CHAPTER 10 ■ PATHOPHYSIOLOGY AND TREATMENT OF DYSLIPIDEMIA IN DIABETES

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Atherosclerosis is the leading cause of death among individuals with diabetes, accounting for 80% of all mortality. Approximately 75% of deaths result from coronary atherosclerosis and 25% from cerebral or peripheral arterial disease. Greater than 75% of hospitalizations for diabetic complications are due to atherosclerosis (1). Mortality rates for ischemic heart disease are two- to fourfold greater for individuals with diabetes compared to those without diabetes (2). The decision to make diabetes a coronary heart disease (CHD) risk equivalent is supported by a landmark study by Haffner et al. in 1998 (3), which showed that patients with diabetes who had never experienced a myocardial infarction (MI) had a comparable risk of cardiovascular disease (CVD) mortality as individuals without diabetes who had already experienced an MI. This study formed the basis for more aggressive treatment of CVD risk factors, particularly dyslipidemia, in individuals with diabetes. In this chapter, we review the pathophysiology of diabetic dyslipidemia as it relates to insulin resistance, the results of lipid-lowering trials of prevention of CVD in diabetes, and current treatment guidelines for diabetic dyslipidemia.

THEORETICAL CONSIDERATIONS

Historically, diabetes has been considered a disorder primarily related to abnormal glucose metabolism. More recently, it has been appreciated that obesity, or the products of excess adipose tissue, often precede the abnormalities of glucose metabolism (4). In particular, elevated plasma free (nonesterified) fatty acids (FFA) play a paramount role in the development of type 2 diabetes by causing insulin resistance. Indeed, insulin resistance can be caused even if the FFA are elevated for more than a few hours. In starvation or the second half of pregnancy, for example, such induction of insulin resistance by FFA can be beneficial for preserving carbohydrate for use by the brain and other vital tissues. In contrast, in periods of excess energy, induction of insulin resistance by FFA is not desirable, eventually leading to elevated glucose levels when the secretion of insulin by the pancreas is insufficient to compensate for the insulin resistance (4).

Role of FFA in the Pathogenesis of Insulin Resistance, Diabetes, and Dyslipidemia

A number of tissues plays a paramount role in the pathophysiology of diabetic dyslipidemia. These include adipose tissue, liver, skeletal muscle, pancreas, and intestine. Each of these will be considered separately in this chapter along with their interrelationships.

Metabolism of Triglycerides in Adipocytes

In the normal postprandial state, FFA are delivered to the adipocyte following the hydrolysis of triglycerides (TG) by lipoprotein lipase (LPL) in the TG-rich lipoproteins (TRL) at the surface of endothelial cells (5) (Fig. 10.1). After crossing the endothelial cells and entering the adipocyte, the FFA are activated and incorporated into TG, a process referred to as "fatty acid trapping." The final step in this process is the addition of a fatty acid CoA to diacylglycerol (DAG) through the action of diacylglycerol acyltransferase (DGAT) (Fig. 10.1). Insulin plays an important role in this process since it increases LPL activity as well as stimulates the formation of TG (Fig. 10.1). The acylation-stimulating protein (ASP) also stimulates the incorporation of FFA into TG in adipocytes, an effect that is independent and additive of that of insulin (see also Chapter 8) (6). The interaction of insulin with its receptor also normally inhibits the activity of hormone-sensitive lipase (HSL) in the postprandial state, decreasing the efflux of FFA from the adipocyte (Fig. 10.1). In contrast, catecholamines upregulate HSL, thereby increasing the release of FFA from the adipocyte (Fig. 10.1). When the adipocyte is resistant to the effect of insulin, there is decrease in both fatty acid trapping and the inhibition of HSL by insulin. Both of these pathologic effects of insulin resistance will increase the flux of FFA to liver and muscle (Fig. 10.1) (see following text).

Molecules That Decrease the Flux of FFA from Adipose Tissue to Liver and Muscle. An inhibitory G protein–coupled receptor, GPR109A, on adipocytes also suppresses the release of FFA by HSL (5) (Fig. 10.1). Both β-hydroxybutyrate and niacin are ligands for GPR109A that may initiate the inhibitory G-protein signal that decreases cAMP via adenyl cyclase, leading to reduced PKA activation and lower HSL activity (5) (Fig. 10.1). The AMP-activated protein kinase (AMPK) system also normally suppresses activation of HSL (5) (Fig. 10.1). AMPK appears to facilitate a balance between the amount of FFA released from TG by HSL, and that released from the cell or, alternatively, oxidized. Otherwise, excess FFA in adipocytes will be recycled back into TG, a process that requires ATP. Adiponectin activates AMPK-increasing oxidation of FFA and insulin sensitivity (5) (Fig. 10.1). Peroxisome proliferator-activated receptor (PPAR)-α agonists, such as fibrates, increase plasma adiponectin in patients with CVD, dyslipidemia, and insulin resistance, an effect that is proportional to the improvements in TG and high-density lipoprotein cholesterol (HDL-C) (5). PPAR-α can be expressed in adipose tissue where it upregulates genes oxidation of FFA. Agonists of PPAR-γ, such as thiazolidinediones (TZDs) also increase adiponectin in diabetic individuals

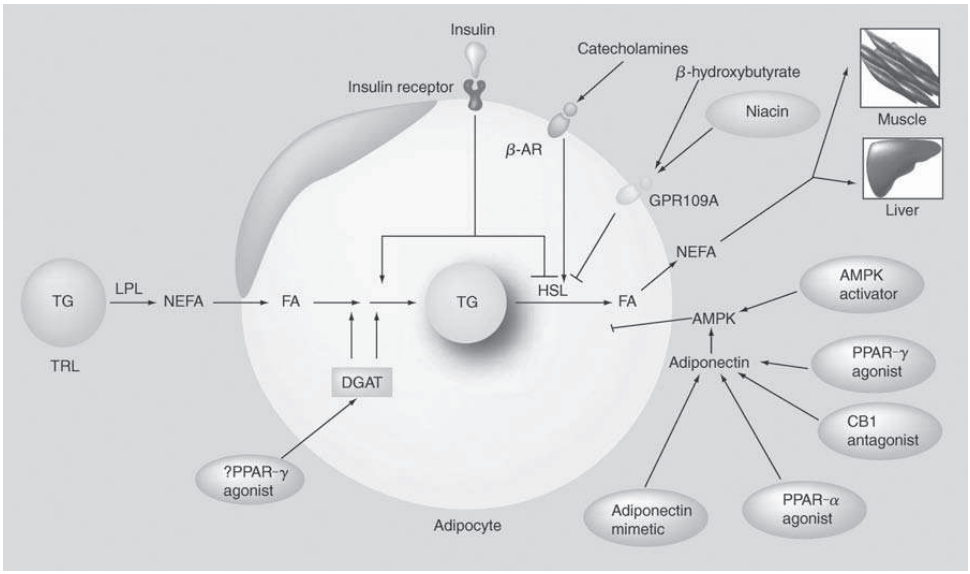

FIGURE 10.1 Metabolism of TG in adipocytes. In the postprandial state, FFA are delivered to adipocytes following the hydrolysis of TG by LPL. After crossing the endothelial cells and entering the adipocyte, the FFA are activated and incorporated into TG, a process referred to as "fatty acid trapping." The final step in this process is the addition of a fatty acid CoA to diacylglycerol through the action of DGAT. Insulin both increases LPL activity and stimulates the formation of TG. The interaction of insulin with its receptor (IR) normally inhibits the activity of HSL in the postprandial state, decreasing the efflux of FFA from the adipocyte. In contrast, catecholamines upregulate HSL, thereby increasing the release of FFA from the adipocyte. When the adipocyte is resistant to the effect of insulin, there is a decrease in both FFA trapping and the inhibition of HSL by insulin, increasing the flux of FFA to liver and muscle. In contrast, the inhibitory G protein-coupled receptor, GPR109A, on adipocytes suppresses the release of FFA by HSL. Both β-hydroxybutyrate and niacin are ligands for GPR109A that may initiate the inhibitory G-protein signal that decreases cAMP via adenyl cyclase, leading to reduced PKA activation and lower HSL activity. The AMPK system also normally suppresses activation of HSL. Adiponectin activates AMPK by increasing FFA oxidation and insulin sensitivity. FFA, free fatty acids; TG, triglycerides; LPL, lipoprotein lipase; DGAT, diacylglycerol acyltransferase; NEFA, non-esterified fatty acids; PPAR gamma, Peroxisome Proliferator-Activated Receptor-gamma; TRL, triglyceride-rich lipoproteins; beta-AR, beta adrenergic receptor. HSL, hormone-sensitive lipase; AMPK, AMP-activated protein kinase. (Reproduced from Toh S-A, Rader DJ. Dyslipidemia in insulin resistance: clinical challenges and adipocentric therapeutic frontiers. *Expert Rev Cardiovascular Ther*. 2008;6:1007–1022, with permission.)

leading to improvement of insulin sensitivity and dyslipidemia. It has been pointed out that the metabolic improvements seen with PPAR-γ agonists are similar to those observed with rimonabant, an inhibitor of the endocannabinoid receptor, suggesting cross talk between the endocannabinoid system and PPAR-γ (5) (see also Chapter 24).

