

# Regulation of Plasma Triglycerides in Insulin Resistance and Diabetes

As the leading cause of death among type 2 diabetic patients, coronary heart disease is prevalent in women and younger patients.

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**T**ype 2 diabetes is associated with a three- to four-fold increase in coronary heart disease (CHD) risk,<sup>1,2</sup> which is particularly evident in younger age groups and women. Diabetic women lose much of the CHD protection seen in nondiabetic women. Type 2 diabetic patients have a 50% greater in-hospital mortality and a twofold increased rate of death within 2 years of surviving a myocardial infarction. CHD is the leading cause of death among type 2 diabetic patients.

Much of the increased disease is associated with well-characterized risk factors for CHD like lipids and lipoprotein abnormalities.<sup>3,4</sup> The combination of elevated triglycerides (TG), low HDL cholesterol and relatively normal LDL cholesterol carried in small, dense, cholesterol-poor LDL particles, has been called diabetic dyslipidemia. Significant evidence supports a key role for insulin resistance in the development of this condition.<sup>5</sup> Nondiabetic insulin resistant patients have lipid profiles nearly identical to those seen in the majority of type 2 diabetic patients. In this review, we look at the role of insulin resistance in the regulation of TG.

## LIPOPROTEIN COMPOSITION

Lipoproteins are macromolecular complexes carrying lipids and proteins in plasma.<sup>6</sup> Lipoprotein particles vary in composition, size, density and function (Table 1). Lipids are mainly free and esterified cholesterol, TG and phospholipids. Hydrophobic TG and cholesteryl esters comprise the core of lipoproteins, while a unilamellar surface containing mainly amphipathic 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, on the surface of lipoproteins, help to solubilize core lipids. They have a critical role in the regulation of plasma lipid and lipoprotein transport (Table 2). Apo B100 is required for the generation of hepatic-derived very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL) and LDL. Apo B48 is a truncated form of apo B100 required for secretion of chylomicrons from the small intestine. Apo AI is the major structural protein in HDL. Apo AII is also an important protein on HDL.

## CHYLOMICRON INTERACTIONS

After a meal, dietary fat and cholesterol are absorbed into cells in the small intestine and incorporated into the cores of nascent chylomicrons. The newly formed chylomicrons are secreted into the lymphatic system and enter circulation via the superior vena cava. Chylomicrons acquire apo CII, apo CIII and apo E, and they interact with the enzyme lipoprotein lipase (LPL) in the capillary beds of adipose tissue and muscle.

Fatty acids (FA) can be taken up by fat cells and reincorporated 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. Apo CIII can inhibit lipolysis. The balance of apo CII and apo CIII, in part, determines the efficiency that LPL hydrolyzes chylomicron TG. Chylomicron remnants have lost about 75% to 85% of TG and are relatively enriched in cholesteryl esters. They are also enriched in apo E2, which interacts on hepatocytes, rapidly removing them from circulation. Uptake of chylomicron remnants involves binding to the LDL receptor, the LDL receptor related protein (LRP), hepatic lipase (HL) and cell-surface proteoglycans.<sup>7</sup>

Chylomicron and chylomicron-remnant metabolism can be significantly altered in insulin resistance and type 2 diabetes. Recent studies indicate that the association of apo B 48 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.<sup>8</sup> It is not clear if this happens in humans.

### CHARACTERISTIC OF INSULIN RESISTANCE

Increased postprandial hyperlipidemia is characteristic of insulin resistance dyslipidemia.<sup>3</sup> Although clearance of postprandial TG is usually reduced, increased production of chylomicron particles may also play a role. LPL is clearly regulated by insulin at several levels that include gene expression, synthesis and secretion. LPL is modestly reduced in insulin resistant type 2 diabetic patients.<sup>9</sup> Increased secretion of VLDL, which is common in diabetic patients (see below), results in competition of VLDL with chylomicrons for LPL-mediated lipolysis.<sup>10,11</sup>

