Cardiovascular Disease and Diabetes: Modifying Risk Factors Other Than Glucose Control

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Patients with type 2 diabetes have a significantly increased risk of developing cardiovascular disease. Atherosclerosis kills more diabetic patients than all other causes combined. Multiple risk factors tend to cluster in some patients in a syndrome termed insulin resistance syndrome or "Syndrome X." Increasing evidence has changed the recommended management of diabetes from simple glucose control to aggressive lipid management and control of the other components of the metabolic syndrome to prevent development of cardiovascular disease. One mechanism linking hyperglycemia and atherogenesis is nonenzymatic glycation of proteins. Hyperglycemia increases the linkage of glucose to proteins producing insoluble complexes, termed advanced glycation end products, that cause endothelial cell changes. Glycation of lipoproteins increases their atherogenic potential. It is not clear whether intensive glucose control in diabetic patients significantly lowers the rate of long-term macrovascular complications, and glucose control by itself may not be sufficient to prevent cardiovascular disease. Elevated triglyceride levels in diabetic patients are risk factors for cardiovascular disease. Though LDL-cholesterol levels are not necessarily elevated in type 2 diabetes, higher levels (or LDL phenotype B) are shown to be more atherogenic. The association between obesity and hypertension is well documented, and obesity can worsen other risk factors. Glycemic control may not always normalize lipid and lipoprotein levels, particularly in type 2 diabetes. Trials of intensive glycemic control have not shown a significant reduction in coronary events despite significant decreases in microvascular complications. Medical nutrition therapy and exercise remain the cornerstone for nonpharmacologic treatment with a goal of improved insulin sensitivity.

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Patients with type 2 diabetes have a significantly increased risk of developing cardiovascular disease (CVD), and, once clinical cardiovascular disease develops, these patients have a poorer prognosis than normoglycemic patients. Hyperglycemia, the major problem in diabetes, plays a direct role in inducing endothelial changes that contribute to atherosclerosis. All cardiovascular risk factors except smoking are more prevalent in patients with type 2 diabetes. In recent years, type 2 diabetes has been associated with a group of other conditions that contribute to atherosclerosis, collectively known as the metabolic syndrome or "Syndrome X". The syndrome consists of hypertension, atherogenic dyslipidemia, and a procoagulant state in addition to the disorder of glucose metabolism. Increasing evidence has changed our management of diabetes from simple glucose control to aggressive lipid management and control of the other components of the metabolic syndrome to prevent development of CVD or to decrease morbidity and mortality in patients already known to have CVD. In addition to weight control, exercise, aspirin therapy, and blood pressure control, therapy to control the diabetic dyslipidemia is usually necessary. The choice of agent or combination of statins, bile acid sequestrants, fibric acid derivatives, and nicotinic acid depends on the lipid profile and characteristics of the individual patient.

Epidemiology of Cardiovascular Disease in Diabetics

Approximately 12 million Americans have type 2 diabetes and an estimated 20 million more Americans have some degree of glucose intolerance (1). Atherosclerosis accounts for approximately 80% of all mortality in diabetic patients, and more than 75% of hospitalizations for diabetes complications are attributable to CVD (2,3). Mortality from coronary artery disease is approximately 3- to 10-fold higher in patients with type 1 diabetes (4) and about 2-fold higher in men and 4-fold higher in women with type 2 diabetes (5). Coronary artery disease, strokes, and peripheral vascular disease are approximately 2.5 times more prevalent in white and Hispanic men with diabetes compared with nondiabetics. Diabetes also is the most common cause of heart disease in young people. At the time of first diagnosis of type 2 diabetes, more than 50% of patients are found to have preexisting CVD (6). In women, there is a 3.5- to 4.5-fold greater risk for these complications associated with diabetes (7-9), and women with diabetes lose the protection against coronary heart disease (CHD) observed in premenopausal women without diabetes. In the Framingham Heart Study, the age-adjusted incidence of myocardial infarction at the 26-year follow-up was higher in diabetic women than in diabetic men (13.8 per 1000 persons vs. 13.1 per 1000 persons) (7), and the risk of recurrent myocardial infarction in women with diabetes was twice that in diabetic men (10).