Initiation of Insulin Resistance in Adipocytes. The initiation of insulin resistance in the adipocyte is an area of intense investigation (5,6). Excessive caloric intake leads to adipocyte hypertrophy and increases visceral adipose tissue. Adipose tissue is an endocrine organ that secretes many cytokines and adipokines. Proinflammatory cytokines include tumor necrosis factor (TNF)-α, interleukin (IL)-1, -4, and -6, monocyte chemotactic protein (MCP)-1, interferon (IFN)-γ, and nitric oxide synthase (NOS)-1 (5). These cytokines can promote inflammation, insulin resistance, and dyslipidemia. Increased secretion of the chemotactic molecule MCP-1 by adipocytes recruits monocytes/macrophages into adipose tissue. MCP-1 is also known as the C-C motif chemokine ligand (CCL)-2 that binds to the C-C chemokine receptor (CCR) (5). CCL-2 is highly expressed in obese subjects and its interaction with CCR appears to promote insulin resistance. Further, proinflammatory cytokines such as IFN-γ influence the macrophage to express a proinflammatory profile (macrophage M1) (5,6). Conversely, adipocytes that are smaller and not hypertrophied secrete increased amounts of adiponectin that helps prevent insulin resistance, inflammation, and dyslipidemia (5). Under this last scenario, macrophages are not proinflammatory (macrophage M2) (5,6) and secrete anti-inflammatory molecules such as IL-10 (5).

Metabolism of TG in Hepatocytes

In the liver FFA are normally activated (fatty acid CoA) and then oxidized or incorporated into TG or cholesteryl esters. When the increased flux of FFA to the liver from insulin-resistant adipocytes exceeds the ability of the oxidative or storage pathways to metabolize fatty acid CoA, intermediates of fatty acid metabolism such as DAG, PA, LPA, and ceramide (see also Chapter 4) accumulate and can activate a number of different serine kinases that negatively regulate insulin action (6).

Apolipoprotein B-100 (apoB-100) is constitutively made in the liver. Only some of the apoB-100 molecules that are made survive and become incorporated into very low density lipoprotein (VLDL); the remainder are degraded by proteolytic enzymes. As apoB-100 interacts with cholesteryl esters, it likely assumes a new conformation leading to decreased degradation of apoB and thus to its increased production. TG is then incorporated into this complex through the action of microsomal triglyceride transfer protein (MTP), producing VLDL. Insulin normally decreases cholesterol synthesis and thereby inhibits apoB secretion, effects that are opposite to those seen in most patients with diabetes and insulin resistance who manifest increased hepatic synthesis of cholesterol, apoB-100, TG, and VLDL. Enhanced secretion of VLDL leads to increased production of small, dense LDL particles and low HDL-C (7) (see Fig. 1.7, page 17) (see also the following text).

Implications of Insulin Resistance for Glucose Production in Liver. The main function of insulin in the liver is the control of endogenous glucose production (EGP), which is the sum of gluconeogenesis (GNG) (the formation of glucose from nonglucose precursors), and glycogenolysis (GL) (the formation of glucose from the hydrolysis of glycogen) (8). In normals, insulin sharply reduces GL, modestly decreases GNG, and thereby lowers EGP. FFA produce insulin resistance in liver by inhibiting the acute insulin suppression of GL, resulting in increased EGP that contributes to hyperglycemia.

Metabolism of TG in Myocytes

The myocytes in skeletal muscle are responsible for most of the insulin-stimulated glucose uptake. In the face of increased flux of FFAs to the myocytes, FFAs are activated and incorporated into DAG, which then forms long-chain acyl-CoA (LCCoA). LCCoA activates protein kinase C (PKC) that interrupts insulin signaling by increasing serine phosphorylation and decreasing tyrosine phosphorylation of the insulin receptor substrate-1 (IRS-1) (4) (Fig. 10.2). Serine phosphorylation can lead to the degradation of IRS-1. This sequence of events decreases the binding and activation of phosphatidylinositol (PI)-3-kinase to IRS-1, leading to reduced transport of GLUT4 to the cell surface and decreased glucose uptake (4). As a result, the cells become resistant to insulin-stimulated glucose transport (Fig. 10.2). Thus, it is not the accumulation of TG per se that causes insulin resistance but rather the effect of other molecules such as DAG that initiate a cascade of effects that lead to insulin resistance.

An increase of DAG levels in the myocytes can also promote the activation of the nuclear factor (NF)-κB pathway (4) (Fig. 10.2). NF-κB is involved in the pathogenesis of atherosclerosis (4) and may contribute to the increase of CVD in diabetic individuals. FFAs can also cause insulin resistance by increasing oxidative stress (4). Reactive oxygen species can activate PKC and the NF-κB pathway (Fig. 10.2).

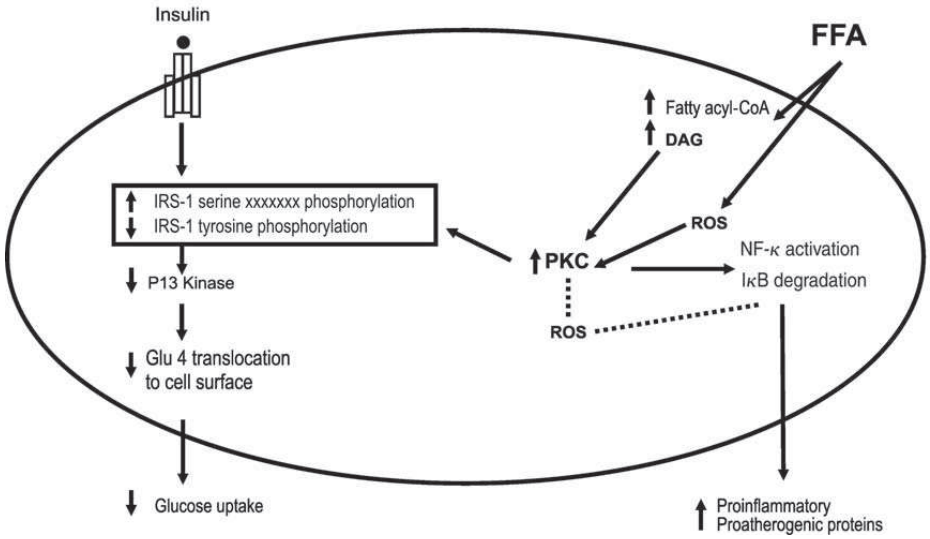

FIGURE 10.2 Potential mechanisms of free fatty acids (FFA) on insulin resistance in human muscle. An increase in plasma FFA is followed by an increased uptake of FFAs. An intramyocellular accumulation of fatty acyl-CoA and DAG activates several isoforms of PKC. Activation of PKC appears to interrupt insulin signaling by serine phosphorylation of IRS-1, resulting in decreased tyrosine phosphorylation of IRS-1. Activation of PKC also leads to production of proatherogenic and inflammatory proteins by the activation of the IκB-α/NF-κB pathway. The broken lines indicate that activation of PKC by ROS and activation of the IκB-α/NF-κB pathway by ROS has not been proven in human muscle but has been shown in bovine aortic smooth muscle and endothelial cells. PI, phosphatidyl inositol. DAG, diacylglycerol; PKC, phosphokinase C; IRS-1, insulin receptor substrate-1; ROS, reactive oxygen species. (Reproduced from Boden G, Laakso M. Lipids and glucose in type 2 diabetes. *Diabetes Care*. 2004;27: 2253–2259, with permission.)

