

Lipids and Lipoproteins in Patients With Type 2 Diabetes

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Insulin resistance and type 2 diabetes are associated with a clustering of interrelated plasma lipid and lipoprotein abnormalities, which include reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglyceride levels. Each of these dyslipidemic features is associated with an increased risk of cardiovascular disease. Increased hepatic secretion of large triglyceride-rich VLDL and impaired clearance of VLDL appears to be of central importance in the pathophysiology of this dyslipidemia. Small dense LDL particles arise from the intravascular processing of specific larger VLDL precursors. Typically, reduced plasma HDL levels in type 2 diabetes are manifest as reductions in the HDL_{2b} subspecies and relative or absolute increases in smaller denser HDL_{3b} and HDL_{3c}. Although behavioral interventions such as diet and exercise can improve diabetic dyslipidemia, for most patients, pharmacological therapy is needed to reach treatment goals. There are several classes of medications that can be used to treat lipid and lipoprotein abnormalities associated with insulin resistance and type 2 diabetes, including statins, fibrates, niacin, and thiazolidinediones. Clinical trials have shown significant improvement in coronary artery disease after diabetic dyslipidemia treatment.

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Type 2 diabetes is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglycerides (1). These abnormalities occur in many patients despite normal LDL cholesterol levels. These changes are also a feature of the insulin resistance syndrome (also known as the metabolic syndrome), which underlies many cases of type 2 diabetes. In fact, pre-diabetic individuals often exhibit an atherogenic pattern of risk factors that includes higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower levels of HDL cholesterol than individuals who do not develop diabetes (2,3). Insulin resistance has striking effects on lipoprotein size and subclass par-

ticle concentrations for VLDL, LDL, and HDL (4,5).

There is evidence that each of these dyslipidemic features is associated with increased risk of cardiovascular disease, the leading cause of death in patients with type 2 diabetes. Numerous studies have demonstrated an association between LDL size or density and coronary artery disease (CAD) (6–13). Moreover, recent reports have indicated that LDL particle concentrations, and specifically levels of small dense LDL, are predictive of coronary events and that this is independent of other coronary disease risk factors (14–16).

Although lowering LDL cholesterol is important in decreasing cardiovascular disease morbidity and mortality, there are a number of other factors contributing to

the disease process that can be favorably affected by drug therapy. Among these factors are subspecies of the major lipoprotein classes, such as triglyceride-rich lipoprotein remnants and small dense LDL, that are not detected by standard lipid testing. It is therefore possible that at least part of the CAD benefits observed in CAD prevention trials can be attributed to pharmacological effects on specific types of lipoprotein particles.

This article will review the pathophysiology of diabetic dyslipidemia and the relationship between reduced HDL levels, increased small dense LDL particles, elevated triglycerides, and cardiovascular risk. Current therapeutic options for the management of diabetic dyslipidemia and clinical trials that provide evidence of the benefits of treating this atherogenic dyslipidemia also will be discussed.

PATHOPHYSIOLOGY OF DIABETIC DYSLIPIDEMIA

Altered metabolism of triglyceride-rich lipoproteins is crucial in the pathophysiology of the atherogenic dyslipidemia of diabetes. Alterations include both increased hepatic secretion of VLDL and impaired clearance of VLDL and intestinally derived chylomicrons. An important consequence of retarded clearance is prolonged plasma retention of both VLDL and postprandial chylomicrons as partially lipolyzed remnant particles (Fig. 1). These remnants, which include cholesterol-enriched intermediate-density lipoproteins (IDLs), are particularly atherogenic in humans and in a number of animal models (17,18).

Increased hepatic production and/or retarded clearance from plasma of large VLDL also results in increased production of precursors of small dense LDL particles. As many as seven distinct LDL subspecies, which differ in their metabolic behavior and pathological roles, have been identified (Table 1) (19). Plasma VLDL levels correlate with increased density and decreased size of LDL (22,23). In addition, LDL size and density are inversely related to plasma levels of HDL, especially the HDL₂ subclass (24). Small dense LDL particles appear to arise from