Recent evidence links insulin resistance with overproduction of both apo CIII and VLDL apo B100.<sup>12</sup> 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 acts on HDL TG and phospholipids, has also been implicated in remnant removal.<sup>13</sup> Deficiency of HL may be associated with reduced remnant clearance. However, several studies have indicated that HL is elevated in insulin resistance individuals with or without type 2 diabetes and may be an important contributor to low HDL cholesterol levels in this disease.<sup>3</sup>

Removal of chylomicron remnants by the liver is the final step in postprandial lipid metabolism. LDL receptors play a key role in this process, and they can be regulated at the

gene expression level by insulin.<sup>14</sup> Studies suggest that severe diabetes, with relative or absolute insulin deficiency, is accompanied by decreased clearance of LDL.<sup>15</sup> Whether this extends to chylomicron remnant clearance is unknown.

### VLDL METABOLISM

VLDL is initially assembled in the endoplasmic reticulum of hepatocytes. During and after synthesis of apo B100, phospholipids, TG and both free and esterified cholesterol are added in the endoplasmic reticulum and possibly the Golgi. VLDL TG derives from the combination of glycerol with 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.

Regulation of the assembly and secretion of VLDL by the liver has been under investigation for the past 25 years.<sup>16-18</sup> Of particular relevance, there is significant posttranscriptional and posttranslational regulation of the hepatic assembly of apo B100 with lipids to form VLDL. Studies in cultured liver cells indicate that a significant proportion of newly synthesized apo B100 may be degraded before secretion. This degradation is inhibited when hepatic lipids are abundant. There is evidence that microsomal TG transfer protein is essential for the assembly and secretion of VLDL.<sup>19</sup>

Once in plasma, VLDL TG is hydrolyzed by LPL. This step can be modified by the ratio of apo CII to apo CIII. Lipolysis generates smaller and denser VLDL and, subsequently, IDL. The liver can remove these small VLDL and IDL, or they can undergo further catabolism at the surface of the hepatocyte (TG hydrolysis by HL) to become LDL. Blood levels of VLDL TG will be determined by the rates of secretion of VLDL TG and apo B100; by the rates of lipolysis of VLDL TG

**TABLE 1. PHYSICAL-CHEMICAL CHARACTERISTICS OF THE MAJOR LIPOPROTEIN CLASSES**

Lipoprotein	Density*	MW†	Diameter‡	Lipid (%)		
				TG	CHOL	PL
Chylomicrons	0.95	400x10	675-1200	80-95	2-7	3-9
VLDL	0.95-1.00	610-80x106	30-80	55-80	5-15	10-20
IDL	1.006-1.019	5-10x106	25-35	20-50	20-40	5-25
LDL	1.019-1.063	2.3x106	18-25	5-15	40-50	20-25
HDL	1.063-1.21	1.7-3.6x106	5-12	5-10	15-25	20-30

\* Density: gm/dL

† MW: daltons

‡ Diameter: nm

|| Lipids (%): percent composition of lipids; apolipoproteins make up the rest

by LPL; and by the rates of both removal of small VLDL from the circulation and its conversion to IDL. Insulin resistance can affect each of these.

### EFFECTS OF INSULIN RESISTANCE

Overproduction of VLDL appears to be the central and most important etiology of increased plasma VLDL in patients with insulin resistance or type 2 diabetes.<sup>5</sup> The series of steps that assemble apo B100 with lipids and VLDL secretion is regulated posttranscriptionally. Recent studies have provided significant insights regarding the mechanisms whereby insulin resistance can drive increased VLDL secretion. The targeting of apo B100 for secretion as VLDL is regulated by the availability of its lipid ligands, particularly TG. If hepatic lipids are unavailable for assembly into VLDL, apo B can be degraded by the proteasome after cotranslational ubiquitination.<sup>17</sup> 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 TG as a component of VLDL, IDL and chylomicron remnants; and de novo lipogenesis (Figure 1).