Metabolism of TG in Pancreatic Cells

The effect of FFA in the pancreas has provided some insight into why some obese, insulin-resistant patients develop diabetes and others do not, despite the fact that FFA are promoting insulin resistance in liver and muscle in both groups. FFA are known potent insulin secretagogues, and in obese patients with normal pancreatic B cells, FFA compensate for the insulin resistance that they produce (4). Conversely, in patients genetically predisposed to develop diabetes (such as first-degree relatives of type 2 diabetic individuals), FFA are *unable* to compensate sufficiently by producing enough insulin to counterbalance the insulin resistance that they produce (4). This genetic predisposition to pancreatic B cell failure involves a defect in the stimulation of the secretion of insulin by both FFA and glucose.

Metabolism of TG in Intestinal Cells

It is well known that excessive postprandial lipemia is quite prevalent in obese, insulin-resistant patients and type 2 diabetes. Postprandial dyslipidemia is characterized by hypertriglyceridemia due to the presence of intestinally derived chylomicrons and chylomicron remnants and hepatic-derived VLDL and VLDL remnants (9) (see also Chapter 7). When they are small enough, both chylomicron and VLDL remnants can enter the vascular wall and promote atherosclerosis by virtue of their cholesterol moiety. Increased small, dense LDL particles and a low HDL are also often part of the postprandial dyslipidemia. This dyslipidemia is due in no small part to the anabolic and catabolic abnormalities of lipid metabolism that accompany insulin resistance, namely increased hepatic production of apoB-100-containing VLDL and decreased activity of LPL and increased expression of apolipoprotein C-III (apoC-III), an inhibitor of LPL (5) (see also the preceding text).

In insulin resistance, however, there is also overproduction of intestinal apoB-48-containing chylomicrons (10) (see also Chapter 7). Intestinal lipoprotein production can be stimulated by elevation of FFA that occurs in insulin resistance. Enhanced intestinal fat absorption also occurs through upregulation of CD36/fatty acid translocase (FAT). Both of these states promote the formation of fatty acid CoA, DAG, and TG. TG decrease the proteolysis of apoB-48, leading to enhanced biosynthesis of chylomicrons by MTP and increased secretion (9). Finally, of the panoply of intestinally derived peptides, two, glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), appear to be important regulators of intestinal lipid absorption and lipoprotein production (10). Further details concerning the processing of dietary lipids can be found in two reviews (10,11).

Gene Variants, Insulin Resistance, and Dyslipidemia

Both genetic and environmental factors influence the development of insulin resistance and dyslipidemia. As outlined above (see also Figs. 1.7, 10.1, and 10.2), there are a panoply of proteins, whose expression and function might be altered by gene variants (i.e., polymorphisms or mutations). A detailed discussion of all these variants is beyond the scope of this chapter, and the reader is referred to a more comprehensive review (12). Rather some selected variants will be discussed as examples of gene variants that primarily affect insulin action or dyslipidemia (13).

Gene Variants Primarily Regulating Insulin Action

PC-1. PC-1 is a class II transmembrane glycoprotein that inhibits insulin receptor (IR) tyrosine kinase activity (11). The K121Q polymorphism in exon 4 of the PC-1 gene is associated with hyperglycemia and insulin resistance in most but not all studies. Little information is available on the effect of this polymorphism on dyslipidemia (13).

IRS-1. IRS-1 (see above) is a major substrate for the IR (Fig. 10.2). It regulates insulin signaling in adipose tissue (Fig. 10.1), skeletal muscle (Fig. 10.2), and the vasculature (13). A common variant in the IRS-1 gene is the Gly972Arg substitution that causes a decrease in the normal binding and activation of PI-3-kinase to IRS-1 (Fig. 10.2). Carriers of this variant have insulin resistance and dyslipidemia. Their blood pressure is also elevated. Obesity accentuates these abnormalities, a convergence that suggests the presence of the metabolic syndrome (13).

PPAR-γ2. PPAR-γ2 is expressed in adipose tissue and regulates glucose homeostasis and body weight. Rare loss-of-function mutations result in lipodystrophy while rare gain-of-function mutations increase body fat mass (13). A more common polymorphism in the PPAR-γ gene, a Pro12Ala substitution, is significantly associated with lower body mass index, greater insulin sensitivity, higher HDL-C, and lower levels of TG (13). In contrast, the Pro12Pro genotype increases susceptibility to type 2 diabetes. Of interest, the Pro12Pro genotype interacts with the K121Q genotype of PC-1 (see also the preceding), producing higher fasting blood glucose levels and greater insulin resistance than those who were carriers of Pro12Pro and K121K (13).

These genetic studies further emphasize the pharmacologic importance of PPAR-γ and PPAR-α in the dyslipidemia associated with diabetes (see also the following text). Fibric acid derivatives are agonists of PPAR-α in the liver and decrease TG by upregulating LPL and downregulating apoC-III, an inhibitor of LPL. HDL-C levels also increase (see also the following text). The TZDs are agonists of PPAR-γ and improve insulin sensitivity and provide a modest improvement in the dyslipidemia of diabetes (see also the following text).

Gene Variants Primarily Regulating Dyslipidemia

Hepatic Lipase. Hepatic lipase (HL) plays a paramount role in the hydrolysis of TG and phospholipid (PL) in both LDL and HDL, producing small dense LDL and HDL in the syndromes of insulin resistance and VLDL overproduction (Fig. 1.7) (see also Chapter 8). Genetic variants in the promoter region of the HL gene, such as the C-514T polymorphism, are strongly associated with the dyslipidemic triad (see also Chapter 8).

Other Gene Variants Regulating Lipoprotein Levels and LDL Particle Size. In addition to the HL gene, other genes involved in the endogenous lipoprotein pathway and the generation of small, dense LDL (Fig. 1.7), such as those for LPL, CETP, and apolipoprotein E (apoE), may influence the levels of TG, HDL-C, and small, dense LDL.

Fatty Acid Binding Protein Type 2. The intestinal fatty acid binding protein (FABP)-2 gene is a member of a family of more than 20 FABP genes (13). The FABP-2 gene is only expressed in the intestinal epithelial cells, where it promotes the transport of hydrophobic FFA from the plasma membrane to the

endoplasmic reticulum and the subsequent esterification of FFA to TG. A common polymorphism in the FABP-2 gene, Ala54Thr, may promote insulin resistance since increased dietary fat absorption leads to higher plasma FFA and TG (13) that may adversely affect insulin action in the hepatocytes and skeletal muscle cells (see also the preceding text). While the Ala54Thr polymorphism appears to contribute to increased postprandial dyslipidemia (see also the preceding text) it does not increase the risk of type 2 diabetes (13).

Pathophysiology of Diabetic Dyslipidemia in Relation to the Prediabetic State

Both type 2 diabetes and CVD are hypothesized to spring from a "common soil" of metabolic antecedents, including impaired glucose tolerance, hypertension, dyslipidemia, and abdominal obesity (14). The clustering of these CVD risk factors is thought to result from an underlying insulin-resistance syndrome, also known as the metabolic syndrome or Syndrome X, which precedes the onset of type 2 diabetes. Reaven (15) first summarized the insulin-resistance syndrome as resistance to insulin-stimulated glucose uptake, hyperinsulinemia, impaired glucose tolerance, hyperglycemia, hypertension, elevated TG, and decreased HDL-C. The presence of dyslipidemia related to insulin resistance prior to the onset of type 2 diabetes may explain why >50% of patients with newly diagnosed type 2 diabetes already have evidence of coronary artery disease at the time of diagnosis. In the San Antonio Heart Study, Haffner et al. showed that compared to individuals who remained nondiabetic, individuals who eventually developed diabetes had higher TG and lower HDL-C several years before diagnosis (14).

