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REVIEW ARTICLE

Regulation of Plasma Triglycerides in Insulin Resistance and Diabetes

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Increased plasma levels of triglycerides (TG) in very low density lipoproteins (VLDL) are not only common characteristics of the dyslipidemia associated with insulin resistance and type 2 diabetes mellitus (T2DM) but are the central pathophysiologic feature of the abnormal lipid profile. Overproduction of VLDL leads to increased plasma levels of TG which, via an exchange process mediated by cholesterol ester transfer protein (CETP), results in low levels of high density lipoprotein (HDL) cholesterol and apolipoprotein A-I, and the generation of small, dense, cholesterol ester depleted low density lipoproteins (LDL). Increased assembly and secretion of VLDL by the liver results from the complex, post-transcriptional regulation of apolipoprotein B (apoB) metabolism in the liver. In the presence of low levels of hepatic TG and cholesterol, much of the constitutively synthesized apoB is degraded by both proteasomal and non-proteasomal pathways. When excess TG, and to a lesser extent, cholesterol, are present, and in the presence of active microsomal triglycerides transfer protein, apoB is targeted for secretion. The major sources of TG in the liver: uptake of fatty acids (FA) released by lipolysis of adipose tissue TG, uptake of TGFA in VLDL and chylomicrons remnants, and hepatic de novo lipogenesis (the synthesis of FA from glucose) are all abnormally increased in insulin resistance. Treatment of the dyslipidemia in insulin resistant individuals and patients with T2DM has been successful in reducing cardiovascular disease; LDL cholesterol, TG, and HDL cholesterol are all appropriate targets for therapy when diet, exercise, and weight loss do not achieve goals.

Key Words: Insulin resistance, Diabetes, Triglycerides, Lipoprotein, Metabolism, Treatment.

Introduction

Numerous prospective cohort studies have indicated that type 2 diabetes mellitus (T2DM) is associated with a three- to fourfold increase in risk for coronary artery disease (CHD) (1,2). The increase in risk is particularly evident in both younger age groups and women. Females with T2DM appear to lose a great deal of the protection that characterizes non-diabetic females. Furthermore, patients with T2DM have a 50% greater in-hospital mortality, and a twofold increased rate of death within 2 years of surviving a myocardial infarction. Overall, CHD is the leading cause of death in individuals with T2DM.

Much of this increased disease is associated with the presence of well-characterized risk factors for CHD, including characteristic abnormalities of plasma lipids and lipoprotein concentrations (3,4). This combination of abnormalities, elevated blood levels of triglycerides (TG), low levels of high density lipoprotein (HDL) cholesterol, and relatively normal levels of low density lipoprotein (LDL) cholesterol carried in small, dense, cholesterol-poor LDL particles, has been called the diabetic dyslipidemia. Significant evidence supports a key role for insulin resistance, which is a central pathophysiologic feature of T2DM in the development of the diabetic dyslipidemia (5). Indeed, insulin-resistant individuals who are not diabetic have lipid profiles that are nearly identical to those seen in the large majority of subjects with T2DM. In this review, we will focus on the role of insulin resistance in the regulation of plasma TG levels, as elevations in TG determine, to a significant degree, the levels of HDL cholesterol and the composition of LDL. Normal lipid and lipoprotein physiology will be reviewed briefly as a base from which we will examine the role of insulin resistance.

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Lipoprotein Composition

Lipoproteins are macromolecular complexes carrying various lipids and proteins in plasma (6). Several major classes of lipoproteins have been defined by their physical-chemical characteristics, particularly by their flotation characteristics during ultracentrifugation. However, lipoprotein particles actually form a continuum, varying in composition, size, density and function (Table 1). The lipids are mainly free and esterified cholesterol, TG, and phospholipids. The hydrophobic TG and cholesteryl esters comprise the core of the lipoproteins, while a unilamellar surface containing mainly the amphipathic (both hydrophobic and hydrophilic) phospholipids, small amounts of free cholesterol, and proteins form the surface. Hundreds to thousands of TG and cholesteryl ester molecules are carried in the core of different lipoproteins.

