muscle proliferation.

However, before the antiatherogenic actions of any oral antihyperglycemic

Table 3. Summary of Options for Managing Cardiovascular Risk Factors in Patients With Diabetes

<ul style="list-style-type: none"> ■ Stop smoking ■ Lower the low-density lipoprotein cholesterol level below 100 mg/dL (initiate at 100* to 130 mg/dL) ■ Improve atherogenic lipid profile <ul style="list-style-type: none"> - Lifestyle modification - Antihyperglycemic agents - Statins - Fibrates ■ Reduce insulin resistance (especially by achieving normal body weight) ■ Reduce clotting risk (aspirin) ■ Lower blood pressure (< 130/85 mm Hg) ■ Screen for and treat microalbuminuria ■ Reduce hyperglycemia <ul style="list-style-type: none"> - Lifestyle modifications - Sulfonylureas - Metformin - Thiazolidinediones - Acarbose - Insulin
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*In patients with 1 risk factor or evidence of atherosclerosis.

agents can be cited as having specific advantages in lowering cardiovascular risk, much more clinical testing is required. As we learn more about the amalgam of cardiovascular risks in individuals with diabetes, we will be better able to design and test more targeted and evidence-based interventions. As a result, we will be able to reduce the considerable clinical and economic burden of diabetes-related cardiovascular complications.

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