Mechanisms for Atherogenesis in Diabetes

Hyperglycemia

One mechanism linking hyperglycemia and atherogenesis is nonenzymatic glycation of proteins, including circulating lipoproteins. Linkage of glucose to proteins produces insoluble complexes termed advanced glycation end products (AGEs), the formation of which is increased in hyperglycemia. AGE proteins cause endothelial cell changes such as:

- Increasing endothelial permeability
- Impairment of endothelium-dependent vasodilation by depletion of nitric oxide
- Smooth muscle cell proliferation through cytokine induction resulting from binding of AGE-bound proteins to specific macrophage receptors
- Increased secretion of platelet-derived growth factor and enhanced chemotaxis of blood monocytes
- Procoagulatory changes on the endothelial cell surface and increased oxidative stress by binding to endothelial cells (11-13).

Glycation of lipoproteins increases their atherogenic potential. Glycation of low density lipoprotein (LDL) can prolong its half-life, increasing the likelihood that it will be trapped in the vascular wall where it is more susceptible to oxidation (14). Glycation of high density lipoprotein (HDL) causes increased HDL clearance, while glycation of very low density lipoprotein (VLDL) and apolipoproteins E and C can prolong the persistence of VLDL or apoliproprotein remnants in the blood stream (15,16).

Based on results from a limited number of interventional clinical trials, it is not clear whether intensive glucose control in diabetic patients significantly lowers the rate of long-term macrovascular complications. One of the first large trials, the University Group Diabetes Program, showed inconclusive results (17). In the Diabetes Control and Complications Trial (DCCT) (18), the risk of macrovascular disease was reduced by 41% in type 1 diabetic patients on intensive therapy, although this difference was not statistically significant. In patients with type 2 diabetes, neither the Kumamoto study (19) nor the VA Cooperative trial of intensive therapy (20) showed benefits in reducing CHD with improved glycemic control. The United Kingdom Prospective Diabetes Study (UKPDS) (8), another large study evaluating the effect of intensive glucose control in newly diagnosed type 2 diabetics, showed a reduction of macrovascular disease but it did not reach statistical significance ($p=0.052$) except in a subgroup of obese patients assigned to metformin treatment. The results of these studies suggest that the increased risk of CVD in diabetic patients on treatment to control blood glucose is due to one or more components of the disease process and glucose control by itself may not be sufficient to prevent CVD.

The Metabolic Syndrome or Syndrome X

Multiple risk factors for CVD tend to cluster in some patients as seen in type 2 diabetes. This syndrome was first described by Reaven and was termed insulin resistance syndrome or "Syndrome X" to include insulin resistance, hyperinsulinemia, glucose intolerance or type 2 diabetes, hypertension, and an atherogenic profile (low levels of HDL cholesterol with elevated VLDL triglycerides) (21-23). This syndrome has been expanded to include small, dense LDL cholesterol; postprandial lipemia; high levels of plasminogen activator inhibitor (PAI-I); and obesity, and the syndrome may be present for years before the development of diabetes. High insulin levels have been shown to be a marker for insulin resistance and have been associated with the above risk factors for atherosclerosis.

Lipid abnormalities

Triglycerides, with or without low HDL-cholesterol: Recent studies have shown elevated triglyceride levels in patients with diabetes to be positive and independent risk factors for CVD. In the Paris Prospective Study of men with diabetes or impaired glucose tolerance, the only significant, independent risk factor for CHD mortality on multivariate analyses was an elevated triglyceride

level (24,25). The study demonstrated that the mean annual CHD mortality was approximately three times higher in men with elevated triglyceride (>123 mg/dL) and cholesterol (>220 mg/dL) levels compared with men with lower levels. In 1998, the Copenhagen Male Study demonstrated hypertriglyceridemia as a risk factor for CHD, independent of HDL-cholesterol levels (26). Elevated triglyceride levels are associated with a procoagulant state that may accelerate atherogenesis in patients with diabetes. When triglyceride levels are elevated, the activity of factor VII and factor X is heightened, and PAI-I concentrations as well as platelet aggregability are increased.

In the VA Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT) (12), gemfibrozil, a fibric acid derivative, increased HDL cholesterol levels and decreased triglyceride levels compared with placebo in men with and without diabetes who had CHD and low HDL cholesterol levels as the primary lipid abnormality. After 5 years, VAHIT investigators found that the risk of a major coronary event was 22% lower and the risk of the combined outcome of CHD death, nonfatal myocardial infarction, or stroke was 24% lower in gemfibrozil-treated patients compared with placebo-treated patients ($P<0.05$ for major coronary event and combined outcome).

Baseline data from the UKPDS showed that both decreased HDL and elevated LDL predicted CHD (8). In observational studies, HDL may be the most consistent predictor of CHD in type 2 diabetes subjects, followed by triglycerides and total cholesterol (27).