Increased FA in blood and increased FA flux to the liver occur in insulin resistant humans with and without type 2 diabetes. Plasma albumin bound FA are a source of VLDL TG.<sup>20-21</sup> Recently, Lewis et al showed that acutely raising plasma FA could increase VLDL secretion in normal individuals.<sup>22</sup> We confirmed the role of FA in chronically catheterized normal mice.<sup>23</sup> We have also shown, in a mouse model of insulin resistance and increased secretion of VLDL, that FA flux to the liver was increased.<sup>24</sup> Similar findings were observed in a sucrose-fed hamster model of insulin resistance and increased VLDL secretion.<sup>25</sup> Mice that lack hormone sensitive lipase, one of the adipocyte enzymes needed to release FA from cell TG, have low levels of FA in the blood and secrete less VLDL TG.<sup>26</sup>

Hepatic uptake of remnant lipoproteins plays an important role in regulating postprandial and fasting levels of blood TG. Uptake of TG-containing lipoproteins will stimulate VLDL assembly and secretion as the liver attempts to maintain homeostasis regarding FA and TG content. Delivery of excess remnant TG FA will lead to increased VLDL secretion. This has been demonstrated in cultured liver cells<sup>27</sup> and in humans.<sup>28</sup> Using the mouse model, we showed that infusion of an emulsion of TG and phospholipids could stimulate both apo B and TG secretion.<sup>23</sup> We found that TG FA acid, delivered via remnant uptake were not as potent a stimulus for VLDL secretion as when FA were delivered by albumin.

### SOURCE OF TG

The third source of TG for assembly and secretion with apo B100 is de novo fatty acid synthesis (lipogenesis) in the

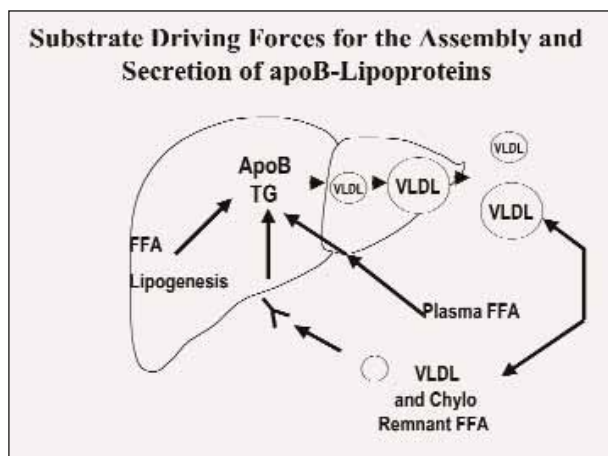


Fig 1. There are three major sources of TG, the main substrate regulating apo B secretion as VLDL. They are FA from peripheral tissues, particularly adipose tissue; chylomicron and VLDL remnants; and de novo hepatic lipogenesis. In insulin resistance, FA flux through the plasma to the liver is increased, peripheral removal (by lipolysis) of chylomicron and VLDL TG is reduced, which leaves TG-enriched remnants for hepatic uptake, and de novo lipogenesis can be increased. All of these sources of TG may contribute to the increased VLDL secretion present in insulin resistant people.

liver. In rodents, lipogenesis is an important source of VLDL TG. Data in humans is less abundant, but several recent papers have shown that lipogenesis does contribute to VLDL TG and is increased in obese individuals with insulin resistance.<sup>29-31</sup> Goldstein and Brown defined in detail the regulation of hepatic lipogenesis by sterol response element binding protein isoform one (SREBP1-c).<sup>32</sup> Their work indicated that hepatic SREBP1-c gene expression was regulated by insulin through liver-x-receptor; SREBP1-c gene expression was increased in hyperinsulinemic ob/ob mice.<sup>33</sup> 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.<sup>33</sup>

### LIPOGENESIS IS INCREASED

In our recent studies, we found that lipogenesis is increased in the apo B/BATless mouse, a model of moderate obesity, insulin resistance and increased VLDL secretion,<sup>24</sup> but that SREBP1-c expression or activity was not altered. The expression and activity of PPARgamma was increased in the livers of apo B/BATless mice. That finding, together with data indicating an important role of PPARgamma in hepatic lipogenesis in other mouse models of obesity and insulin resistance,<sup>34</sup> suggests that a similar situation may exist in patients with obesity, insulin resistance and fatty livers.