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Abbreviations: apo, apolipoprotein; CAD, coronary artery disease; CHD, coronary heart disease; IDL, intermediate-density lipoprotein; SCRIP, Stanford Coronary Risk Intervention Project; TZD, thiazolidinedione; VA-HIT, Department of Veteran's Affairs HDL Intervention Trial.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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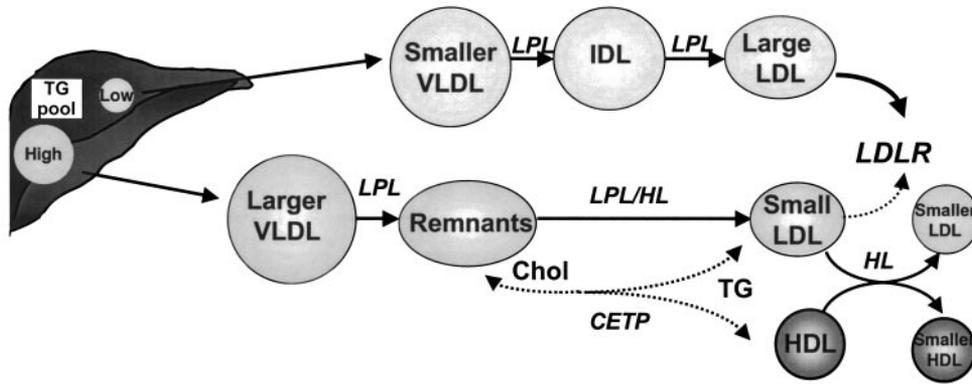


Figure 1—Hypothetical scheme for the relation of altered metabolism of triglyceride-rich lipoproteins to the development of an atherogenic lipoprotein phenotype. CETP, cholesterol ester transfer protein; Chol, cholesterol; HL, hepatic lipase; LDLR, LDL receptor; LPL, lipoprotein lipase; TG, triglyceride.

the intravascular processing of specific larger VLDL precursors through a series of steps, including lipolysis (19). Further triglyceride enrichment of the lipolytic products through the action of cholesteryl ester transfer protein, together with hydrolysis of triglyceride and phospholipids by hepatic lipase, leads to increased production of small dense LDL particles (17,18). Plasma residence time of these LDL particles may be prolonged because of their relatively reduced affinity for LDL receptors (19).

HDL particles are heterogeneous, and multiple subclasses differing in diameter and density have been identified, ranging from the small dense HDL_{3c}, HDL_{3b}, and HDL_{3a} to the larger HDL_{2a} and HDL_{2b} (Table 1) (20). The reductions in HDL associated with type 2 diabetes and insulin resistance are multifactorial, but a major factor appears to be increased transfer

of cholesterol from HDL to triglyceride-rich lipoproteins, with reciprocal transfer of triglyceride to HDL. Triglyceride-rich HDL particles are hydrolyzed by hepatic lipase and, as a result, are rapidly catabolized and cleared from plasma (25). Typically, the reduced HDL levels in plasma of patients with type 2 diabetes are manifest as reductions in the HDL_{2b} subtypes and relative or absolute increases in smaller denser HDL_{3b} and HDL_{3c}.

Insulin resistance may play a pivotal role in the development of diabetic dyslipidemia by influencing several factors. In insulin resistance and type 2 diabetes, increased efflux of free fatty acids from adipose tissue and impaired insulin-mediated skeletal muscle uptake of free fatty acids increase fatty acid flux to the liver (26,27). The fact that free fatty acid levels are elevated in individuals with impaired glucose tolerance suggests that in-

sulin resistance associated with elevated free fatty acid levels occurs before the onset of hyperglycemia (28). One study conducted in patients without diabetes showed that decreased glucose utilization in muscle was associated with acute elevation of free fatty acids (29). Epidemiologic studies have also demonstrated a relationship between plasma free fatty acid levels and insulin resistance (30). In the presence of insulin resistance, free fatty acids in the form of triglycerides are deposited in muscle, liver, heart, and pancreas. Notably, agents that lower elevated free fatty acids, such as the thiazolidinediones (TZDs), have been shown to improve insulin sensitivity in muscle, liver, and adipose tissues (31,32).

Insulin resistance also increases hepatic lipase activity, which as noted above, is responsible for hydrolysis of phospholipids in LDL and HDL particles and leads to smaller and denser LDL particles and a decrease in HDL₂ (33–35).