LDL Phenotype: LDL-cholesterol levels are not necessarily elevated in type 2 diabetes. However, an increase in the small, dense LDL cholesterol (or LDL phenotype B), shown to be more atherogenic, is twice as prevalent in diabetic men with normal lipid levels than in nondiabetic normolipidemic men (52% versus 24%) (28). LDL phenotype B is closely associated with increased levels of triglycerides, apolipoprotein B, VLDL, and intermediate-density lipoprotein mass, and decreased HDL cholesterol. The risk of myocardial infarction is increased nearly 3-fold in persons with LDL phenotype B, even when adjusted for other CHD risk factors (29). In the Stanford Coronary Risk Project (30), LDL Phenotype B was one of three predictors of coronary risk in men and women (the other two predictors being cigarette smoking and high total levels of non-HDL cholesterol). Moreover, patients with LDL phenotype B were shown to have a better response to hypolipidemic therapy, regardless of lifestyle modifications (diet, exercise, etc.) or pharmacologic therapy as assessed by angiography and changes in lipoprotein parameters, than patients with LDL phenotype A.

Increased LDL phenotype B results in functional endothelial damage to the arterial wall. Endothelial cells, smooth muscle cells, and macrophages in the arterial wall can oxidize LDL, which acts as a chemoattractant for circulating monocytes. Oxidized LDL cholesterol is taken up much more rapidly via scavenger receptors than is native LDL. Platelets aggregate and adhere to the area of endothelial injury and release thromboxane, a potent vasoconstrictor and proaggregant, and growth factors that stimulate smooth muscle cell proliferation and migration. All of these processes can lead to the formation of an atherosclerotic plaque, which tends to propagate itself, and, in the final stages of plaque development, thrombi accumulate and smooth muscle cells die, resulting in a plaque consisting of fibrotic debris with lipid and calcium deposits.

Obesity

Obesity is a prominent feature of the metabolic syndrome. The association between obesity and hypertension is well documented, and obesity can worsen other risk factors (31). Obesity in patients with type 2 diabetes is associated with atherogenic changes in lipids and lipoproteins. For example, triglyceride levels are generally higher in obese persons than in lean persons. The distribution of fat, rather than overall obesity, determines risk. The reported association between increased abdominal (upper body) fat and an increased risk of CHD relates to visceral fat, for which the waist-to-hip ratio is a convenient index. A waist-to-hip ratio of greater than 1.0 in men and 0.8 in women indicates abdominal obesity (32). The waist circumference alone also correlates well with the amount of visceral fat, and the relationship is similar in men and women (33).

Treatment of Dyslipidemia in Diabetes

Glycemic control may not always normalize lipid and lipoprotein levels, particularly in type 2 diabetes. Although there is some evidence that glycemic control may affect atherogenesis, trials of intensive glycemic control have not shown a significant reduction in coronary events despite significant decreases in microvascular complications (34). A number of clinical trials (though not studied directly in diabetics) have shown promising results in lowering the risk of coronary artery disease by lipid control. In the Scandinavian Simvastatin Survival Study (4S), simvastatin (HMG CoA reductase inhibitor or "statin") significantly reduced CHD incidence and total mortality in diabetic subjects with high LDL cholesterol and with previous clinical CHD. In the Cholesterol and Recurrent Events (CARE) trial, pravastatin reduced CHD incidence significantly in diabetic subjects with average LDL levels and with previous clinical CHD by 27%. In the Helsinki Heart Study, gemfibrozil was found to produce reductions of 8.1% in total cholesterol, 6.5% in LDL, and 30.7% in triglycerides and an increase of 11% in HDL in 135 patients with type 2 diabetes. However, the 68% decrease in CHD risk in the diabetic population did not achieve statistical significance owing to the small number of diabetic patients enrolled (34).

The American Diabetes Association updated its recommendations for the management of dyslipidemia in adults with

diabetes based on a companion Technical Review. The new guidelines divide atherosclerosis risk in diabetic patients into three categories based on lipoprotein levels. Higher risk levels are defined as LDL 130 mg/dL or greater, HDL less than 35 mg/dL, or triglycerides 400 mg/dL or greater. Lower risk levels are defined as LDL less than 100 mg/dL, HDL greater than 45 mg/dL and triglycerides less than 200 mg/dL. Borderline risk levels are defined as lipid levels between the values for higher and lower risk. For all diabetic patients, the goal is reduction of LDL cholesterol levels to 100 mg/dL or less and triglycerides to 200 mg/dL or less. Medical nutrition therapy (MNT) is initiated in all diabetic patients with LDL greater than 100 mg/dL. This is also the threshold for initiation of pharmacologic therapy in diabetic patients unless they are completely free of coronary, peripheral vascular, and cerebrovascular disease and have no other CHD risk factors. In the latter group of patients, an LDL level of 130 mg/dL or greater is the level for initiating drug therapy. Diabetic patients with triglycerides 1000 mg/dL or greater require immediate and aggressive treatment to lower triglycerides to less than 400 mg/dL to lessen the risk of acute pancreatitis. Secondary goals of therapy include reducing triglycerides to less than 200 mg/dL and increasing HDL cholesterol levels to greater than 35 mg/dL in men and 45 mg/dL in women.