Compared to individuals without diabetes, those with diabetes typically have higher TG and lower HDL-C. In studies of both diabetic and nondiabetic individuals, TG are positively correlated with direct measures of insulin resistance (16–18) as well as serum insulin levels (19,20). Individuals with type 2 diabetes have three characteristic abnormalities in their lipid profiles—(i) hypertriglyceridemia, (ii) small, dense LDL particles, and (iii) low HDL-C. In the Strong Heart Study, diabetic women had lower HDL-C levels compared to women without diabetes, and both men and women with diabetes had smaller LDL particle size than their nondiabetic counterparts (18). Type 2 diabetes is also associated with a higher prevalence of small, dense LDL particles (7,21–23).

Hypertriglyceridemia and Small, Dense LDL Particles

Insulin resistance causes several abnormalities in lipoprotein metabolism that lead to elevated TG, including impaired degradation of TG in VLDL by LPL, impaired FFA trapping, and increased FFA flux to the liver due to decreased inhibition of HSL by insulin (Fig. 10.1), leading to increased hepatic synthesis of VLDL (Fig. 1.7).

LPL, the enzyme responsible for degradation of TG, is activated by insulin; however, in the setting of insulin resistance and diabetes, LPL is not activated to the same degree. In addition, apoC-III, an inhibitor of LPL, is increased on TG-rich VLDL in insulin resistance, further slowing the degradation of TG (5,22). As a result, VLDL is cleared more slowly, producing partially lipolyzed VLDL remnants that can be converted to intermediate-density lipoproteins (IDLs). IDLs, when small enough, penetrate through the endothelium into the vascular wall, where they are taken up by macrophages and promote atherosclerosis.

Effect of Cholesterol Ester Transfer Protein and Hepatic Lipase in the Production of Diabetic Dyslipidemia. Cholesterol ester transferase protein (CETP), which is increased in VLDL overproduction, transfers TG from TG-enriched lipoproteins for cholesteryl ester on both LDL and HDL (Fig. 1.7). This transfer of TG for cholesteryl esters has several adverse consequences. The TG-rich remnants become cholesterol enriched, making them potentially more atherogenic. The TG in the cholesterol-poor LDL are a substrate for HL and the resultant LDL particle is smaller and denser (7,22,23) (Fig. 1.7). HL also acts on the TG in HDL, making it a smaller particle that is removed more avidly by the kidney (see also Chapter 8). Endothelial lipase also hydrolyzes TG in HDL, promoting a smaller HDL particle (5).

Clinical Significance of Small, Dense LDL Particles. Small, dense LDL particles behave differently than normal-sized LDL particles (7,22,23) (see also Chapter 8). ApoB-100, the ligand for the LDL receptor, has a different orientation on the surface of the small, dense LDL particle leading to decreased affinity for the LDL receptor and prolonged residence time in plasma. Small, dense LDLs have a greater propensity for transport into the subendothelial space, enhance vascular permeability, and are associated with increased binding to arterial wall proteoglycans. Small, dense LDLs also are more easily oxidized in the arterial wall (7,22,23). As well, small, dense LDLs appear to promote the formation of PAI-1 and thromboxane that are thrombogenic. The hypothesis has been put forward that these biochemical factors in aggregate might be atherogenic. However, recent data indicate that the most important factor to accelerate CVD is the total *number* of LDL particles, regardless of whether they are small and dense (see also Chapters 15 and 16). Clearly, however, in diabetes and in many patients with CVD, there is an increased production of LDL particles, most of which are small and dense. The measurement of LDL-C significantly underestimates the total number of LDL particles in many diabetic individuals (7) (see also Chapters 2 and 16).

Clinical Significance of Low HDL-C. The small HDL particles that are produced as a result of insulin resistance and VLDL overproduction (Fig. 1.7) (see also the preceding text) are more avidly cleared by the kidney leading to a lower number of HDL particles to participate in reverse cholesterol transport (see also Chapter 9). The particles themselves may have an abnormal composition that might result in less efficient reverse cholesterol transport.

CLINICAL TRIALS OF HMG-CoA REDUCTASE INHIBITORS (STATINS) THAT INCLUDE PATIENTS WITH DIABETES MELLITUS

A primary prevention trial is one in which the subjects are free of clinical CVD at entry, while a secondary prevention trial is one in which the subjects have manifest CVD at entry. Some clinical trials contain both a primary and a secondary component. Of the eight clinical trials listed in Table 10.1, two are primary, four are secondary, and two are both primary and secondary. Most of the clinical outcome data investigating the benefit of LDL-C

lowering in diabetic individuals derive from subgroup, post hoc analyses of these statin trials. For example, only two clinical trials, the Collaborative Atorvastatin Diabetes Study (CARDS) and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) studied *exclusively* patients with diabetes.

STUDIES OF LIPID-LOWERING THERAPY IN TYPE 2 DIABETES

The lipoprotein abnormalities outlined above are predictive of CVD in epidemiologic studies, although most of the studies did not specifically examine the role of dyslipidemia in predicting CVD in diabetic individuals. Both primary and secondary clinical trials, however, have confirmed that treating dyslipidemia in diabetic individuals is beneficial in preventing CVD. Most of the data are derived from studies of LDL-C lowering. In this section, the results of clinical trials of lipid-lowering therapy for CVD prevention in individuals with diabetes are summarized.

Primary Prevention Trials of Statins in Patients with Diabetes

ASCOT

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was one of the first primary CVD prevention trials of lipid-lowering therapy to include a substantial number of diabetic individuals (24,25). In the lipid-lowering arm of the multinational, ASCOT study (ASCOT-LLA), 10,305 hypertensive patients with no history of coronary disease, but at least three CVD risk factors were randomly assigned to receive 10-mg atorvastatin or placebo, and followed for a median of 3.3 years. Of the total participants, 2,532 had diabetes, and the mean baseline LDL-C was 125 mg/dL. The primary endpoint was total CVD events and procedures (CVD mortality, nonfatal MI [symptomatic plus silent], unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, retinal vascular thrombosis, revascularization procedures, transient ischemic attacks, and reversible ischemic neurologic deficits). Atorvastatin therapy lowered LDL by 34% in those with diabetes and reduced their risk of the primary CVD endpoint by 23% ($p = 0.036$). There was a trend toward a 16% reduction in fatal and nonfatal MI that was comparable to the nondiabetic participants ($p = 0.14$); however, because the study was stopped prematurely, lower than anticipated coronary events occurred within the diabetic subset, resulting in insufficient power to compare the efficacy of atorvastatin with placebo in any of the individual endpoints. In addition to providing the earliest substantial evidence on the benefits of statin therapy in the primary prevention of CVD in diabetic individuals, ASCOT reinforced guidelines that were advocating at that time a more aggressive approach to LDL-lowering therapy in diabetes without CVD (i.e., a goal of LDL-C < 100 mg/dL).

CARDS

A number of clinicians found the ASCOT trial unconvincing in regards to the safety and efficacy of pursuing more aggressive LDL targets in diabetic individuals without CVD. The Collaborative Atorvastatin Diabetes Study (CARDS) was therefore designed to define better the role of statins in the primary prevention of CVD in type 2 diabetes (26). In CARDS, 2,383 individuals (mean age 62 years, LDL-C < 160 mg/dL, mean LDL-C 118 mg/dL) with diabetes but no history of CVD, and at least one risk factor, including hypertension, smoking, retinopathy, and micro- or macroalbuminuria, were randomized to atorvastatin 10 mg/day versus placebo. The primary endpoint was the time to first occurrence of the

TABLE 10.1

PRIMARY AND SECONDARY PREVENTION TRIALS OF LIPID-LOWERING THERAPY WITH HMG-CoA REDUCTASE INHIBITORS (STATINS) ON CVD IN DIABETES MELLITUS

Study (reference)	Number	Treatment groups	Relative risk reduction in CVD[a]
Primary prevention			
HPS (36)	2,912	Simvastatin 40 mg vs. Placebo	27% ($p < 0.00001$)
CARDS (26)	2,383	Atorvastatin 10 mg vs. Placebo	37% ($p < 0.001$)
ASPEN (37)	1,905	Atorvastatin 10 mg vs. Placebo	3% (NS)
ASCOT (24,25)	2,532	Atorvastatin 10 mg vs. Placebo	23% ($p = 0.036$)
Secondary prevention			
HPS (36)	3,051	Simvastatin 40 mg vs. Placebo	26% ($p < 0.00001$)
4S (28)	483	Simvastatin 20 to 40 mg vs. Placebo	42% ($p < 0.001$)
ASPEN (37)	505	Atorvastatin 10 mg vs. Placebo	18% (NS)
CARE (27)	586	Pravastatin 40 mg vs. Placebo	25% ($p = 0.05$)
LIPID (29)	1,077	Pravastatin 40 mg vs. Placebo	21% ($p < 0.008$)
TNT (35)	1,500	Atorvastatin 10 mg vs. 80 mg	25% ($p = 0.026$)