Table 1—Principal LDL and HDL subclasses as distinguished by density and particle diameter (19–21)

	Density (g/ml)	Diameter (Å)*	Changes in diabetic dyslipidemia
LDL			
1	1.019–1.023	272–285	Reduced
2a	1.023–1.028	265–272	Reduced
2b	1.028–1.034	256–265	Reduced
3a	1.034–1.041	247–256	Increased
3b	1.041–1.044	242–247	Increased
4a	1.044–1.051	233–242	Variable
4b	1.051–1.063	220–233	Variable
HDL			
2b	1.063–1.100	98–129	Reduced
2a	1.100–1.125	88–98	Variable
3a	1.125–1.147	82–88	Variable
3b	1.147–1.167	77–82	Increased
3c	1.167–1.200	72–77	Increased

From refs 19–21. *Determined by non-denaturing gradient gel electrophoresis.

RELATIONSHIP BETWEEN REDUCED HDL, SMALL DENSE LDL, ELEVATED TRIGLYCERIDES, AND CARDIOVASCULAR DISEASE RISK

It is well documented that reduced HDL cholesterol levels are associated with an increased risk of coronary heart disease (CHD) (36). A number of functions of HDL particles may contribute to direct cardioprotective effects, including promotion of cellular cholesterol efflux and direct antioxidative and anti-inflammatory properties. Moreover, low HDL cholesterol levels are often accompanied by elevated triglyceride levels (37), and the combination has been strongly associated with an increased risk of CHD (38–40). In the Quebec Cardio-

vascular Study, it appeared that HDL₂ particles contributed to the cardioprotective effects of high HDL cholesterol levels more than HDL₃ particles (41). However, the nature of this association may depend on the characteristics of the HDL particle distribution in the particular population being studied. For example, in men with CHD selected for HDL cholesterol levels of <40 mg/dl in the Department of Veteran's Affairs HDL Intervention Trial (VA-HIT), reduced CHD events in men treated with gemfibrozil were associated with levels of HDL₃, reflecting the fact that these were the predominant form of HDL in the study cohort (42). Hence, increased levels of both HDL₂ and HDL₃ particles may have cardioprotective effects.

Individuals with type 2 diabetes and CHD tend to have small HDL particles (43). In addition, hyperinsulinemia and hypertriglyceridemia are independently associated with low levels of HDL₂ and small HDL particle size. In individuals with visceral obesity and insulin resistance, small HDL particle size represents another feature of the dyslipidemic profile that is common in this patient population (44).

Increased atherogenic potential of small dense LDL appears to be related to a number of physicochemical and metabolic properties of these particles, including reduced LDL receptor affinity (45,46), greater propensity for transport into the subendothelial space (47), increased binding to arterial wall proteoglycans (48), and susceptibility to oxidative modifications (49–51). Although these are *in vitro* findings, they support the concept that small dense LDL contributes to arterial damage in patients with the characteristic dyslipidemia associated with diabetes.

The evidence for a relationship between plasma triglyceride levels and the risk of CAD is largely based on epidemiologic studies. A meta-analysis of 17 population-based prospective studies found that for each 1-mmol/l increase in plasma triglyceride there is a 32% increase in coronary disease risk for men and a 76% increase in risk for women (52). Adjustment for the effects of HDL cholesterol and other risk factors attenuated the risk to 14% in men and 37% in women, but these values remained statistically significant. Direct atherogenic effects of triglyceride-rich particles, especially IDL and remnant lipoproteins, may account

for this independent contribution of plasma triglyceride levels to coronary disease risk (17,18).

Taken together, these data suggest that the characteristic dyslipidemia associated with insulin resistance and type 2 diabetes is highly correlated with increased cardiovascular risk.

MANAGEMENT OF DIABETIC DYSLIPIDEMIA

— Lifestyle interventions such as diet, physical activity, weight loss, and smoking cessation are an integral part of any diabetes management plan. Epidemiologic and intervention studies have shown significant improvement in the features of diabetic dyslipidemia with medical nutrition therapy and physical activity (53,54). Current recommendations for the management of dyslipidemia in patients with type 2 diabetes include these behavioral interventions (1). Of interest is the increasing evidence of the benefit of low-carbohydrate diet programs in achieving weight loss and improving lipid and lipoprotein levels (55–57). Although behavioral interventions can improve diabetic dyslipidemia to some extent, pharmacological therapy will be needed to reach treatment goals in many patients. There are several classes of medications used in the treatment of lipid and lipoprotein abnormalities associated with insulin resistance and type 2 diabetes.

