Pathophysiology of Diabetic Dyslipidemia

Tsutomu Hirano

Department of Medicine, Division of Diabetes, Metabolism, and Endocrinology, Showa University School of Medicine, Tokyo, Japan

积聚的临床证据表明，血清甘油三酯（TG）是导致动脉粥样硬化心血管疾病的主要预测因素，与低密度脂蛋白（LDL）胆固醇（C）在2型糖尿病患者中相当，这超过了糖化血红蛋白A1c的预测能力。动脉粥样硬化性糖尿病中，TG多脂蛋白（TRLs）升高，小而密的低密度脂蛋白（LDL）比例升高，高密度脂蛋白（HDL2-C）比例降低。中央血脂异常是TG多脂蛋白（TRLs）升高，其他血脂异常是代谢关联性升高的TRLs。胰岛素通过抑制肝脏VLDL的产生和刺激VLDL的代谢来调节血清VLDL水平。争议的是，过高的胰岛素水平是否与过量的VLDL产生有关。本研究介绍了实验和临床观察，揭示了胰岛素抵抗，而不是过高的胰岛素水平导致肝脏的VLDL产生。LDL和HDL是由不同大小和密度的脂蛋白组成的。apoB-depleted小而密的LDL和apoA-rich HDL2亚群特别受到胰岛素抵抗的影响，并且可以称为“代谢性LDL和HDL”。“代谢性LDL和HDL”。我们建立了直接测定小而密的LDL-C和小而密的HDL（HDL3-C）子群的方法。I将解释测量LDL和HDL子群的临床意义。糖尿病肾病（DKD）进一步恶化了血脂谱，从而增加了动脉粥样硬化风险。最后，我将简要地回顾DKD相关脂代谢的病理生理学，这是其他综述文章没有充分关注的。

**Key words:** Triglyceride-rich lipoproteins, Small dense LDL, HDL subspecies, Insulin resistance, Diabetes

**Introduction**

糖尿病是一种由高血糖引起的疾病，是糖尿病的主要风险因素。然而，严重高胆固醇血症在糖尿病患者中并不常见，而是动脉粥样硬化性心血管疾病（CVD）的主要风险因素。尽管如此，严重的高胆固醇血症在糖尿病和严重高密度脂蛋白（HDL-C）更常见。一个代表性的日本人群研究，2型糖尿病已经揭示了血清甘油三酯（TG）水平是预测CVD，相当的LDL-C，以及超过糖化血红蛋白A1c的预测能力。这种观察简单地意味着糖尿病性脂代谢比高血糖，即使在血糖水平明显升高的糖尿病患者中，更重要。因此，了解基于不足的胰岛素作用的病理生理学是重要的。

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vations. Hypertriglyceridemia is metabolically associated with a preponderance of small dense (sd) LDL particle and low HDL2-C levels. We established the direct assays for quantifying sdLDL-C and HDL3-C levels, respectively. I will discuss clinical relevance of measurements of sdLDL-C and HDL2-C levels. Diabetic kidney disease (DKD) are frequently developed in poor glycemic controlled diabetic patients, which further worsens the nature and degree of diabetic dyslipidemia. I will finally discuss the unique lipoprotein abnormalities in patients with DKD, which may partially explain substantial high incidence of CVD in these patients.

Mechanism of Hypertriglyceridemia in Diabetes

Hypertriglyceridemia is the most common serum lipid abnormality in diabetic populations. Serum TG levels are not simply elevated along with the degree of hyperglycemia, but hyperinsulinemia compensated by insulin resistance is closely correlated with TG levels[1]. TG consists of three molecules of fatty acids, the availability of circulating fatty acids (free fatty acids (FFA)) plays a crucial role in TG production in the liver[5, 6], and partly in the intestine[6, 7]. Reaven et al[1] proposed that three distinct syndromes of hypertriglyceridemia occur as a result of abnormalities of glucose metabolism. In patients with impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia increased VLDL-TG secretion. Patients with impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia increased VLDL-TG secretion. Patients with impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia increased VLDL-TG secretion. Patients with impaired glucose tolerance, the basic defect is postulated to be the loss of normal insulin sensitivity, leading to compensatory hyperinsulinemia increased VLDL-TG secretion.