[a]The relative risk reduction in CVD refers to the primary endpoint of the study.
HPS, Heart Protection Study; CARDS, Collaborative Atorvastatin Diabetes Study; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin-Dependent Diabetes Mellitus; NS, Non-significant; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; TNT, Treating to New Targets.

following: acute coronary events, coronary revascularization, or stroke. The secondary endpoint was the rate of death. The trial was terminated 2 years earlier than expected (at 3.9 years) after achieving the early stopping rule for efficacy. Atorvastatin therapy lowered LDL-C by 40%, and reduced the composite primary endpoint by 37% ($p < 0.001$), thus providing compelling evidence for the benefits of statins in primary CVD reduction in diabetic patients. This effect was independent of pretreatment LDL-C.

Secondary Prevention Trials with Statins That Include Patients with Diabetes Mellitus

4S

The Scandinavian Simvastatin Survival Study (4S) was one of the earliest of such trials. 4S was a multinational randomized controlled trial comparing 20 to 40 mg of simvastatin therapy with placebo and included 483 diabetic subjects among the 4,398 participants (mean age 59 years, 83% men), all of whom had coronary disease and marked hypercholesterolemia (mean LDL-C 186 mg/dL) (28). The patients were followed for 5.4 years. All-cause mortality was the primary endpoint. Major coronary events (coronary death, nonfatal MI, and resuscitated ischemic cardiac arrest) constituted the secondary endpoint. In the 483 diabetic subjects, simvastatin lowered LDL-C by 36%, and reduced the risk of major coronary events by 42% ($p = 0.001$). The nonsignificant trend toward lower all-cause mortality in the diabetic subjects (relative risk reduction of 21%; $p = 0.34$) was likely due to the relatively small sample size.

CARE

The Cholesterol and Recurrent Events (CARE) trial was a multinational study investigating statin therapy in 4,159 patients with preexisting coronary disease who had average (136 mg/dL) LDL-C levels (27). A post hoc analysis evaluated the efficacy of statin therapy in 586 diabetic participants. Participants were randomized to 40 mg of pravastatin or placebo and followed for a median of 5 years. The primary outcome was a composite of coronary events (coronary death, nonfatal MI, coronary artery bypass grafting [CABG], and percutaneous transluminal coronary angioplasty [PTCA]). Pravastatin therapy lowered LDL-C in diabetic individuals by 27%, and reduced the composite of coronary events by 25% ($p = 0.05$). A trend toward similar risk reductions in the pravastatin-treated group was seen for the individual CVD endpoints, albeit a nonsignificant one, secondary to small sample size. Importantly, CARE showed in patients with CHD and relatively lower, more representative, baseline LDL-C that substantial CVD benefits could still be achieved with statin therapy.

LIPID

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial in Australia and New Zealand showed that cholesterol-lowering treatment with pravastatin reduced mortality and CHD events by 24% ($p < 0.001$) in 9,014 patients aged 31 to 75 years with known CHD and a total cholesterol (TC) of 155 to 271 mg/dL. Subsequently, the effects of pravastatin therapy, 40 mg/day over 6 years, on the risk of coronary death or nonfatal MI and other CVD outcomes were examined in 1,077 LIPID patients with diabetes and 940 patients with impaired fasting glucose (IFG) (29). Pravastatin therapy reduced the risk of a major CHD event in the diabetic group by 19% ($p = 0.11$), a reduction that was not significantly different from the reductions in other groups. Of note, pravastatin reduced the risk of any CVD event by 21% ($p = 0.008$) in patients with diabetes and by 26% ($p = 0.003$) in the IFG group. Finally, pravastatin reduced the risk of stroke by 39% ($p = 0.02$) in the diabetic group and by 42% ($p = 0.09$) in the IFG group. Pravastatin did not reduce the incidence of diabetes (29). This is in contrast to the results from the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention trial in hypercholesterolemic subjects treated with pravastatin 40 mg/day, where statin treatment reduced the chance of developing diabetes by 30% (30). Over 6 years, pravastatin therapy prevented one major CHD event (CHD death or nonfatal MI) in 23 patients with IFG and 18 patients with diabetes.

In another post hoc substudy from LIPID, the effect of pravastatin 40 mg/day was examined in 2,073 patients aged 31 to 75 years with baseline LDL-C $\leq$ 140 mg/dL and HDL-C $\leq$ 40 mg/dL and TG $\leq$ 300 mg/dL (31). Pravastatin treatment reduced major coronary events by 27%, CHD mortality by 27%, all-cause mortality by 21%, and stroke by 51%. The number needed to treat to prevent a major coronary event over 6 years was 22 (31). Treatment with pravastatin in patients with known CVD and both low LDL-C and low HDL-C significantly reduced major coronary events, stroke, and all-cause mortality, indicating that statins are the starting drugs of choice in such patients.

When CARE and LIPID were combined, it was observed that overall risk reduction was not significant in participants who had low baseline LDL-C < 125 mg/dL (32). When those with LDL-C < 125 mg/dL were compared with those whose LDL-C was $\geq$125 mg/dL, they were more likely to be diabetic (15% vs. 9%), hypertensive (46% vs. 41%), and male (89% vs. 83%); they had higher TG (169 mg/dL vs. 154 mg/dL), lower HDL-C (36.5 mg/dL vs. 38 mg/dL), but similar body mass index (27 kg/m^2). During a mean 5.8-year follow-up, HDL-C and TG were both significantly stronger predictors of recurrent coronary events in participants with LDL-C < 125 mg/dL than $\geq$ 125 mg/dL. Of particular note, in diabetic participants with low LDL-C, pravastatin decreased coronary events by 44% ($p = 0.004$), significantly different from the 21% reduction in nondiabetic participants with low LDL-C (p-value for interaction = 0.005) (32). Thus, these results support the recommendation that statins be used as first-line agents in diabetics with low HDL-C and high TG but low LDL-C.

After statin treatment in diabetics, fibrates or niacin can be added if necessary to reduce further TG, decrease the number of small, dense particles, and increase HDL-C (see also the following text).

In 2004, a randomized trial showed that intensive LDL-C reduction to a level of <70 mg/dL with high-dose statin therapy was shown to be more beneficial than pursuing more conventional LDL-C targets of <100 mg/dL in nondiabetic patients with acute coronary syndrome (33). Based on the findings of this trial, in 2006 the American Diabetes Association (ADA) (34) recommended that high-dose statin therapy be used as a therapeutic option in diabetic patients with CVD in order to achieve an LDL-C level of <70 mg/dL.

TNT

Treating to New Targets (TNT) trial was a multinational study designed to test whether a similarly intensive lipid-lowering strategy benefits patients with stable coronary disease (35). TNT was composed of 10,001 participants, 1,500 of whom were patients with diabetes, and LDL-C of <130 mg/dL. The participants were randomized to double-blind therapy with either atorvastatin 10 or 80 mg/day. Patients were followed for a median of 4.9 years. The primary endpoint was major CVD events, defined as death from coronary disease, nonfatal non-procedure-related MI, resuscitated cardiac arrest, or fatal or nonfatal stroke. In diabetic participants, atorvastatin 80 mg/day lowered LDL-C levels 22% more than when used 10 mg/day and reduced the risk of major CVD events by an additional 25% ($p = 0.026$) (35). There were no significant differences between treatment groups in the rates of treatment-related adverse events, including myalgias, and persistent elevations in liver function tests. TNT thus provided further evidence for the currently accepted LDL-C target of <70 mg/dL in diabetic patients with CVD and lent further support to the tenet that benefits of statin therapy are independent of baseline LDL-C.