Statins (HMG-CoA reductase inhibitors)

The primary actions of statins on lipoprotein metabolism are mediated by increased LDL receptor activity, although reduced hepatic lipoprotein secretion also appears to play an important role. In addition to LDL lowering, statins can, to varying degrees, lower plasma triglyceride levels and raise HDL cholesterol. Statins lower plasma levels of all LDL subclasses and IDL to an equivalent extent, although greater lowering of small LDL has been reported in conjunction with triglyceride reduction (58). Nevertheless, most studies have not reported a reversal of the small dense LDL phenotype associated with diabetic dyslipidemia.

Fibrates (peroxisome proliferator-activated receptor- α agonists)

A major effect of peroxisome proliferator-activated receptor- α agonists is the reduction of levels of triglyceride-rich lipoproteins. This is mediated by tran-

scriptional regulation of genes that promote clearance of triglyceride-rich lipoproteins (e.g., increased lipoprotein lipase and its activator apolipoprotein [apo]CII) and inhibition of apoCIII, a protein that reduces lipolysis of triglyceride-rich lipoproteins and clearance of their remnants (59). Fibrates also raise HDL, apparently because of the increased production of HDL apoproteins and reduced transfer of cholesteryl ester from HDL to VLDL (60,61). Although the effects of fibrates on LDL cholesterol are variable, average reductions are generally small. A number of studies have shown that fibrates can reduce levels of small dense LDL and reverse the small dense LDL phenotype (62–64). It is likely that beneficial effects on triglyceride-rich lipoprotein metabolism, possibly coupled with reduced cholesteryl ester transfer activity, contribute to this effect. It has been shown that fenofibrate treatment can be effective in normalizing the atherogenic dyslipidemic phenotype in patients with type 2 diabetes (65,66).

The combination of a statin and fenofibrate can be highly beneficial in patients with type 2 diabetes and combined hyperlipidemia (i.e., increased LDL cholesterol, low HDL cholesterol, and elevated triglycerides). After 24 weeks of treatment with the combination, LDL cholesterol was reduced by 46%, triglycerides were reduced by 50%, and HDL cholesterol was increased by 22% ($P < 0.0001$ for all) (67). Similar findings were reported in patients with combined hyperlipidemia and metabolic syndrome, in whom levels of small dense LDL levels were also shown to be reduced by combined statin-fenofibrate therapy (68). Although concerns have been raised regarding increased toxicity of statin-fibrate combination therapy, recent studies have indicated that this risk appears to be much greater with gemfibrozil than with fenofibrate (69), although caution must be exercised in patients with impaired renal function.

Niacin

Nicotinic acid (niacin) significantly reduces triglyceride levels, increases HDL levels, and increases LDL particle size and buoyancy, thereby improving the atherogenic lipoprotein profile. Niacin reduces fatty acid release from adipose tissue and suppresses hepatic production of VLDL. In turn, these effects decrease triglyceride

levels and reduce the number of small dense LDL particles. Recent studies indicate that the HDL-raising effect of niacin is potentiated by an increase in the effective half-life of HDL due to reduced uptake by the receptor responsible for intrahepatic degradation of HDL (70).

However, use of niacin in patients with type 2 diabetes has been discouraged in the past because of reports that high doses can worsen glycemic control. In a recent 16-week double-blind placebo-controlled study, 148 patients with type 2 diabetes and dyslipidemia were randomized to treatment with placebo or 1,000 or 1,500 mg/day of extended-release niacin (71). Almost half of the patients also received concomitant statin therapy. Niacin, 1,000 and 1,500 mg/day, increased HDL cholesterol by 19 and 24%, respectively, compared with placebo ($P < 0.05$ for both) and reduced triglyceride levels by 13 and 28%, respectively ($P < 0.05$ for the 1,500-mg dose). Changes in glycemic control were minimal with the 1,000 mg dose, although higher doses of niacin appeared to disrupt glycemic control and worsen insulin resistance. In the group who received 1,500 mg extended-release niacin, glycosylated hemoglobin levels increased slightly from 7.2% at baseline to 7.5% at week 16 ($P = 0.048$ vs. placebo). Most patients were able to tolerate niacin therapy for the duration of the study; however, four patients discontinued therapy because of inadequate glycemic control.

TZDs (peroxisome proliferator-activated receptor- γ agonists)

TZDs have an insulin-sensitizing effect that can effectively lower glucose concentrations in patients with type 2 diabetes. Although these agents are not indicated for treatment of dyslipidemia, evidence suggests that TZDs can exert beneficial effects on lipoproteins and may improve some aspects of the dyslipidemia observed in patients with diabetes. Studies indicate that the currently available TZDs, rosiglitazone and pioglitazone, exert similar effects on lipid profiles in patients with diabetes (72–76). Overall, total and LDL cholesterol tend to increase with TZD therapy, and there is a consistent increase in HDL cholesterol. Triglyceride levels are generally decreased with pioglitazone therapy and also are reduced with rosiglitazone in patients with elevated baseline triglyceride levels (72,73,77,78).