Chylomicrons in Diabetes

Chylomicrons are temporarily produced in the small intestine after dietary fat ingestion. Abnormal increase in serum TG levels after meal is called postprandial hyperlipidemia[8], which is often observed in diabetic patients and reported to be associated with the incidence of CVD[9]. Chylomicron production is not only influenced by the amount of dietary fat but also by insulin resistance on enterocytes[10]. Similar to VLDL production in the liver, chylomicron production in the intestine is regulated by insulin and circulating FFA[11]. Lipoprotein lipase (LPL), which is attached to the luminal surface of vascular endothelium plays a major role in chylomicron removal by hydrolysing chylomicron-TGs[12]. LPL is upregulated by insulin, and conversely, insulin resistance diminishes LPL activity[13]. Severe chylomicronemia (so-called diabetic lipemia[14]) occasionally occurs in patients with insulin-depleted diabetes due to LPL deficiency. In type 2 diabetes with insulin resistance, chylomicron levels are often elevated by both overproduction and catabolic defect of chylomicrons[6, 7]. Increased secretion of apoC3 (an inhibitor of LPL) into plasma contributes to less efficient lipolysis of chylomicron-TGs[15]. Although about 80% of the increase in TGs after a fat-load meal comes from chylomicrons[16], approximately 80% of the increase in particle number is accounted for by VLDL particles containing apoB100[17]. Chylomicrons and VLDL particles are cleared from the circulation by common pathways and, therefore, compete for clearance[18]. For this reason, increased secretion of VLDL by the liver is an important predictor of postprandial accumulation of chylomicrons[19].

Intestinal Cholesterol Absorption

Cholesterol homeostasis in the body is tightly balanced by de novo biosynthesis, intestinal absorption, and biliary and fecal excretion. Niemann-Pick C1-Like 1 (NPC1L1) mediates intestinal cholesterol absorption and facilitates cholesterol transport through the liver, which is a molecular target of an agent for hypercholesterolemia (ezetimibe)[20]. Intestinal NPC1L1 expression was increased in patients with diabetes[21]. ATP binding cassette (ABC) proteins G5/G8 stimulate cholesterol excretion from the intestine. Reduced ABCG5/ G8 expression was observed in the intestine of diabetic patients[22]. Microsomal triglyceride transfer protein (MTP) is central to the formation of the chylomicron in the intestine. Intestinal MTP expression has been shown to increase in diabetes[23]. These abnormal gene expressions in the intestine are associated with high prevalence of hypercholesterolemia as well as hyperchylomicronemia.

Hepatic VLDL Production

Increased assembly and secretion of VLDL by the liver is not strictly regulated by the gene expression of apoB100, a central constitutive protein of VLDL particle, but post-transcriptional regulation of apoB
plays a crucial role. In the presence of low levels of hepatic lipids, much of the synthesized apoB is degraded intracellularly. When hepatic TG is increased, degradation of apoB is reduced, and VLDL production is facilitated. The major sources of fasting TG in the liver are 1) fatty acids derived from adipose tissue and enters into the liver, 2) fatty acids derived from chylomicron and VLDL remnants taken up by the liver, and 3) fatty acids produced by hepatic de novo lipogenesis (DNL). Among them, circulating FFA is the major source of VLDL-TG.

FFA

Insulin resistance is associated with reduced inhibition of hormone-sensitive lipase in adipose tissue by insulin, leading to increased lipolysis, and thereby augmented portal flux of FFA to the liver. Endoplasmic reticulum (ER) is a central organelle where apoB is degraded in the hepatocytes. FFA such as oleic acid-albumin complex rapidly enhances apoB secretion by hepatocytes because of the suppression of apoB degradation in ER. However, high doses of FFA for a long period inhibit apo B secretion in association with induction of ER stress, which induces steatohepatitis. FFA-induced VLDL-particle (apoB) secretion is not always associated with VLDL-TG secretion, suggesting FFA per se suppresses apoB degradation before being synthesized to TG. Cholesterol ester (CE) biosynthesis from FFA does not play a significant role in apoB degradation because changes in CE synthesis by free cholesterol or a statin did not affect the oleate-induced suppression of apoB degradation.