Studies conducted over a number of years in cultured liver cells have indicated that insulin not only stimulates lipogenesis, but also plays a key role in determining whether apo B is targeted for secretion or degradation.<sup>35,36</sup> Recently, 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.<sup>37</sup> Results in cultured cells have been extended to in vivo studies in rodents and humans. In the latter, Lewis and colleagues<sup>38</sup> and Malmstrom and coworkers<sup>39</sup> showed decreased VLDL secretion in normal subjects treated with large quantities of insulin and glucose. The effects of insulin on apo B degradation appear to diminish significantly if insulin resistance is present; this is true in cultured cells,<sup>40</sup> whole animals<sup>41</sup> and humans.<sup>38,39</sup>

### FATTY LIVERS

A potentially important, clinically relevant finding relates to the increasing prevalence of fatty livers in people with obesity and insulin resistance. Although such patients 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 to unload the TG via VLDL secretion. If there is moderate insulin resistance and, in particular, adequate insulin signaling of the insulin-mediated apo B degra-

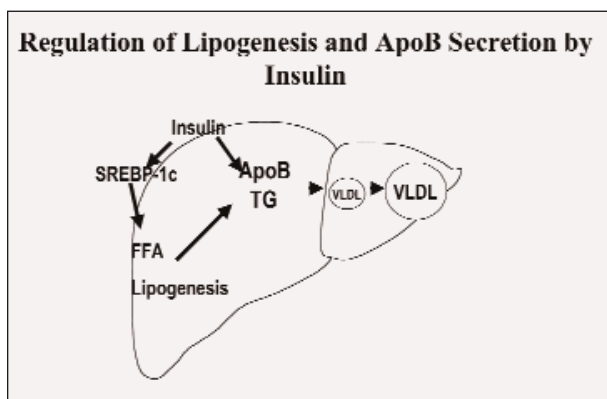


Figure 2. Insulin regulates de novo hepatic lipogenesis, mainly through its ability to increase the gene expression of SREBP1-c, the major lipogenic transcription factor. Insulin also can target nascent apoB for degradation posttranslationally. In an insulin resistant liver, the relative effects of insulin 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.

dation pathway, then TG will accumulate and fatty liver will develop (Figure 2). This hypothesis requires further investigation.

### SMALL DENSE LDL

In people with insulin resistance and type 2 diabetes, regulation of plasma LDL is complex. In the presence of hypertriglyceridemia, dense, cholesteryl ester-depleted, TG-enriched LDL are present. Thus individuals with type 2 diabetes and mild to moderate hypertriglyceridemia may have the Pattern B profile of LDL described by Austin and Krauss.<sup>42</sup> 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 is associated with lipoproteins, particularly HDL. It can mediate the exchange of VLDL TG for LDL cholesteryl ester, creating a TG-enriched, cholesteryl ester-depleted LDL particle. This exchange is increased when hypertriglyceridemia exists. The TG in LDL can then be lipolyzed by LPL or HL, generating small dense LDL. Because small dense LDL is present in insulin resistant and type 2 diabetes patients even when they have relatively normal TG levels, other factors may also play a role. One factor is HL. As noted earlier, it is increased in insulin resistance and can more effectively hydrolyze TG in LDL. Higher levels of blood FA have also been shown to stimulate exchange of cholesterol ester and TG between LDL (or HDL) and VLDL.

HDL cholesterol and apo AI levels are characteristically reduced in insulin-resistant people. Much of this derives from the action of CETP-mediated transfer of cholesteryl ester from HDL to TG-rich lipoproteins; this process is the same as described above for TG-rich lipoproteins and LDL. A consistent finding is the inverse relationship between plasma insulin concentrations and HDL. Fractional catabolism of apo AI is increased in type 2 diabetes with low HDL, as it is in nondiabetic people with similar lipoprotein profiles.<sup>43</sup> Although apo AI levels are reduced consistently, correction of hypertriglyceridemia does not usually completely normalize apo AI.<sup>3</sup> Studies have demonstrated that apo AI may dissociate from TG-enriched HDL and be cleared by the kidney.<sup>43</sup> Increased HL activity in insulin resistance, with increased hydrolysis of TG and the generation of smaller HDL, may also play a role. The fact that low HDL and apo AI are frequently present – even when TG levels are relatively normal – suggests non-CETP mechanisms are also important.