Combined Primary and Secondary Prevention Trials with Statins That Include Patients with Diabetes Mellitus

HPS

The Heart Protection Study (HPS) is the largest CVD outcome trial to date to study the effects of lipid-lowering therapy in diabetic patients (36). The HPS included a subset of 5,963 diabetic individuals over 40 years of age, 2,912 of whom had no known CVD (Table 10.1). Patients were randomized to treatment with 40 mg of simvastatin or placebo and followed for 4.8 years. Simvastatin therapy lowered LDL-C by 30% and significantly reduced the risk of major primary and secondary CVD events by 25% and 17%, respectively (36). The relative risk reduction achieved by statin therapy was independent of pretreatment LDL-C (including those with baseline LDL-C < 116 mg/dL, preexisting CVD, type or duration of diabetes, or adequacy of glycemic control). Importantly, the HPS provided perhaps the first extensive clinical trial evidence supporting the recommendations of National Cholesterol Education Panel (NCEP) and ADA that the goal of treatment of diabetic patients was to achieve an LDL-C level of < 100 mg/dL. Before the publication of HPS, the recommendations were based on theoretical extrapolations from epidemiologic studies showing a positive graded risk relationship between LDL-C levels and CVD events and mortality in individuals with diabetes.

ASPEN

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) was a multinational trial investigating the CVD benefit of 10 mg of atorvastatin in a mixed primary and secondary CVD prevention cohort consisting entirely of individuals with type 2 diabetes (37). A total of 2,410 subjects (mean age 61 years, 66% men, 84% white) who had type 2 diabetes for at least 3 years were randomized to 10 mg of atorvastatin or placebo in a 4-year, double-blind, parallel-group study. The primary endpoint served as a composite of CVD death, nonfatal MI, nonfatal stroke, revascularization, CABG, resuscitated cardiac arrest, or worsening of unstable angina requiring hospitalization. Despite achieving a 30% LDL-C reduction with simvastatin, the ASPEN trial did not find a significant reduction in the primary endpoint in either the primary prevention (3%; p = NS) or secondary prevention cohort (15%, p = NS) (Table 10.1). Similarly, 10 mg of simvastatin resulted in a nonsignificant relative risk reduction in fatal and nonfatal MI of 19% ($p = 0.41$) and 36% ($p = 0.11$) for primary and secondary prevention cohorts, respectively. The authors noted that the trend in relative risk reduction was comparable to that of the other statin trials, and would have perhaps reached statistical significance had it not been for a low event rate. The authors attributed the comparably smaller risk reduction in endpoints for subjects without prior CVD to their otherwise underlying "low-risk" profile for subsequent CVD events.

As a result of the strongly concordant studies outlined above on the use of statins in diabetics, the ADA (38) has now extended their recommendation of optionally pursuing an aggressive LDL-C target in diabetic individuals without CVD, but with multiple risk factors.

Trials of Fibric Acid Derivatives That Include Patients with Diabetes

HHS

The Helsinki Heart Study (HHS) was a 5-year primary prevention trial in which 4,081 middle-aged, Finnish men with primary dyslipidemia (defined as non-HDL-cholesterol > 200 mg/dL) were randomized to gemfibrozil 600 mg twice daily or placebo (Table 10.2). The mean baseline lipid profile of these study patients was the following: HDL-C 47 mg/dL, LDL-C 189 mg/dL, and TG 175 mg/dL. Because patients with diabetes often have a normal or borderline-elevated LDL-C, lower HDL-C and high TG, only a small subgroup of 135 diabetics qualified for the study (Table 10.2). Nevertheless, treatment with gemfibrozil versus placebo resulted in a 60% reduction in the combined endpoint of nonfatal MI and cardiac death in the diabetic individuals, a treatment effect that failed to reach statistical significance due to a small sample size and too few events (39,40).

VA-HIT

The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) was a 5-year secondary prevention trial that enrolled 2,531 elderly men (mean age 65 years) with preexisting coronary disease but no serious coexisting conditions (Table 10.2). Lipid criteria for inclusion were the following: HDL-C ≤ 40 mg/dL (mean 31 mg/dL), LDL-C ≤ 140 mg/dL (mean 101 mg/dL), and TG ≤ 300 mg/dL (mean 166 mg/dL). Subjects were randomized to gemfibrozil 600 mg twice daily or placebo. The primary study outcome was nonfatal MI or coronary death (41). In the subgroup of 769 patients with diabetes, treatment with gemfibrozil resulted in a 24% reduction in the primary endpoint ($p = 0.05$), and a significant 32% relative risk reduction in the composite endpoint of stroke, coronary death, or nonfatal MI ($p = 0.004$). This latter result was driven largely by reductions in coronary death (41%; $p = 0.02$) and stroke (40%; $p = 0.046$). It is noteworthy that gemfibrozil-treated diabetic individuals experienced a much

TABLE 10.2

PRIMARY AND SECONDARY PREVENTION TRIALS OF LIPID-LOWERING THERAPY WITH FIBRATES ON CVD IN DIABETES MELLITUS

Study (reference)	Number	Treatment groups	Relative risk reduction in CVD[a]
Primary prevention			
HHS (39,40)	135	Gemfibrozil 600 mg b.i.d. vs. Placebo	60% (NS)
Secondary prevention			
VA-HIT (41)	759	Gemfibrozil 600 mg b.i.d. vs. Placebo	24% ($p = 0.05$)
FIELD (42)	9,795	Fenofibrate 200 mg vs. Placebo	11% ($p = 0.16$)

[a]The relative risk reduction in CVD refers to the primary endpoint of the study.
HHS, Helsinki Heart Study; VA-HIT, the Veterans Affairs High-density Lipoprotein Intervention Trial; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes.

greater reduction in the relative risk of coronary death and stroke as compared to their nondiabetic counterparts (41% vs. 3%, and 40% vs. 10%, respectively).

FIELD

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) is the largest clinical endpoint trial to date of fibrate therapy solely in diabetic patients (42). FIELD was a 5-year, multinational trial involving 9,795 well-controlled type 2 diabetic participants (mean HbA_{1c} 6.9%, 63% male, 93% white, mean age 62 years). Seventy-eight percent of the participants did not have prior CVD. The mean baseline lipid profile was the following: HDL-C 42 mg/dL, LDL-C 118 mg/dL, and TG 153 mg/dL. Treatment with fenofibrate 200 mg/day resulted in a nonsignificant 11% reduction in the relative risk of the primary endpoint (nonfatal MI and coronary death; $p = 0.16$) (42) (Table 10.2). When the individual endpoints comprising the primary outcome were examined, treatment with fenofibrate resulted in a significant 24% relative risk reduction in nonfatal MI ($p = 0.01$), offset by a 19%, albeit nonsignificant, increase in coronary death. There was, however, a statistically significant 11% relative risk reduction in the secondary endpoint of total CVD events ($p = 0.035$), largely driven by the aforementioned reduction in nonfatal MI, along with significant relative risk reductions in revascularization procedures. The groups did not differ in coronary death or other secondary outcomes (e.g., total mortality, CVD mortality, total stroke, nonhemorrhagic stroke). The absence of a treatment effect in many of the individual outcomes was thought to be explained by a significantly greater initiation of statin therapy in patients allocated to placebo than in those on fenofibrate (17% vs. 8%).

A post hoc subgroup analysis of study patients in FIELD without prior CVD showed that fenofibrate therapy resulted in significant relative reductions in risk for both the primary and secondary study outcomes (25% [$p = 0.014$] and 19% [$p = 0.0004$], respectively), whereas no significant treatment effect was seen in major outcome for fenofibrate-treated patients with prior CVD. In light of this post hoc analysis, fibrate therapy appears to be more effective as a potential primary prevention strategy to be used either in conjunction with statins or in lieu of statins in those who are intolerant. The role of fibrate therapy in diabetic individuals with prior CVD remains a source of debate in light of the conflicting results provided via the VA-HIT and FIELD trials. This is in contrast to statin therapy, for which an accumulation of solid clinical evidence strongly supports its use in diabetic patients for both primary and secondary prevention.