Fatty Acids Derived from Chylomicron and VLDL Remnants

Chylomicron and VLDL are received lipolysis and metabolized into its remnants. Remnants are quickly taken up by the liver and supply TGs to hepatocytes. Exogenous VLDL treatment stimulates apoB secretion in hepatocytes by supplying fatty acids for TG synthesis. However, the contribution of TRL remnants flux to newly produced VLDL-TG is estimated to be far small compared with that of FFA. In diabetes, the role of TRL remnant uptake in VLDL production is complex because insulin resistance increases serum concentrations of remnants, whereas it suppresses the particle uptake due to reduced activity of hepatic lipoprotein receptors.

Endogenous Fatty Acids

Hepatic DNL is mainly regulated by the transcription factor sterol response element binding protein-1c (SREBP-1c), and SREBP-1c regulates nearly all genes involved in fatty acids and TG synthesis in the liver. Increased DNL stimulates VLDL-TG secretion but, unlike FFA flux, increases in DNL are not associated with increase in VLDL particle number but enlarges VLDL particle size with enrichment of TG in a particle. DNL is stimulated by insulin via SREBP-1c and regulates the storage of hepatic TG. VLDL enlargement is also stimulated by high glucose via carbohydrate response element binding protein. DNL is stimulated by insulin through insulin receptor substrate 1 (IRS1); however, IRS-1 is not downregulated by hyperinsulinemia. Thus, DNL keeps work and contributes to produce VLDL-TG even though insulin resistance is developed. Insulin resistance may indirectly potentiate DNL by suppressing AMP-protein activated kinase which inhibits ATP consuming lipogenic processes. Nevertheless, the proportion of VLDL-TG production through DNL is minor, but majority of the proportion of hepatic VLDL-TG production is derived from circulating FFA. Therefore, VLDL-TG production should be reduced by hyperinsulinemia, such as insulin injection, via marked reduction in FFA flux into the liver. Similarly, patients with insulinoma are hyperinsulinemic but not hypertriglyceridemic.

Direct Effect of Insulin on VLDL Production

Insulin suppresses VLDL-TG production by reduction in FFA, but insulin could directly suppress VLDL production independent of substrate availability. Incubation of insulin suppresses VLDL secretion into the medium in hepatocytes. The suppressive effects of insulin on VLDL production requires phosphoinositide 3-kinase activity, a downstream of insulin signaling. MTP transfers neutral lipids to nascent apoB, which is a rate-limiting step in hepatic VLDL production. Insulin downregulates MTP expression via activation of the mitogen-activated protein kinase pathway and suppression of forkhead box protein O1 (FOXO1) phosphorylation. Thus, insulin resistance stimulates MTP activity and thereby enhances VLDL assembly. Lewis et al. demonstrated in humans that insulin infusion reduced VLDL-TG production under FFA clump by infusions of TG-emulsion and heparin. Interestingly, this direct suppressive effect of insulin on VLDL production was blunted in obese subjects with insulin resistance. Similar to exogenous insulin, sulfonylurea suppressed VLDL-TG production and reduced serum TG levels, suggesting that hyperinsulinemia suppresses VLDL secretion irrespective of the route of insulin delivery (portal or systemic). Conversely, hepatic VLDL-apo B secretion was increased in liver-specific insulin receptor knockout mice, a model of pure hepatic insulin resistance. These mice develop hyperinsulinemia, but their livers are unable to respond to it. Taken together, there is no evidence that hyper-
insulinemia directly stimulates VLDL secretion. However, one cannot deny a possibility that long-term hyperinsulinemia, for instance, by excess amount of insulin injections or sulfonylureas, causes massive obesity, which provides enough FFA to overcome the suppressive effect of insulin on VLDL production. In fact, we demonstrated that adiposity powerfully regulates VLDL-TG production in massive obese rats, which was independent of the degrees of hyperinsulinemia or insulin sensitivity.

VLDL Subspecies

VLDL particles are separated into two main classes: large TG-rich VLDL1 particles and smaller more dense VLDL2 particles. VLDL particle is either secreted from the liver as VLDL2 or further lipidated to form a mature, TG-rich VLDL (i.e., VLDL1). Insulin infusion has a greater effect on the secretion of VLDL-TGs than VLDL-apoB and suppresses mainly VLDL1-apoB production with little effect on VLDL2-apoB production. The reverse is true in the insulin-resistant state; VLDL1 production is preferentially increased without affecting VLDL2 production. Overproduction of VLDL1 particles is considered to be a central lipoprotein abnormality characterizing diabetic dyslipidemia, which promotes the generation of sdLDL particles and reduces HDL-C levels.