MNT and exercise remain the cornerstone for nonpharmacologic treatment. The American Heart Association (AHA) dietary guidelines recommend total cholesterol intake of less than 300 mg/d and total fat intake constituting less than 30% of total calories, with saturated fat accounting for less than 10% of total calories and polyunsaturated and monounsaturated fat accounting for equal portions of the remainder of fat calories (step I AHA diet) (35). This is further reduced to total cholesterol intake of less than

Table. Summary of drugs available for treatment of dyslipidemia and their mechanism of action

Drug	Lipoprotein effects (%)			Major side effects	Glucose levels
	LDL	TG	HDL		
Firstline agents					
LDL lowering HMG-CoA reductase inhibitors (statins)					
Atorvastatin	40-60% ↓	20-40% ↓	5-12% ↑	GI symptoms, headache, hepatotoxicity, myopathy	↔
Fluvastatin	20-32% ↓	NA	NA		
Lovastatin	24-40% ↓	10-19% ↓	7-10% ↑		
Pravastatin	22-34% ↓	15-24% ↓	7-12% ↑		
Simvastatin	24-33% ↓	10-19% ↓	7-12% ↑		
Triglyceride lowering fibric acid derivative					
Gemfibrozil	Variable ↓	30-50% ↓	5-15% ↑	GI symptoms, hepatotoxicity, myopathy, BM depression	↔, ↓
Second line agents					
Bile acid sequestrants	15-35% ↓	5-30% ↑	↔ or ↑	GI symptoms	↔
Nicotinic acid	10-40% ↓	20-50% ↓	10-30% ↑	Flushing, itching, rash, GI symptoms, worsening glucose intolerance	

GI = gastrointestinal (abdominal pain, flatulence, diarrhea, constipation) ↑ indicates increase; ↓ indicates decrease; ↔ indicates no effect or unchanged
HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides

200 mg/d and limitation of saturated fat to less than 7% of total cholesterol (step II AHA diet) if lipid goals are not met within 3-4 months. The AHA has suggested that maximal MNT typically reduces LDL cholesterol by 15-25 mg/dL, thus, if the LDL cholesterol exceeds the goal by more than 25 mg/dL, pharmacologic therapy may be started at the same time as dietary therapy. Pharmacologic therapy should also be instituted if lifestyle changes do not result in achievement of lipid goals by the third to sixth month.

Improved insulin sensitivity is a desirable goal of treatment. Two classes of oral agents, metformin and the thiazolidinediones, have been shown to decrease insulin resistance while exerting some degree of benefit on triglyceride levels and other risk factors for cardiovascular disease. Metformin lowers LDL and triglycerides while modestly elevating HDL levels, whereas the thiazolidinediones may increase HDL and LDL levels. In patients with persistent triglyceride elevations despite maximal oral hypoglycemic therapy, insulin may be necessary to improve both residual hyperglycemia and dyslipidemias.

If residual dyslipidemia remains after an adequate period of glycemic control (3-6 months) or, in any event, after 6 months of hypoglycemic treatment, pharmacologic hypolipidemic therapy should be considered. A number of agents available for treatment of dyslipidemia have been shown to be effective in dyslipidemic diabetics (Table).

Summary

Atherosclerosis kills more patients with diabetes than all other causes combined. The aggressive treatment and reversal of dyslipidemias have been shown to prevent coronary events in type 2 diabetics. Glycemic control is often only partially effective in normalizing lipid values in type 2 diabetes. An intensive nonpharmacologic approach plus lipid-regulating agents, particularly HMG-CoA reductase inhibitors, is often necessary to normalize diabetes-associated dyslipidemias. Addressing each component of the metabolic syndrome is necessary for the proper management of the diabetic patient.