### TREATMENT OF DIABETIC DYSLIPIDEMIA

**Weight Loss.** There is universal agreement that weight reduction is essential to the treatment of insulin resistance and type 2 diabetes. Several groups have shown that when weight reduction is achieved and maintained in type 2 dia-

betic patients, there is a sustained decrease in TG. Studies with weight loss in diabetic Pima Indians<sup>44</sup> revealed decreased VLDL synthesis without a change in VLDL removal rate and LPL activity. We showed that weight loss in nondiabetic patients who were likely to be insulin resistant was associated with reductions in apo B100 secretion across the range of VLDL to LDL.<sup>45</sup> Most studies show an increase in HDL cholesterol as well as an improvement in the ratio of total to HDL cholesterol in type 2 diabetic patients who lose weight.

**Glycemic Agents.** Some of the therapeutic choices available for the treatment of type 2 diabetes, such as metformin and the thiazolidinediones (TZDs), can lower plasma triglyceride concentrations 10% to 15% and 15% to 25%, respectively.<sup>46</sup> TZDs 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 TZDs, and such changes could lead to lower hepatic TG synthesis and reduced VLDL secretion. These agents also modestly improve hepatic insulin sensitivity; raising the possibility of direct hepatic actions that

could affect VLDL secretion also modestly improve hepatic insulin sensitivity. TZDs could also increase LPL gene expression, and this would improve the clearance of TG from circulation. Of interest, pioglitazone lowers plasma TG levels but rosiglitazone does not. The basis for this difference is unclear.<sup>47</sup>

#### LIPID-LOWERING DRUGS

**HMG-CoA Reductase Inhibitors.** TG and HDL abnormalities are prominent in patients with type 2 diabetes, while LDL levels are usually not different. However, the increased risk of CHD together with the clearly demonstrated benefits of LDL-lowering therapy indicate that LDL should be a primary target of pharmacotherapy in these patients.

During the past 15 years, the treatment of hypercholesterolemia has undergone a revolution with the availability of HMG-CoA reductase inhibitors. The most potent statins at their highest doses can lower LDL cholesterol by up to 45% to 60% and decrease TG 20% to 45%. Statins can raise HDL cholesterol by up to 10%, but the typical increase is

**TABLE 2. CHARACTERISTICS OF THE MAJOR APOLIPOPROTEINS**

Apolipoprotein	MW	Lipoproteins	Metabolic functions
apo AI	28,016	HDL, chylomicrons	Structural component of HDL; LCAT activator
apo AII	17,414	HDL, chylomicrons	Unknown
apo AIV	46,465	HDL, chylomicrons	Unknown; possibly facilitates transfer of apos between HDL and chylomicrons
apo AV	39,000	HDL	Associated with lower TG levels; mechanism unknown
apo B48	264,000	Chylomicrons	Necessary for assembly and secretion of chylomicrons from the small intestine
apo B100	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 CI	6,630	chylomicrons, VLDL, IDL, HDL	may inhibit hepatic uptake of chylomicrons, VLDL remnants
apo CII	8,900	chylomicrons,	Activator of lipoprotein lipase
apo CIII	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

about 5%. They 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 type 2 diabetes.

### NON-STATIN LDL LOWERING

Cholestyramine, colestipol and colesevalam 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. This 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 hepatocytes and, therefore, decreased plasma LDL concentrations. At recommended doses, resins can lower LDL cholesterol levels about 15% to 20%. A drawback to the use of bile acid binding resin in diabetic patients is the increase in hepatic VLDL TG production and plasma TG levels commonly associated with their use. The mechanism for this rise in VLDL TG is not fully defined, but it is not associated with changes in insulin resistance. A newer bile acid binding resin, colesevalam has little effect on VLDL levels.