Apolipoproteins are the proteins on the surface of the lipoproteins. They not only help to solubilize the core lipids, but also play critical roles in the regulation of plasma lipid and lipoprotein transport. The major apolipoproteins are described in Table 2. Apolipoprotein (apo) B100 is required for the generation of hepatic-derived very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and low density lipoproteins (LDL). Apo B48 is a truncated form of apo B100 that is required for secretion of chylomicrons from the small intestine. Apo AI is the major structural protein in high-density lipoproteins (HDL). Apo AII is also an important protein on HDL. Other apolipoproteins will be discussed in the context of their roles in lipoprotein metabolism.

Postprandial Chylomicron Metabolism

After ingestion of a meal, dietary fat (TG) and cholesterol are absorbed into the cells of the small intestine and are incorporated into the cores of nascent chylomicrons. Apo B48 is required for the assembly of chylomicrons. The newly formed chylomicrons are secreted into the lymphatic system and then enter the circulation via the superior vena cava. In the lymph and the blood, chylomicrons acquire apo CII, apo CIII, and apo E. In the capillary beds of adipose tissue and muscle, chylomicrons interact with the enzyme lipoprotein lipase (LPL), which is synthesized and secreted by those tissues. LPL is activated by apo CII, and the chylomicron core TG is hydrolyzed. The lipolytic products, fatty acids (FA), can be taken up by fat cells and re-incorporated into TG, or by muscle cells where they can be used for energy. Some FA can bind to albumin and circulate back to the liver for uptake there. Apo CIII can inhibit lipolysis, and the balance of apo CII and apo CIII determines, in part, the efficiency with which LPL hydrolyzes chylomicron triglyceride. Chylomicron remnants, the product of this lipolytic process, have lost about 75–85% of the triglyceride and are relatively enriched in cholesteryl esters (both from dietary sources and from HDL-derived cholesteryl ester which has been transferred to the chylomicron). The chylomicron remnants are also enriched in apo E, and this protein is important for the interaction of chylomicron remnants with several pathways on hepatocytes that rapidly remove them from the circulation. Uptake of chylomicron remnants involves binding to the LDL receptor, the LDL receptor related protein (LRP), hepatic lipase (HL), and cell-surface proteoglycans (7).

Postprandial Chylomicron Metabolism: Effects of Insulin Resistance

Chylomicron and chylomicron-remnant metabolism can be altered significantly in insulin resistance and T2DM. Recent studies indicate that, like apo B100 (see below), the association of apo B48 with dietary lipids to form chylomicrons is dysregulated in the presence of insulin resistance; increased apo B48 secretion has been demonstrated in the insulin-resistant, sucrose-fed hamster (8). It is not clear if this happens in humans. However, increased postprandial hyperlipidemia is characteristic of the insulin resistance dyslipidemia (3), and although clearance of postprandial TG clearance is usually reduced, increased production of chylomicron particles may play a role as well. On the other hand, LPL is clearly regulated by insulin at several levels, including gene expression, synthesis, and secretion, and LPL is modestly reduced in insulin resistant T2DM subjects (9). Additionally, increased secretion of VLDL, which is characteristic of the insulin-resistant state (see below), leads to

Table 1. Physical-chemical characteristics of the major lipoprotein classes

Lipoprotein	Density	MW	Diameter	Lipid (%)		
				TG	CHOL	PL
Chylomicrons	0.95	400×10^6	75–1200	80–95	2–7	3–9
VLDL	0.95–1.006	$10–80 \times 10^6$	30–80	55–80	5–15	10–20
IDL	1.006–1.019	$5–10 \times 10^6$	25–35	20–50	20–40	15–25
LDL	1.019–1.063	2.3×10^6	18–25	5–15	40–50	20–25
HDL	1.063–1.21	$1.7–3.6 \times 10^6$	5–12	5–10	15–25	20–30

Density, g/dL; MW, daltons; diameter, nm; lipids (%), percent composition of lipids; apolipoproteins make up the rest.