References

1. Opara JU, Levine JH. The deadly quartet—the insulin resistance syndrome. South Med J 1997; 90: 1162-1168.
2. Detection and management of lipid disorders in diabetes. American Diabetes Association. Diabetes Care 1993; 16:828-834.
3. Garber AJ, Vinik AI, Crespin SR. Detection and management of lipid disorders in diabetic patients: A commentary for clinicians. Diabetes Care 1992; 15:1068-1074.
4. Krolewski AS, Kosinski EJ, Warram JH, et al. Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 1987; 59:750-755.
5. Krolewski AS, Warram JH, Valsania P, et al. Evolving natural history of coronary artery disease in diabetes mellitus. Am J Med 1991; 90 (suppl 2A): 56S-61S.
6. Margolis JR, Kannel WB, Feinleib M, et al. Clinical features of unrecognized myocardial infarction: Silent and symptomatic. Eighteen year follow-up: The Framingham Study. Am J Cardiol 1973; 32:1-7.
7. Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. Am Heart J 1985; 110:1100-1107.
8. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23). BMJ 1998; 316: 823-828.
9. Wei M, Mitchell BD, Haffner SM, et al. Effects of cigarette smoking, diabetes, high cholesterol, and hypertension on all-cause mortality and cardiovascular disease mortality in Mexican Americans. The San Antonio Heart Study. Am J Epidemiol 1996; 144: 1058-1065.
10. Abbott RD, Donahue RP, Kannel WB, et al. The impact of diabetes on survival following myocardial infarction in men vs. women: The Framingham Study. JAMA 1998; 260:3456-3460.
11. Bierman EL. George Lyman Duff Memorial Lecture. Atherogenesis in diabetes. Arterioscler Thromb 1992;12:647-656.
12. Rubins HB, Robins SJ, Collins D, et al. 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 1999; 341:410-418.
13. Schwartz CJ, Valente AJ, Sprague EA, et al. Pathogenesis of the atherosclerotic lesion. Implications for diabetes mellitus. Diabetes Care 1992; 15:1156-1167.
14. Haffner SM. Management of dyslipidemia in adults with diabetes. Diabetes Care 1998; 21:160-178.
15. Halpern MJ. Lipids and atherosclerosis. Mol Aspects Med 1995; 16: 509-710.
16. Sowers JR, Epstein M. Diabetes mellitus and associated hypertension, vascular disease, and nephropathy. An update. Hypertension 1995; 26 (6 pt 1):869-879.
17. Knatterud GL, Klimt CR, Levin ME, et al. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. VII: Mortality and selected nonfatal events with insulin treatment. JAMA 1978; 240:37-42.
18. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993; 329:977-986.
19. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28:103-117.
20. Abraira C, Colwell J, Nuttall F, et al. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes. Arch Intern Med 1997; 157:181-188.
21. DeFronzo RA, Ferrannini E. Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14:173-194.

22. Donahue RP, Orchard TJ. Diabetes mellitus and macrovascular complications. An epidemiological perspective. Diabetes Care 1992; 15:1141-1155.
23. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988; 37:1595-1607.
24. Cambien F, Jacqueson A, Richard JL, et al. Is the level of serum triglyceride a significant predictor of coronary death in "normocholesterolemic" subjects? The Paris Prospective Study. Am J Epidemiol 1986; 124:624-632.
25. Fontbonne A, Eschwege E, Cambien F, et al. Hypertriglyceridemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989; 32:300-304.
26. Suadicani P, Hein HO, Gyntelberg F. Socioeconomic status and ischaemic heart disease mortality in middle-aged men: importance of the duration of follow-up. The Copenhagen Male Study. Int J Epidemiol 2001; 30:248-255.
27. American Diabetes Association. Consensus statement: Management of Dyslipidemia in Adults with diabetes. Diabetes Care 2001; (suppl 1): S58-S61.
28. Feingold KR, Grunfeld C, Pang M, et al. LDL subclass phenotypes and triglyceride metabolism in non-insulin dependent diabetes. Arterioscler Thromb 1992;12:1496-1502.
29. Austin MA, Breslow JL, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 1988; 260:1917-1921.
30. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. Circulation 1996; 94:2146-2153.
31. Pi-Sunyer FX. Medical hazards of obesity. Ann Intern Med 1993; 119: 655-660.
32. Stunkard AJ. Current views on obesity. Am J Med 1996; 100:230-236.
33. Despres JP. Dyslipidaemia and obesity. Baillieres Clin Endocrinol Metab 1994; 8:629-660.
34. Garber AJ. Vascular disease and lipids in diabetes. Med Clin North Am 1998; 82:931-948.
35. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines. Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. Stroke 2000; 31:2751-2766.

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