Ezetimibe is a very recent addition to the drugs that can be used to lower LDL cholesterol. It is the inhibitor of intestinal cholesterol absorption. This agent appears to interact with a recently identified receptor for cholesterol transport across the brush border of enterocytes in the small intestine.<sup>48</sup> 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. 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 type 2 diabetes. There is no evidence that insulin sensitivity is affected by ezetimibe.

Plant stanol and sterol esters compete with intestinal cholesterol for incorporation into micelles, thereby reducing cholesterol absorption. At 1 to 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 available in the United States. Several other derivatives 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 type 2 diabetes results in lowering of TG from 20% to 35% and increases in HDL from 10% to 20%. Effects on LDL 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. The usual dose is 600 mg twice daily of gemfibrozil and 148 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 levels that were low (111 mg/dL) at baseline and did not change during the trial.<sup>49</sup> The treated group did show a 7% increase in HDL and a 25% reduction in TG. These effects were associated with a 24% reduction in CHD events.

Similarly, The Diabetes Atherosclerosis Intervention Study showed that treatment with fenofibrate was associated with lower TG and higher HDL levels and decreases in focal CAD by angiography in subjects with type 2 diabetes.<sup>50</sup> 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 do not prove – that while gemfibrozil together with a statin might have a risk of myositis about 1%, the risk will be significantly lower with fenofibrate.<sup>51</sup>

As a recent addition to the drugs that may be used for lowering LDL cholesterol, ezetimibe inhibits the absorption of intestinal cholesterol.

**Niacin.** Niacin, when used in pharmacologic doses has the ability to potently lower TG (25% to 40%) and raise HDL (10% to 25%). Niacin also lowers LDL, 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 AI. 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 FA 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 has rekindled interest for its potential in this population.<sup>52</sup> Results 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 type 2 diabetes.

People with insulin resistance have a characteristic dyslipidemia with an overproduction of VLDL and hypertriglyceridemia. Regulation of the hepatic assembly and secretion of apo B-lipoproteins has been investigated extensively for the past several decades and much is known

about how lipid substrates and insulin signaling regulate the formation and secretion of VLDL. New information about the molecules involved in both lipogenesis and the synthesis, degradation and association of apo B with hepatic and intestinal lipids may provide novel approaches to future therapies. Until then, diet, exercise, weight loss, and, when needed, pharmacotherapy should be used to correct dyslipidemia, which is a major contributor to the risk of CHD in patients with insulin resistance. ■