Table 2. Characteristics of the major apolipoproteins

Apolipoprotein	MW	Lipoproteins	Metabolic functions
apo A-I	28,016	HDL, chylomicrons	Structural component of HDL; LCAT activator
apo A-II	17,414	HDL, chylomicrons	Unknown
apo A-IV	46,465	HDL, chylomicrons	Unknown; possibly facilitates transfer of apos between HDL and chylomicrons
apo A-V	39,000	HDL	Associated with lower TG levels; mechanism unknown
apo B-48	264,000	Chylomicrons	Necessary for assembly and secretion of chylomicrons from the small intestine
apo B-100	514,000	VLDL, IDL, LDL	Necessary for the assembly and secretion of VLDL from the liver; structural protein of VLDL, IDL and LDL; ligand for the LDL receptor
apo C-I	6,630	Chylomicrons, VLDL, IDL, HDL	May inhibit hepatic uptake of chylomicrons VLDL remnants
apo C-II	8,900	Chylomicrons, VLDL, IDL, HDL	Activator of lipoprotein lipase
apo C-III	8,800	Chylomicrons, VLDL, IDL, HDL	Inhibitor of lipoprotein lipase and of uptake of chylomicron and VLDL remnant by the liver
apo E	34,145	Chylomicrons, VLDL, IDL, HDL	Ligand for binding of several lipoproteins to the LDL receptor, LRP and proteoglycans
apo(a)	250,000–800,000	Lp(a)	Composed of LDL apoB linked covalently to apo(a); function unknown but is an independent predictor of CAD

increased levels of VLDL that compete with chylomicrons for LPL-mediated lipolysis (10,11). Of note, studies in cell culture systems and in rodents suggest that apo CIII gene expression is regulated by insulin, with increased apo CIII production in insulin-deficient or -resistant states. Recent evidence from studies in humans links insulin resistance with overproduction of both apo CIII and VLDL apo B100 (12). If apo CIII synthesis is increased in humans with insulin resistance, LPL action could be impaired.

HL, which both hydrolyzes chylomicron- and VLDL-remnant TG and also acts on HDL TG and phospholipids, has also been implicated in remnant removal (13). Deficiency of HL might, therefore, be associated with reduced remnant clearance. However, several studies (3) have indicated that HL is elevated in individuals with insulin resistance with or without T2DM, and may be an important contributor to low HDL cholesterol levels in this disease.

Removal of chylomicron remnants by the liver is the final step in postprandial lipid metabolism. As stated earlier, LDL receptors play a key role in this process. LDL receptors can be regulated, at the gene expression level, by insulin (14), and studies of humans with diabetes suggest that severe diabetes, with relative or absolute insulin deficiency, is accompanied by decreased clearance of LDL (15). Whether this extends to chylomicron remnant clearance is unknown.

Several studies have demonstrated an association between postprandial hyperlipidemia and the presence of CHD in non-diabetics (16). This association has not been demonstrated in patients with T2DM, possibly because all insulin-resistant individuals have postprandial hyperlipidemia.

VLDL Metabolism

VLDLs are initially assembled in the endoplasmic reticulum of hepatocytes. During and after synthesis of apo B100, the protein required for VLDL assembly, phospholipids, TG, and both free and esterified cholesterol are added in the ER and possibly the Golgi. VLDL TG derives from the combination of glycerol with 3 FA that have either been taken up from plasma or synthesized in the liver. VLDL cholesterol is either synthesized in the liver from acetate or delivered to the liver by lipoproteins, mainly chylomicron remnants, and LDL. Apo B100, phospholipids, and a small amount of free cholesterol form the surface of VLDL, whereas TG and esterified cholesterol are positioned in the core of the particle. Although some apo CI, apo CII, apo CIII, and apo E are present on the nascent VLDL particles as they are secreted from the hepatocyte, the majority of these molecules are probably added to VLDL after their entry into plasma.