Trials of the Cholesterol Absorption Inhibitor Ezetimibe

Several studies have shown that the cholesterol absorption inhibitor, ezetimibe, lowers LDL-C 15% to 20%. Ezetimibe acts synergistically with statins to produce an additional lowering in LDL-C of 20% to 25% (see also Chapter 23). Ezetimibe can also be added to fenofibrate, producing a mean significant 36% reduction in LDL-C. Such a combination may be particularly useful in patients who are statin intolerant and whose LDL-C levels are too high after treatment with a fibrate. A similar clinical scenario is often seen in diabetic patients who may benefit from such combination therapy (43). However, it has not yet been demonstrated that adding ezetimibe to a statin (or a fibrate) reduces major CVD events further, compared with a statin alone.

ENHANCE

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial examined the effects of 80 mg of simvastatin and 10 mg of ezetimibe on progression of atherosclerosis compared to 80 mg of simvastatin and placebo in 729 north European patients with familial hypercholesterolemia (FH) (44). In this double-blind, randomized trial of 24 months, mean LDL-C was 193 mg/dL in the simvastatin alone group and 141 mg/dL in the combined therapy group at the end of the trial. However, there was no difference between the two groups in the primary endpoint, namely change in carotid artery intimal-medial thickness (IMT), a surrogate for coronary disease (44). These findings may be due to lipid-independent properties of statins that are not found with ezetimibe, or due to more aggressive, early, and long-term treatment of FH patients, providing a notably lower carotid IMT at baseline, obscuring any effect of ezetimibe on the progression of carotid atherosclerosis (44). Future studies evaluating the effect of ezetimibe, as monotherapy or in combination with a statin, will be needed in patients with diabetic dyslipidemia.

Trials of Niacin in Diabetes

Coronary Drug Project

Coronary Drug Project (CDP), conducted during 1966 to 1974, was a randomized, double-blind, placebo-controlled trial of five lipid-modifying agents in 8,341 men with previous MI (45). Among the five drug treatment regimens, only niacin significantly reduced the risk of subsequent CVD events during a mean follow-up of 6.2 years. After 6.2 years, those in the niacin acid group (N = 1,119) had a significant 29% reduction ($p < 0.005$) in MI, a 17% reduction ($p < 0.005$) in combined coronary death/MI and a 24% ($p < 0.01$) decrease in stroke compared to those in the placebo group (N = 2,787). After an additional 9 years of post-trial follow-up, those in the niacin group had a significant 16% ($p < 0.005$) decrease in total mortality and 14% ($p < 0.05$) decrease in coronary mortality, despite the fact that most had stopped their niacin at the end of the clinical trial. However, the use of niacin in patients with diabetes had been discouraged because high doses can worsen glycemic control, perhaps by increasing insulin resistance. In fact, compared to placebo, niacin was subsequently found to reduce the incidence of MI, combined coronary death or MI, and the 15-year total mortality similarly in patients at all levels of baseline fasting blood glucose (<95, 95 to 104, 105 to 125, and ≥126) (45). Thus, in the CDP the modest increase in plasma glucose with niacin did not translate into any disadvantage in regard to CVD events or total mortality.

In the CDP, niacin decreased TC and TG. However, HDL-C was only measured in 492 patients. A post hoc analysis from the CDP examined the effects of niacin on clinical outcomes in these patients with (N = 150) and without (N = 342) the metabolic syndrome (46). The metabolic syndrome was defined according to NCEP (see also Chapters 23 and 24). Niacin decreased the incidence of 6-year MI and 15-year total mortality to a similar extent in those with and without the metabolic syndrome, supporting its use in either group (46).

ADVENT

The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) was a short-term 16-week double-blind, placebo-controlled study of 148 diabetic patients randomized to placebo (N = 49), 1,000 mg/day (N = 45) or 1,500 mg/day (N = 52) extended-release niacin (47). Dose-dependent increases in HDL-C (+19% to +24%; $p < 0.05$) versus placebo for both niacin dosages and decreases in TG (−13% to −28%; $p < 0.05$) versus placebo for the 1,500-mg dose were observed. HbA_{1c} values were only significantly higher in the 1,500-mg dose versus placebo (7.2% and 7.5%, respectively; $p = 0.048$) (47). Thus, niacin can be used to treat dyslipidemia in patients with well-controlled diabetes.

Trials of Omega-3 Fatty Acids

Omega-3 polyunsaturated fatty acids, found primarily in marine vertebrates, are known for their significant effects on lowering elevated TG. The active components, eicosapentaenoic and docosahexaenoic acids, are combined in a high-concentration oral prescription formulation known as omega-3-acid ethyl esters (Zometa) (48) (see also Chapter 21). One large Italian trial, the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI)-Prevenzione trail, randomized 11,324 patients with MI within the last 3 months to omega-3 polyunsaturated fatty acids, vitamin E, both, or neither and followed individuals for 3.5 years (49). Individuals who received omega-3 polyunsaturated fatty acids had a significantly lower risk of the primary endpoint of death, nonfatal MI, and stroke (relative risk decrease 10%; 95% CI, 1–18) (49). Of the 11,324 individuals studied, 14.8% or 1,676 had diabetes. We are unaware of any subgroup analysis on the diabetic individuals from this study. Given that omega-3 fatty acids have been reported to elevate basal hepatic glucose output and impair insulin secretion (but not change glucose disposal rates) in individuals with type 2 diabetes (50), caution is in order when recommending omega-3 fatty acids in such patients.

Clinical Significance of Differential Effects of TZDs on Atherogenic Dyslipidemia in Type 2 Diabetes

The TZDs are PPAR-γ agonists that lower the levels of fasting glucose and glycated hemoglobin (HbA_{1c}) significantly and to the same degree by improving insulin sensitivity. However, pioglitazone appears to produce a greater effect on diabetic dyslipidemia than rosiglitazone, affecting an additional beneficial effect on TG, HDL-C, and the number of small, dense LDL particles (51). This effect may be related to the greater PPAR-α effect of pioglitazone. Differential data have also been reported for these two TZDs on long-term CVD. Rosiglitazone may be associated with an increased risk of CVD while pioglitazone may have beneficial effects on CVD (51). It has been postulated that these apparent differential effects of these two TZDs on CVD morbidity and mortality may be related to their discrepant effects on diabetic dyslipidemia (51). Future prospective head-to-head trials of these two agents will be required to unequivocally answer the differential effects of these two agents on dyslipidemia and CVD in diabetic patients. In the meantime, pioglitazone appears to be the preferred agent, especially in regard to its effects on diabetic dyslipidemia.

PRACTICAL CONSIDERATIONS

Treatment of Diabetic Dyslipidemia

The primary goal in treating diabetic dyslipidemia is to prevent development of CVD complications. As summarized above, both statins and fibric acid derivatives have been shown to prevent primary and secondary CVD events in individuals with diabetes, and it is likely but unsubstantiated in prospective randomized trials that niacin will do the same (45,46). Because LDL-C lowering with statin therapy has been shown to reduce CVD events, regardless of initial LDL-C, current treatment guidelines are focused primarily on treating LDL-C first. However, because combined hyperlipidemia, including elevated LDL-C, low HDL-C, and elevated TG constitute a very common dyslipidemia in diabetes, simultaneous treatment of multiple lipid abnormalities is often necessary. We will review guidelines for treatment in this section. The ADA has also issued very recent guidelines in this regard (34,38).

Importance of Lifestyle Modification

It is of critical importance to institute treatment with diet, exercise, and weight reduction first, or at the same time by instituting drug treatment (34,38,52) (see also Chapters 19 through 23). Review of the diet with a trained nutritionist is optimal with a goal of reducing total fat, saturated fat, and cholesterol, and eliminating trans fats (see also Chapters 19 and 20). However, concentrated simple sugars must also be reduced because of the hyperglycemia and insulin resistance in diabetic patients. Some of the calories from simple sugars can be replaced with complex carbohydrate. However, the total fat reduction may be modified by replacing saturated fats with monounsaturated fats found in canola oil and olive oil. This approach may make the diet more palatable and likely to facilitate compliance.