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- Wilson PW. Diabetes mellitus and coronary heart disease. *Am J Kidney Dis.* 1998;32:S89-100.
- Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarctions. *N Engl J Med.* 1998;339:229-234.
- Ginsberg HN. Lipoprotein physiology in nondiabetic and diabetic states: Relationship to atherogenesis. *Diabetes Care.* 1991;14:839-855.
- Taskinen MR. Diabetic dyslipidaemia: From basic research to clinical practice. *Diabetologia.* 2003;46:733-749.
- Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest.* 2000;106:453-458.
- Ginsberg HN. Lipoprotein Physiology. Chapter 1. In: *Endocrinology and Metabolism Clinics of North America.* Ed. Jeffrey Hoeg. W.B. Saunders Co. Philadelphia, Pa. 2002.
- Cooper, AD. Hepatic uptake of chylomicron remnants. *J Lipid Res.* 1997;38:2173-2192.
- Haidari M, Leung N, Mahbub F, et al. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. *J Biol Chem.* 2002;277:31646-31655.
- Merkel M, Eckel RH, Goldberg IJ. Lipoprotein lipase: genetics, lipid uptake, and regulation. *J Lipid Res.* 2002;43:1997-2006.
- Brunzell JD, Hazzard WR, Porte D Jr, Bierman EL. Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man. *J Clin Invest.* 1973;52:1578-1585.
- Bjorkregren J, Packard CJ, Hamsten A, et al. Accumulation of large very low density lipoprotein in plasma during intravenous infusion of a chylomicron-like triglyceride emulsion reflects competition for a common lipolytic pathway. *J Lipid Res.* 1996;37:76-86.
- Cohn JS, Patterson BW, Uffelman KD, et al. Rate of production of plasma and very-low-density lipoprotein (VLDL) apolipoprotein C-III is strongly related to the concentration and level of production of VLDL triglyceride in male subjects with different body weights and levels of insulin sensitivity. *J Clin Endocrinol Metab.* 2004;89:3949-3955.
- Zambon A, Bertocco S, Vitturi N, et al. Relevance of hepatic lipase to the metabolism of triacylglycerol-rich lipoproteins. *Biochem Soc Trans.* 2003;31:1070-1074.
- Streicher R, Kolzka J, Muller-Wieland D, et al. SREBP-1 mediates activation of the low density lipoprotein receptor promoter by insulin and insulin-like growth factor-I. *J Biol Chem.* 1996;271:7128-7133.
- Kissebah AH. Low density lipoprotein metabolism in non-insulin-dependent diabetes mellitus. *Diabetes Metabolism Rev.* 1987;3:619-651.
- Davis RA. Cell and molecular biology of the assembly and secretion of apolipoprotein B-containing lipoproteins by the liver. *Biochim Biophys Acta.* 1999;1440:1-31.
- Olofsson SO, Stillemark-Billton P, Asp L. Intracellular assembly of VLDL: two major steps in separate cell compartments. *Trends Cardiovasc Med.* 2000;10:338-345.
- Fisher EA, Ginsberg HN. Complexity in the secretory pathway: The assembly and secretion of apolipoprotein B-containing lipoproteins. *J Biol Chem.* 2002;277:17377-17380.
- Hussain MM, Iqbal J, Anwar K, et al. Microsomal triglyceride transfer protein: a multifunctional protein. *Front Biosci.* 2003;8:S500-506.
- Barter PJ, Nestel PJ. Precursors of plasma triglyceride fatty acids in obesity. *Metabolism.* 1973;22:779-783.
- Kissebah AH, Alfarsi S, Adams PW, et al. Role of insulin resistance in adipose tissue and liver in the pathogenesis of endogenous hypertriglyceridaemia in man. *Diabetologia.* 1976;12:563-571.
- Lewis GF. Fatty acid regulation of very low density lipoprotein production. *Curr Opin Lipidol.* 1999;10:475-477.
- Zhang Y, Ono-Hernandez A, Ko C, et al. Regulation of hepatic lipoprotein assembly and secretion by the availability of fatty acids. I: Differential responses to the delivery of fatty acids via albumin or remnant-like emulsion particles. *J Biol Chem.* 2004;279:19362-19374.
- Siri P, Candela N, Ko C, et al. Post-transcriptional stimulation of the assembly and secretion of triglyceride-rich apolipoprotein B lipoproteins in a mouse with selective deficiency of brown adipose tissue, obesity and insulin resistance. *J Biol Chem.* 2001;276:46064-46072.
- Taghibiglou C, Carpentier A, Van Iderstine SC, et al. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. *J Biol Chem.* 2000;275:8416-8425.
- Haemmerle G, Zimmermann R, Strauss JG, et al. Hormone-sensitive lipase deficiency in mice changes the plasma lipid profile by affecting the tissue-specific expression pattern of lipoprotein lipase in adipose tissue and muscle. *J Biol Chem.* 2002;277:12946-12952.