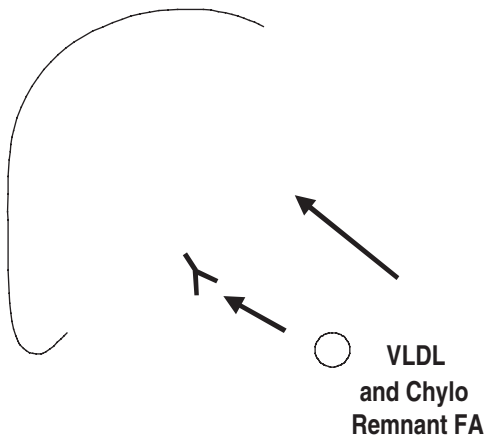
Regulation of the assembly and secretion of VLDL by the liver has been under intense investigation for the past 25 years, and much has been learned (17–19). Of particular relevance to the present review, there is significant post-transcriptional and posttranslational regulation of the hepatic assembly of apo B100 (and in rodents apo B48) with lipids to form VLDL. Thus, studies in cultured liver cells indicate that a significant proportion of newly synthesized apo B100 may be degraded before secretion, and that this degradation is inhibited when hepatic lipids are abundant. Studies in rodents support the tissue culture data. There is also abundant evidence that microsomal triglyceride transfer protein (MTP) is essential for the assembly and secretion of VLDL (20). Once in the plasma, VLDL triglyceride is hydrolyzed by LPL; as with chylomicrons, this step can be modified by the ratio of apo CII to apo CIII. Lipolysis generates smaller and denser VLDL and, subsequently, IDL. These small VLDL, together with IDL, are similar to chylomicron remnants in that small VLDL and IDL itself can be removed by the liver. However, unlike chylomicron remnants, small VLDL (through IDL) and IDL can also undergo further catabolism to become LDL. It also appears that apo E, HL, and LDL receptors play important roles in this metabolic cascade that ends with the generation of LDL. Thus, the

levels of VLDL TG in the blood will be determined by the rates of secretion of VLDL TG and apo B100, rates of lipolysis of VLDL TG by LPL, and the rates of both removal of small VLDL from the circulation and its conversion to IDL. Each of these can be affected by insulin resistance.

VLDL Metabolism: Effects of Insulin Resistance

Overproduction of VLDL, with increased secretion of both triglyceride and apo B100, seems to be the central and most important etiology of increased plasma VLDL levels in patients with insulin resistance or T2DM (5). As noted above, the series of steps whereby apo B100 assembles with lipids and VLDL is secreted is regulated posttranscriptionally. Recent studies in cell culture, rodents, and humans have provided significant insights regarding the mechanisms whereby insulin resistance can drive increased VLDL secretion. First, the targeting of apo B100 for secretion as VLDL is regulated significantly by the availability of its lipid ligands, particularly TG. If hepatic lipids are unavailable for assembly into VLDL, apoB can be degraded by the proteasome, after cotranslational ubiquitination (18). Limited lipid availability can also target apo B100 for posttranslational degradation: some of that is in the ER and some distal to the ER. Insulin resistance is associated with increases in the three main sources of TG for VLDL assembly: FA flux from adipose tissue to the liver, hepatic uptake of VLDL, IDL, and chylomicron remnants, and de novo lipogenesis (Figure 1).