Fructose. A special comment will be made about dietary fructose. It is not generally appreciated that a modest amount of fructose (e.g., 16–20 g/day) can be consumed from fruits but that the typical daily consumption of fructose per day in the United States often amounts to 85 to 100 g of fructose (53). The source of this fructose is from the high intake of sucrose and high fructose corn syrup, a common sweetener used by the food industry. Fructose is readily absorbed and rapidly metabolized by the liver. The exposure of the liver to a high fructose content leads to rapid synthesis of TG, as fructose provides both the glycerol and acyl portions of TG (53). This leads to hepatic accumulation of TG, which reduce insulin sensitivity and drive VLDL production that can result in the dyslipidemic triad (see also the preceding text). Thus, it is critical to decrease markedly the consumption of sucrose and high fructose corn syrup products in the diet of patients with obesity and/or diabetes.

Treatment Targets

The LDL-C goal is <100 mg/dL for patients without overt CVD and <70 mg/dL for patients with overt CVD. If these targets are not reached on the maximal tolerated therapy, a 40% LDL-C reduction is an alternative target as most of the clinical trials of LDL-C lowering within this percentage range produced significant CVD risk reduction (38). As discussed above, lifestyle modification is an important component of therapy, but most patients will also require pharmacologic therapy (see also Chapter 23).

Pharmacologic Treatment of Diabetic Dyslipidemia

The statins are the fist line of treatment in diabetic individuals. If the LDL-C targets cannot be met with statin use, a second drug may need to be added. LDL-C can be lowered by about 15% to 20% with the addition of a cholesterol absorption inhibitor, ezetimibe, or a bile acid sequestrant such as cholestyramine or colesevelam. If the diabetic patient who requires more LDL-C lowering also has borderline-elevated (150 to 199 mg/dL) or elevated (200 to 399 mg/dL) TG, niacin may be a useful second drug to affect all components of the dyslipidemic triad. If the LDL-C targets have been met but the TG are still too high and the HDL-C too low, either niacin or a fibric acid derivative can be added as the second agent. Fibrates also raise HDL-C modestly in addition to lowering TG about 50%. Data from randomized controlled trials show that fibrates can reduce CVD risk in diabetic patients.

If the TG are markedly elevated (>400 mg/dL), a fibrate might be chosen over niacin. If the patient is unable to tolerate a fibrate, treatment with omega-3-acid ethyl esters, or "fish oils," can be added to lower TG about 50% on average. Both niacin and fish oils need to be used circumspectly in diabetic patients (see also the preceding text). Colesevelam reduces fasting blood sugar and HbA1c in patients already treated for their diabetes (54), and appears to decrease the number of small, dense LDL particles in diabetes despite increasing TG modestly (55). A detailed discussion about the mechanisms of action and side effects of these six major classes of lipid-lowering agents may be found in Chapter 23.

An algorithm for priorities in managing diabetic dyslipidemia is summarized in Fig. 10.3 (34,38,52). For patients without marked hypertriglyceridemia (fasting TG < 400 mg/dL), LDL-C lowering with a statin is addressed first, aiming for the targets

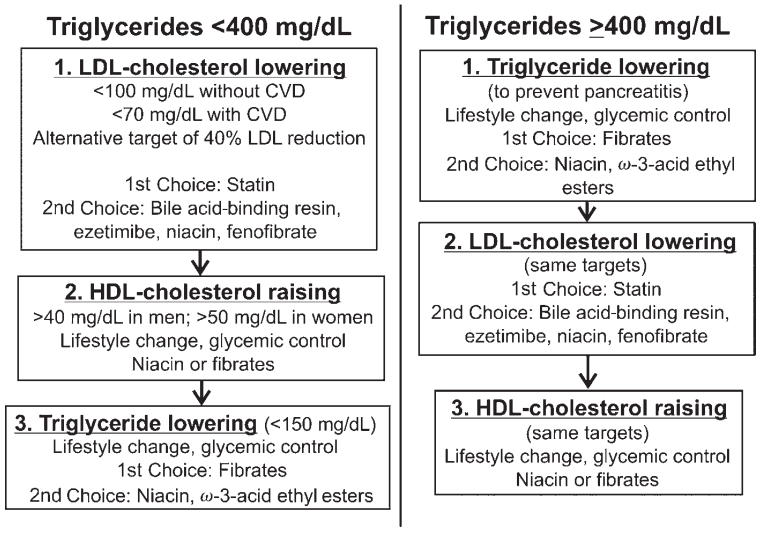

FIGURE 10.3 Pharmacologic approach to treat diabetics who have marked hypertriglyceridemia as their primary lipid abnormality.

suggested above, depending on whether the patient has CVD. For patients who are intolerant of statins or have contraindications to their use, second-line agents for decreasing LDL-C include the bile acid-binding resins, ezetimibe, niacin, or fibrates (34,38).

The next target of therapy is to raise HDL-C. Poor glycemic control is associated with greater insulin resistance and contributes to low HDL-C; therefore, glycemic control should be achieved, targeting a $HbA_{1c} < 7\%$, which may help to raise HDL-C (34). In addition, weight loss and increased physical activity will also help to raise HDL-C. If HDL-C remains low after intensifying glucose control and implementing lifestyle change, fibrates or niacin can be used to help raise levels further.

The third priority in treating diabetic dyslipidemia is lowering TG. As with low HDL-C, hypertriglyceridemia can be exacerbated by poor glycemic control, obesity, and physical inactivity; therefore, these therapeutic approaches should be implemented first. If the TG remain elevated, fibrates are the first-line therapy with omega-3-acid ethyl esters and niacin being second-line therapies.

A separate pharmacologic approach is used to treat diabetic individuals who have marked hypertriglyceridemia as their primary lipid abnormality (Fig. 10.3). Patients with TG $\geq$ 400 mg/dL may be at increased risk of pancreatitis and therefore need their TG lowered as a first priority. Also, when TG are elevated in this range, LDL-C cannot be calculated using the Friedewald formula (see also Chapter 2). Lowering TG will also allow LDL-C to be estimated without direct measurement. In this clinical scenario, markedly elevated TG are lowered first, using fibrates as the first-line therapy and omega-3-acid ethyl esters as second-line therapy. High doses of omega-3-acid ethyl esters are required (4 g/day). Once the marked TG are lowered, then LDL-C and HDL-C are treated to their targets using the same pharmacologic approach outlined above (Fig. 10.3).

Caveats Regarding Combination Lipid-lowering Therapies

Because most diabetic patients have a combined hyperlipidemia, most often the dyslipidemic triad, namely increased numbers of small, dense LDL particles, low HDL-C, and higher TG, it is often necessary for patients to be treated with combination lipid-lowering therapy, although there are no randomized controlled clinical trial data using combined therapies. When combination therapy is used, it should be done with caution and patients should be warned about potential side effects. When fibrates are combined with statins, the risk of myositis or rhabdomyolysis is increased, particularly in patients with renal insufficiency; however, the risk appears to be lower when statins are combined with fenofibrate compared to gemfibrozil (38). When niacin is combined with statins, there is an increased risk of elevated hepatic transaminases and possibly myositis that need to be monitored. Very high doses of niacin can cause worsening of glycemic control; however, most recent studies show that at modest doses of 750 to 2,000 mg/day, glycemic control does not deteriorate significantly and is usually amenable to adjustments in glucose-lowering therapies (38,47).

SUMMARY

Atherosclerosis remains the leading cause of death in individuals with diabetes and it is therefore important to be aggressive and treat all CVD risk factors, especially dyslipidemia. The pathophysiology of diabetic dyslipidemia is well-understood, and the adverse effects of elevated FFA on insulin resistance in a number of tissues, including adipose tissue, liver, skeletal muscle, small intestine, and pancreas, cause multiple biochemical and cellular abnormalities. Trials of lipid-lowering therapy show that statins are extremely effective in the primary and secondary prevention of CVD in diabetes, at both low and high baseline LDL-C levels. Data showing that lowering TG and raising HDL-C for the prevention of CVD in diabetes are incomplete and this remains an important area of investigation since the dyslipidemic triad is the most common lipid pattern in individuals with diabetes. These multiple lipid alterations often require combined lipid-altering drugs. When TG are elevated over 400 mg/dL, it is important to lower them aggressively to prevent pancreatitis. While much focus is given to pharmacologic treatments, measures to change bad dietary habits, lower body weight, and increase exercise remain of paramount importance. The prevention of diabetes and obesity and their associated insulin resistance, dyslipidemia, and CVD will require both a population and individual approach.

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