In an observational cohort study,

treatment with a TZD significantly increased LDL particle size and increased the larger HDL₂ subfraction by 24% (79). In a double-blind randomized trial, 216 patients with type 2 diabetes treated with rosiglitazone for 8 weeks had significantly increased mean levels of HDL cholesterol (6%) and HDL₂ (12.6%) levels, along with an increase in LDL buoyancy determined by ultracentrifugation (80). Of the 55% of subjects with predominantly small dense LDL, 71% shifted to the buoyant LDL phenotype. These effects are similar to those reported with troglitazone (81,82). When atorvastatin was added to rosiglitazone therapy, there was a further increase in HDL (5%) and significant ($P < 0.0001$) decreases in LDL cholesterol (–39%) and triglycerides (–27%) (80). Pioglitazone also has been shown to positively affect atherogenic dyslipidemia in patients with type 2 diabetes (74,83,84). In a recent analysis of 54 nondiabetic patients with arterial hypertension, small dense LDL levels were found to be elevated in 63% of patients at baseline (84). After 16 weeks of treatment with pioglitazone, dense LDL particles were reduced by 22% ($P = 0.024$).

EVIDENCE FOR BENEFIT OF MANAGEMENT OF ATHEROGENIC DYSLIPIDEMIA ON CHD RISK

— A number of studies have pointed to the benefit of pharmacological lipid management on CHD risk in type 2 diabetes. In particular, post hoc analyses of trials using statins for primary prevention (85) and secondary prevention of CHD (86–88) found a substantially reduced risk for cardiovascular events in diabetic patients. Benefit of statin therapy on CHD risk in diabetic subjects has also been demonstrated prospectively in the recent Heart Protection Study (89).

However, the relationship of improved risk to changes in specific lipoprotein components of diabetic dyslipidemia has been difficult to assess. Such relationships have been sought in two recent trials using fibrate therapy in diabetic patients. The VA-HIT study found that gemfibrozil treatment of men with CHD selected on the basis of HDL levels <40 mg/dl and LDL levels <140 mg/dl resulted in significant reductions in CHD end points without a significant reduction in LDL cholesterol concentration (42). A portion of the treatment benefit was associated

with an increase in HDL. In the subgroup of 769 men with diabetes, treatment with gemfibrozil resulted in a 32% reduction in major cardiovascular events ($P < 0.004$) and a 41% reduction in CHD death compared with placebo ($P = 0.02$) (90). Moreover, among 1,733 nondiabetic men with CHD in VA-HIT, increased plasma fasting insulin, as well as insulin resistance assessed by the homeostasis model assessment of insulin resistance (calculated as fasting insulin [μ U/ml] \times fasting glucose [mmol/l]/22.5), were predictive of increased major cardiovascular events as well as greater benefit from gemfibrozil treatment (90,91). Notably, the rate of new cardiovascular events and reduction of events with gemfibrozil was greater in insulin-resistant subjects (Table 2); cardiovascular events were more highly correlated with the presence of insulin resistance than with either baseline HDL cholesterol or triglyceride levels (91). However, it has recently been reported that in a subset of the total VA-HIT cohort, 55% of the benefit of gemfibrozil on CHD end points could be attributed to reductions in concentrations of LDL particles and increases in HDL particles, independent of other standard risk factors (92).

The effects of fenofibrate on angiographic measures of CAD progression were assessed in the Diabetes Atherosclerosis Intervention Study (93). There was significant reduction in CAD progression in the fenofibrate-treated group ($n = 198$), and this was related to on-treatment concentrations of LDL cholesterol, triglyceride, apoB, and peak LDL particle diameter as determined by gradient gel electrophoresis (94). Moreover, in fenofibrate-treated subjects, both on-treatment LDL cholesterol concentration and final LDL particle size, as well as on-treatment apoB concentration and final LDL particle size, contributed significantly to the progression of CAD. The strength of this relationship was not improved further by inclusion of triglyceride or HDL cholesterol in the model.