Substrate Driving Forces for the Assembly and Secretion of apoB-Lipoproteins



isoform one (SREBP1-c) (33). Their work indicated that hepatic SREBP1-c gene expression was regulated by insulin through another transcription factor, the liver-x-receptor (LXR); in hyperinsulinemic ob/ob mice, SREBP1-c gene expression was increased (34). Of note, in their studies with ob/ob mice, it appeared that although insulin resistance might exist in the pathway regulating gluconeogenesis, this resistance did not extend to insulin's ability to stimulate lipogenesis (34).

In our recent studies (unpublished), we have found that lipogenesis is increased in the apoB/BATless mouse, a model of moderate obesity, insulin resistance and increased VLDL secretion (25), but that SREBP1-c expression or activity was not altered. On the other hand, the expression and activity of the peroxisome proliferators activated receptor gamma (PPARgamma) was increased in the livers of apoB/BATless mice, and that finding, together with published data indicating an important role of PPARgamma in hepatic lipogenesis in other mouse models of obesity and insulin resistance (35), has led us to pursue this interesting and potentially clinically relevant finding.

Studies conducted over a number of years in cultured liver cells have indicated clearly that insulin not only stimulates lipogenesis but also plays a key role in determining whether apo B is targeted for secretion or degradation (36,37). Insulin, acting via a P-I-3 kinase pathway, can target insulin for degradation. This degradation is posttranslational and probably post-endoplasmic reticulum. In recent studies, Fisher and colleagues suggested that insulin's stimulation of apo B degradation may be linked to high levels of oxidant stress in insulin treated hepatocytes (38). Results in cultured cells have been extended to in vivo studies in rodents and humans. In the latter, both Lewis and colleagues (39) and Malmstrom and co-workers (40) showed decreased VLDL secretion, both TG and apoB, in normal subjects treated with large quantities of insulin and glucose (euglycemic clamps). Importantly, the effects of insulin on apo B degradation appear to diminish significantly if insulin resistance is present; this is true in cultured cells (41), whole animals (42), and humans (39,40). In ongoing studies in our laboratory (unpublished), we are looking at the extreme case of hepatic insulin resistance in mice that lack insulin receptors only in the liver; called LIRKO mice. Our preliminary results indicate that in the presence of decreased SREBP1-c and PPARgamma gene expression, and reduced TG secretion, the rates of secretion of apo B100 and apo B48 from the liver are either normal or increased. This dissociation of TG and apoB secretion supports a direct role of insulin; in the absence of insulin signaling, less apo B is degraded, and more is secreted, even when hepatic lipid availability and secretion is reduced.

A potentially important and clinically relevant extension of the finding described above relates to the increasing prevalence of fatty livers in people with obesity and insulin resistance, with or without T2DM. Although such individuals seem to be able to increase VLDL secretion as they attempt to maintain hepatic lipid homeostasis in the face of increased sources of TG, some cannot "keep up" and TG accumulates. It is possible that the relative degrees of both insulin resistance and hyperinsulinemia determine whether fatty liver will develop. If there is severe insulin resistance, then despite increased uptake of albumin bound FA and TG-containing remnants, and regardless of the level of lipogenesis, there will be enough apo B (because of reduced insulin-mediated degradation) to unload the TG via VLDL secretion. If there is moderate insulin resistance and, in particular, there is adequate insulin signaling of the insulin-mediated apo B degradation pathway, then TG will accumulate and a fatty liver will develop (Figure 2). This hypothesis requires further investigation.

VLDL Catabolism in Insulin Resistance

As described earlier in the section on chylomicron metabolism, modest reductions in postheparin LPL levels have been reported (3) in some T2DM, and this may contribute significantly to elevated TG levels, particularly in severely hyperglycemic patients. Additionally, as described above, VLDL and chylomicrons can compete for the same LPL-mediated pathway for TG removal from the circulation. Also described earlier in this review, hepatic uptake of VLDL remnants is a complex process involving several parallel and yet interactive pathways. Insulin resistance might lead to reduced LDL receptors, limiting remnant removal. HL is increased in many individuals with diabetic dyslipidemia, and although high HL activity may be important for the low