VLDL Catabolism

VLDL-TG removal is impaired in patients with type 2 diabetes, which promotes hypertriglyceridemia accompanied by an increase in secretion of VLDL. The removal defect is mainly caused by reduced activity of LPL, particularly in adipose tissue. Insulin is an activator of LPL, insulin deficiency or insulin resistance diminishes LPL activity. In addition, increased serum levels of apoC3 could also contribute to the decreased VLDL catabolism. ApoC3 deficient mice were hypotriglyceridemic by enhanced VLDL-TG removal, and never developed hypertriglyceridemia even if obesity or diabetes were induced. Insulin sup-

**Fig. 1.** Pathogenesis of insulin resistance on VLDL overproduction and its related changes in other lipoproteins.

Hepatic VLDL1 production is stimulated by insulin resistance, which is a central lipoprotein abnormality in diabetic dyslipidemia. The major sources of triglyceride (TG) in the liver are 1) free fatty acid (FFA) derived from adipose, 2) fatty acids derived from remnants of TRL (VLDL and chylomicron), and 3) de Novo Lipogenesis (DNL). Newly synthesized TG suppress intracellular apoB degradation. Insulin resistance is associated with reduced inhibition of hormone-sensitive lipase in adipose tissue, thereby augmented portal flux of FFA. TG synthesis from FFA or FFA per se strongly inhibits apoB degradation in the liver, thereby stimulates VLDL production. Hepatic uptake of TG-rich lipoprotein (TRL) remnants and DNL supply TG in the liver, but the contribution of these two factors to suppress apoB degradation are minor. Insulin resistance suppresses phosphoinositide (PI) 3-kinase mediated apoB degradation and enhances the action of microsomal triglyceride transfer protein (MTP), a rate-limiting factor of VLDL assembly. In the insulin-resistant state, VLDL1 production is preferentially increased without affecting VLDL2 production. Overproduction of VLDL1 is metabolically associated with preponderance of small dense LDL and reduced large cholesterol-rich HDL2.
are believed to be atherogenic lipoproteins. Nakajima et al. established the immune absorption assay for remnant-like particle (RLP)-C by using monoclonal antibodies to apoA-1 and apoB100. This assay was initially made as an assay for apoB48 containing chylomicron remnants, but it was disclosed that apo B100 containing VLDL particles were also measurable.

RLP-C is highly correlated with plasma TG levels, and subjects with metabolic syndrome and type 2 diabetes have higher levels. ApoB48 concentration, a constitutive protein of chylomicrons, represents particle number of chylomicrons. It remains unknown whether apoB48 is an independent risk factor of CVD upon classical lipid parameters. It is of note that RLP-C concentrations are only 1/20 of LDL-C, and apoB48 concentrations are only 1/200 of apoB100. Therefore, it is no doubt that LDL is the most powerful atherogenic lipoprotein in blood circulation, but remnants could become a leading cause for CVD in special cases, such as Type III dyslipidemia or end-stage kidney diseases where remnants are substantially elevated while LDL-C is reduced.

Unlike nephrotic syndrome or hypothyroidism, diabetes is not a representative disease exhibiting severe hypercholesterolemia. However, LDL-C is the best predictor of CVD, and LDL lowering by statin treatments dramatically reduced the incidence of CVD in diabetes populations. Why do LDL-C concentrations are only 1/20 of LDL-C, and apoB48 concentrations are only 1/200 of apoB100. Therefore, it is no doubt that LDL is the most powerful atherogenic lipoprotein in blood circulation, but remnants could become a leading cause for CVD in special cases, such as Type III dyslipidemia or end-stage kidney diseases where remnants are substantially elevated while LDL-C is reduced.