Other angiographic studies have addressed the relationship of treatment effects on LDL subfractions to changes in angiographic indexes of CAD progression. The Stanford Coronary Risk Intervention Project (SCRIP) was a multifactorial risk-reduction trial in patients with CAD (95). Multifactor risk reduction (diet, exercise, weight loss,

Table 2—Cardiovascular events in relation to insulin resistance with lower and higher risk levels of HDL cholesterol and triglycerides

	No insulin resistance	Insulin resistance	Relative difference in events [% (95% CI)]	P
HDL cholesterol				
<31.5 mg/dl	79/344 (23.0)	75/231 (32.5)	29 (7–46)	0.012
≥31.5 mg/dl	76/404 (18.8)	50/164 (30.5)	38 (16–55)	0.002
P	0.16	0.68	—	—
Triglycerides				
<152 mg/dl	81/418 (19.4)	49/143 (34.3)	43 (24–58)	0.0003
≥152 mg/dl	74/330 (22.4)	76/252 (30.2)	25 (2–43)	0.035
P	0.31	0.40	—	—

Data are event/total n (% events) unless otherwise indicated. Reproduced with permission from Robins et al. (91). Values are shown for the entire placebo group with plasma insulin, glucose, and lipid values measured at baseline (n = 1,143). Subjects with diabetes who were being treated with insulin were excluded from the analyses. HDL cholesterol and triglycerides were separated into higher and lower cardiovascular risk categories at the median value of HDL cholesterol of 31.5 mg/dl and median value of triglycerides of 152 mg/dl. Insulin resistance was defined by the highest tertile of homeostasis model assessment of insulin resistance values. The relative difference in cardiovascular events between groups with and without insulin resistance and between lower and higher levels of HDL cholesterol and triglycerides was calculated by χ^2 .

smoking cessation, and medications) for 4 years favorably altered the rate of luminal narrowing in coronary arteries of men and women with CAD and decreased hospitalizations for cardiac events. In addition, SCRIP provided evidence that lipid-altering therapy (including primarily bile acid binding resins, fibrate, and niacin, alone and in combination) reduced angiographic progression of CAD after 4 years only in patients with the atherogenic lipoprotein phenotype characterized by predominantly small dense LDL, as measured by ultracentrifugation, and not in individuals with large buoyant LDL (96). This occurred despite similar baseline LDL cholesterol levels and similar reductions in LDL cholesterol with therapy.

A more recent analysis of data from the usual care (control) group in SCRIP indicated that plasma levels of the smallest and most dense of the seven LDL sub-species, LDL_{4b}, were most strongly associated with angiographically assessed disease progression and that this was independent of other risk factors (97).

The Bezafibrate Coronary Atherosclerosis Intervention Trial failed to demonstrate a relationship of a shift from smaller to larger LDL particles to reduced progression of CAD in a group of 92 dyslipidemic men with premature coronary disease treated with 200 mg bezafibrate three times daily, but changes in levels of individual subfractions were not reported (98).

In the Familial Atherosclerosis Treat-

ment Study, significant improvement in CAD progression was observed with intensive lipid-lowering therapy in men with documented coronary disease, elevated apoB levels, and a family history of CAD (99). Treatment consisted of colestipol plus lovastatin or niacin plus colestipol. In a subgroup of 88 patients, LDL buoyancy, a parameter closely related to LDL size, was found to be significantly increased with treatment, and this change was strongly correlated with reduced progression or regression of CAD assessed angiographically. In a multivariate analysis, increased LDL buoyancy was the risk factor most strongly associated with CAD regression (100). The increase in LDL buoyancy was also correlated with reduced activity of hepatic lipase, suggesting that this enzyme may be a potential therapeutic target by which LDL density and size may be favorably affected (100,101).

CONCLUSIONS— A cluster of interrelated plasma lipid and lipoprotein abnormalities associated with alterations in VLDL metabolism contribute to the risk for atherosclerosis and CHD in the majority of patients with type 2 diabetes. Insulin resistance plays a key role in the development of diabetic dyslipidemia. Each of the lipid abnormalities (low HDL, small dense LDL, and elevated triglycerides) is associated with an increased risk of CHD. Features of this dyslipidemia can be improved by a variety of therapeutic

modalities, including weight loss and physical activity, and the use of statins, fibrates, nicotinic acid, and TZDs. Additionally, evidence from angiographic trials indicates that reduction in small dense LDL particles can contribute significantly to reduced coronary disease progression observed with these treatments.

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