Regulation of Lipogenesis and ApoB Secretion by Insulin

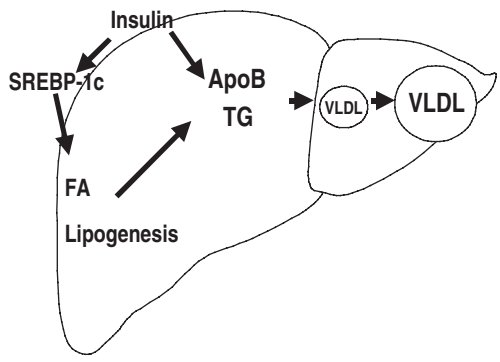


Figure 2. Insulin regulates de novo hepatic lipogenesis, mainly through its ability to increase the gene expression of SREBP1-c, the major lipogenic transcription factor. Insulin also can target nascent apoB for degradation posttranslationally. In an insulin-resistant liver, the relative effects of insulin to increase FA and TG synthesis and to reduce availability of apoB to secrete TG from the liver will be a major determinant of both hepatic TG accumulation and plasma TG levels.

HDL levels and the predominance of small dense LDL characteristic of this lipid complex, it suggests that HL-mediated TG hydrolysis of VLDL remnants is unimportant. Recent studies using new techniques to isolate "remnants" indicate that they are elevated even in fasting blood and more work is needed in this area.

Role of Insulin Resistance in the Generation of Small Dense LDL

In people with insulin resistance and T2DM, regulation of plasma levels of LDL, like that of its precursor VLDL, is complex. In the presence of hypertriglyceridemia, dense, cholesteryl ester-depleted, triglyceride-enriched LDL are present. Thus, individuals with T2DM and mild to moderate hypertriglyceridemia may have the Pattern B profile of LDL described by Austin and Krauss (43). The basis for small dense LDL in insulin resistance is derived in large part from the action of cholesteryl ester transfer protein (CETP). This protein, which is associated with lipoproteins in the blood, particularly HDL, can mediate the exchange of VLDL (or chylomicron) TG for LDL cholesteryl ester, thereby creating a TG-enriched, cholesteryl ester depleted LDL particle. The TG in LDL can then be lipolyzed by LPL or HL, generating the small, dense LDL. The finding that small dense LDL are present in insulin-resistant and T2DM patients even when they have relatively normal TG levels, suggests other factors are at play. One factor is HL which, as noted earlier, is increased in insulin resistance, and can, therefore, more effectively hydrolyze any TG in LDL. Higher levels of blood FA have also been shown to stimulate exchange of CE and TG between LDL (or HDL) and VLDL.

Role of Insulin Resistance in the Generation of Low Levels of HDL Cholesterol

HDL cholesterol and apo AI levels are characteristically reduced in insulin-resistant people. Much of this derives, as in the case of small dense LDL, from the action of CETP-mediated transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins (chylomicrons and VLDL). A consistent finding is the inverse relationship between plasma insulin (or C-peptide) concentrations, which are measures of insulin resistance and HDL cholesterol levels. Fractional catabolism of apo AI is increased in T2DM with low HDL as it is in non-diabetics with similar lipoprotein profiles (44). Although apo AI levels are reduced consistently, correction of hypertriglyceridemia does not usually normalize apo AI levels (3). Studies have demonstrated that apo AI may dissociate from triglyceride-enriched HDL and be cleared by the kidney (44). Increased HL activity in insulin resistance, with increased hydrolysis of TG and the generation of smaller HDL, may also play a role in this scheme. Whether defective ABCA1 mediated efflux of cellular free cholesterol, defective LCAT activity, or increased selective delivery of HDL cholesteryl ester to hepatocytes are involved in the low HDL levels present in insulin resistance is under investigation. However, the fact that the low HDL cholesterol and apo AI are frequently present even when TG levels are relatively normal suggests non-CETP mechanisms are important.