- Craig WY, Nutik R, Cooper AD. Regulation of apolipoprotein synthesis and secretion in the human hepatoma Hep G2. The effect of exogenous lipoprotein. *J Biol Chem.* 1988;263:13880-13890.
- Cohn JS, Wagner DA, Cohn SD, et al. Measurement of very low density and low density lipoprotein apolipoprotein (Apo) B-100 and high density lipoprotein Apo A-I production in human subjects using deuterated leucine. Effect of fasting and feeding. *J Clin Invest.* 1990;85:804-811.
- Diraison F, Moulin P, Beylot M. Contribution of hepatic de novo lipogenesis and reesterification of plasma non-esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease. *Diabetes Metab.* 2003;29:478-485.
- Schwarz JM, Linfoot P, Dare D, et al. Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoennergic diets. *Am J Clin Nutr.* 2003;77:43-50.
- Hellerstein MK. De novo lipogenesis in humans: metabolic and regulatory aspects. *Eur J Clin Nutr.* 1999;53(Suppl 1):S53-65.
- Horton JD, Goldstein JL and Brown MS. SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest.* 2002;109:1125-1131.
- Shimomura I, Matsuda M, Hammer RE, et al. Decreased IRS-2 and increased SREBP-1c lead to mixed insulin resistance and sensitivity in livers of lipodystrophic and ob/ob mice. *Mol Cell.* 2000;6:77-86.
- Matsusue K, Haluzik M, Lambert G, et al. Liver-specific disruption of PPARγ in leptin-deficient mice improves fatty liver but aggravates diabetic phenotypes. *J Clin Invest.* 2003;111:737-747.
- Sparks JD, Sparks CE. Insulin regulation of triacylglycerol-rich lipoprotein synthesis and secretion. *Biochim Biophys Acta.* 1994;1215:9-32.
- Taghibiglou C, Rashid-Kolvear F, Van Iderstine SC, et al. Hepatic very low density lipoprotein-ApoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. *J Biol Chem.* 2002;277:793-803.
- Pan M, Cederbaum AI, Zhang YL, et al. Lipid peroxidation and oxidant stress regulate hepatic apolipoprotein B degradation and VLDL production. *J Clin Invest.* 2004;113:1277-1288.
- Lewis GF, Uffelman KD, Szeto LW, Steiner G. Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals. *Diabetes.* 1993;42:833-842.
- Malmstrom R, Packard CJ, Caslake M, et al. Defective regulation of triglyceride metabolism by insulin in the liver in NIDDM. *Diabetologia.* 1997;40:454-462.
- Taghibiglou C, Rashid-Kolvear F, Van Iderstine SC, et al. Hepatic very low density lipoprotein-ApoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. *J Biol Chem.* 2002; 277:793-803.
- Bourgeois CS, Wiggins D, Hems R, Gibbons GF. VLDL output by hepatocytes from obese Zucker rats is resistant to the inhibitory effect of insulin. *Am J Physiol.* 1995;269(2 Pt 1):E208-215.
- Austin MA, Krauss RM. LDL density and atherosclerosis. *JAMA.* 1995;273:115.
- Horowitz BS, Goldberg IJ, Merab J, et al. Increased plasma and renal clearance of an exchangeable pool of apolipoprotein A-I in subjects with low levels of high density lipoprotein cholesterol. *J Clin Invest.* 1993;91:1743-1760.
- Howard BV. Diabetes and plasma lipoproteins in Native Americans. Studies of the Pima Indians. *Diabetes Care.* 1993;16:284-291.
- Ginsberg HN, Le NA, Gibson JC. Regulation of the production and catabolism of plasma low density lipoproteins in hypertriglyceridemic subjects. Effect of weight loss. *J Clin Invest.* 1985;75:614-623.
- Ginsberg HN, Plutzky J, Sobel BE. A review of metabolic and cardiovascular effects of oral antidiabetic agents: Beyond glucose lowering. *J Cardiovasc Risk.* 1999;6:337-347.
- Van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol.* 2003;23:1744-1749.
- Allmann SW, Davis HR Jr, Zhu LJ, et al. C1 Like 1 protein is critical for intestinal cholesterol absorption. *Science.* 2004;303:1201-1204.
- Rubins HB, Robbins SJ, Collins P, et al. For the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study group. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med.* 1999;341:410-418.
- Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: The Diabetes Atherosclerosis Intervention Study, a randomized study. *Lancet.* 2001;357:905-910.
- Ballantyne CM, Davidson MH. Possible differences between fibrates in pharmacokinetic interactions with statins. *Arch Intern Med.* 2003;163:2394-2395.
- Meyers CD, Kashyap ML. Management of the metabolic syndrome-nicotinic acid. *Endocrinol Metab Clin North Am.* 2004;33:557-575.