Treatment of Diabetic Dyslipidemia: Focus on Insulin Resistance

Weight Loss

Although a discussion of the various dietary approaches to the treatment of insulin resistance and T2DM remains controversial and is beyond the scope of this review, there is universal agreement that weight reduction is an essential part of dietary therapy in individuals with insulin resistance dyslipidemia. Several groups have shown that when weight reduction is achieved and maintained in T2DM patients, there is a sustained decrease in triglyceride levels. Studies with weight loss in diabetic Pima Indians (45) revealed that there was decreased VLDL synthesis, while VLDL removal rate and LPL activity were unchanged. We showed that weight loss in non-diabetic subjects who were very likely to be insulin resistant was associated with reductions in apo B100 secretion across the range of VLDL to LDL (46). Most, but not all, studies show an increase in HDL cholesterol as well as an improvement in the ratio of total to HDL cholesterol in T2DM patients who lose weight.

Glycemic Agents

Some of the therapeutic choices available for the treatment of T2DM, such as metformin and the thiazolidinediones (TZD), can lower plasma triglyceride concentrations 10–15% and 15–25%, respectively (47). The TZDs, which are PPARgamma agonists, improve peripheral hepatic insulin sensitivity, and this leads to inhibition of lipolysis in adipose tissue. Plasma levels of FA fall about 25% at the highest dose of both of the presently available TZDs, and such changes should lead to lower hepatic TG synthesis and reduced VLDL secretion. Hepatic insulin sensitivity is also improved modestly by these agents, raising the possibility of direct hepatic actions that could affect VLDL secretion. Of interest, pioglitazone does lower plasma TG levels but rosiglitazone does not; the basis for this difference is unclear (48). Newer, non-TZD PPARgamma agonists, as well as dual PPARgamma and alpha agonists, are under development.

Lipid-Lowering Drugs

HMG-CoA reductase inhibitors. Although TG and HDL cholesterol abnormalities are prominent in patients with

T2DM, while LDL cholesterol levels are usually not different from those in non-diabetics, the increased risk of CHD together with the clearly demonstrated benefits of LDL-lowering therapy indicates that LDL should be a primary target of pharmacotherapy in patients with T2DM. During the past 15 years, the treatment of hypercholesterolemia has undergone a revolution with the availability of potent, safe HMG-CoA reductase inhibitors, also known as statins. Lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin and rosuvastatin are available drugs in this category in the U.S. They work to competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, which results in both upregulation of LDL receptors and decreased hepatic production of apo B-containing lipoproteins. The overall effect is a dramatic lowering of plasma levels of LDL cholesterol. The most potent statins (simvastatin, atorvastatin, and rosuvastatin), at their highest doses, can lower LDL cholesterol by up to 45–60%, and decrease TG 20–45%. The reduction of TG is directly related to the reduction of LDL cholesterol achieved and to the starting level of TG. Reductase inhibitors can raise HDL cholesterol by up to 10%, but the more typical increase is about 5%. Statins should not be considered as first-line agents for individuals with isolated, very low HDL levels. There is no evidence that statins affect insulin resistance or glycemic levels in patients with T2DM.

Non-statin LDL lowering−bile acid binding. Cholestyramine, colestipol, and colesevalem are resins that bind bile acids in the intestine, thus interrupting the enterohepatic recirculation of those molecules. A fall in bile acids returning to the liver results in increased conversion of hepatic cholesterol to bile acids, which results in a diminution of a regulatory pool of hepatic cholesterol and upregulation of the gene for hepatic LDL receptors. All of these changes lead to increased LDL receptors on the surface of hepatoctyes and, therefore, decreased plasma LDL concentrations. At their recommended doses, the resins can lower LDL cholesterol levels about 15–20%. A drawback to the use of bile acid-binding resin in diabetics is the increase in hepatic VLDL triglyceride production and plasma triglyceride levels commonly associated with their use. The mechanism for this rise in VLDL TG is not fully defined but is not associated with changes in insulin resistance. A newer bile acid-binding resin, colesevalem, has little effect on VLDL levels.

Ezetimibe. A very recent addition to the drugs that can be used to lower LDL cholesterol is the inhibitor of intestinal cholesterol absorption, ezetimibe. This agent appears to interact with a recently identified receptor for cholesterol transport across the brush border of enterocytes in the small intestine (49). At the single recommended dose of 10 mg/day, ezetimibe lowers LDL cholesterol between 15 and 20%. It has little effect on TG or HDL cholesterol. Ezetimibe seems additive when used in combination with statins. There are no published data for ezetimibe in combination with other agents or as a therapy for patients with T2DM. However, there is no evidence that insulin sensitivity is affected by ezetimibe.

Plant stanol and sterol esters. These agents compete with intestinal cholesterol for incorporation into micelles, thereby reducing cholesterol absorption. At 1−3 g/day, the plant sterol and stanol esters reduce LDL cholesterol levels by 15%. They have no known effects on insulin resistance.

Fibric acid derivatives. Fenofibrate and gemfibrozil are the agents available in the United States at present. Several others are available in Europe and Canada. Fibric acid derivatives have potent lipid-altering effects that may be quite useful in diabetics. In general, fibrate use in patients with T2DM results in lowering of triglyceride from 20 to 35% and increases in HDL cholesterol from 10 to 20%. Effects on LDL cholesterol levels are variable. Although their mechanism of action is unclear, these agents appear to work by both decreasing hepatic VLDL production, as well as increasing the activity of LPL. There have been reports of fibrates, which are PPARalpha agonists, increasing insulin sensitivity in rodents; there are few data to support this action in humans. The usual dose is 600 mg twice daily of gemfibrozil and 160 mg once daily for micronized fenofibrate. In the Veterans Administration HDL Intervention Trial, gemfibrozil was efficacious in a group of men who had CHD and LDL cholesterol that was low (111 mg/dl) at baseline and did not change during the trial (50). The treated group did show a 7% increase in HDL cholesterol and a 25% reduction in TG; these effects were associated with a 24% reduction in CHD events. Similarly, The Diabetes Atherosclerosis Intervention Study (DAIS) showed that treatment with fenofibrate was associated with lower TG and higher HDL cholesterol levels, and decreases in focal CAD by angiography in subjects with T2DM (51). The use of fibrates with statins can produce outstanding overall changes in VLDL, LDL, and HDL levels; treatment with this combination has been limited by the risk of myositis. Recent data suggest (but this must be proved) that while gemfibrozil together with a statin might have a risk of myositis about 1%, the risk will be significantly lower with fenofibrate (52).

Nicotinic acid (Niacin). Niacin, when used in pharmacologic doses (1–3 g/day), has the ability to potently lower TG (25–40%) and raise HDL cholesterol (10–25%). Niacin also lowers LDL cholesterol (15–20%) and this adds to its potential efficacy in a high-risk population. The mechanism of action is generally thought to be through lowering hepatic VLDL apo B production and increasing the synthesis of apo A-I. Unfortunately, some studies have demonstrated that niacin therapy worsens diabetic control, likely by inducing insulin resistance. This finding is interesting at a theoretical level, because niacin's ability to inhibit lipolysis and lower plasma free fatty acid levels after a single dose of the drug

might be expected to improve insulin sensitivity. Not all investigators believe that niacin is contraindicated in patients with diabetes and two recent studies with an intermediate-release form of niacin have rekindled interest in its potential in this population (53). The results of these studies suggest that although HbA1c levels tended to rise during niacin treatment, titration of glycemic agents limited the rise. On the other hand, use of niacin compounds in patients with insulin resistance without diabetes carries a risk of converting a patient to T2DM.

Summary

People with insulin resistance have a characteristic dyslipi-

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