**The Effect of Pioglitazone on VLDL Metabolism**

Pioglitazone, a peroxisome proliferator-activated receptor (PPAR) gamma agonist, is an agent for the amelioration of insulin resistance, which might be an appropriate tool to study the relationship between insulin resistance and lipid metabolism. Pioglitazone has shown to improve TG and HDL-C levels and favorable effects on LDL particle size. We examined the effect of pioglitazone on VLDL-TG metabolism in rats with severe insulin resistance. Pioglitazone normalized TG levels by enhancing VLDL-TG removal from the circulation. Pioglitazone activated serum LPL activity and LPL production in adipose tissues in insulin-resistant mice. Unexpectedly, pioglitazone did not suppress VLDL-TG overproduction. Nagashima et al. reported the same results in patients with type 2 diabetes. They found that apoC3 production was suppressed by pioglitazone, which resulted in increasing LPL activity. These results suggest that this insulin sensitizer does not necessarily ameliorate all abnormal lipid metabolism associated with insulin resistance.

**Remnant Lipoproteins**

Chylomicron and VLDL are received lipolysis with LPL and metabolized into its remnants. Remnants are cholesterol-enriched particles, and their size is small enough to penetrate the vessel wall. Therefore, these are believed to be atherogenic lipoproteins. Nakajima et al. established the immune absorption assay for remnant-like particle (RLP)-C by using monoclonal antibodies to apoA-1 and apoB100. This assay was initially made as an assay for apoB48 containing chylomicron remnants, but it was disclosed that apo B100 containing VLDL particles were also measurable.

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**SdLDL**

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**Table 1.** Distinct role of insulin vs. insulin resistance in major abnormalities of VLDL metabolism

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<th>Metabolic abnormalities</th>
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<td>FFA flux into the liver</td>
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<td>Intracellular degradation of apoB</td>
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hypertriglyceridemia, such as chylomicronemia, have only modest increase in CVD risk75). This suggests that measurement of LDL particle size is not sufficient to predict CVD, but the number of LDL particles should be taken account for evaluating the overall risk. We established a direct method for the quantification of sdLDL-C, which is applicable to the auto-analyzer76). This method quantifies only cholesterol in LDL particles of density between 1.044 and 1.063 g/L. Our assay has been employed in many large cohort studies 77, 78) and has revealed that sdLDL-C is a potent predictor of CVD beyond LDL-C. SdLDL-C levels are increased with either levels of TG or LDL-C, and remarkably increased in the combined hyperlipidemia (Type  régime)79).

As shown in Fig. 3, sdLDL-C levels corresponding to LDL-C levels were constantly higher in patients with diabetes or coronary artery diseases than in healthy controls80). SdLDL-C levels are highly (r = 0.94) correlated with sdLDL-apoB levels81), suggesting that measuring sdLDL-C is sufficient to estimate the number of sdLDL particles. The preponderance of sdLDL particle would be an essential mechanism for explaining a high incidence of CVD in diabetes.

**HDL Heterogeneity**

Low HDL-C levels have been an independent

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**Fig. 2.** Overproduction of TG-rich lipoproteins creates small dense LDL.

Production of VLDL and chylomicrons (TG-rich lipoproteins (TRLs)) is stimulated in individuals with type 2 diabetes. The long residence time of TRLs in circulation promotes excessive transfer of TG to LDL and a concomitant transfer of cholesteryl esters (CE) to TRLs via the action of cholesteryl ester transfer protein (CETP). Hepatic TG lipase-mediated hydrolysis of core TG produces cholesterol-poor LDL particles (small dense LDL).
Patients with type 1 diabetes treated with insulin had higher HDL2-C than type 2 diabetes, and insulin-treated type 2 diabetes had higher HDL2-C levels than non-insulin-treated type 2 diabetes. These results suggest that exogenous insulin increases HDL2-C, and conversely insulin resistance blunts the raising effect of insulin on HDL2-C levels. Similar to sdLDL, HDL2-C would be “Metabolic HDL.” HDL function could be causally associated with CVD; thus recent studies have focused more on HDL function than on HDL-C levels. Cholesterol efflux capacity is a key metric of the anti-atherosclerotic functionality of HDL. Cholesterol efflux capacity was decreased in HDL obtained from subjects with metabolic syndrome and diabetes. Hyperglycemia-induced advanced glycation end products, oxidative stress, and low-grade inflammation are possible mechanisms for promoting HDL dysfunction.

**Influence of Diabetic Kidney Disease (DKD)**

It is well known that the incidence of CVD becomes substantially elevated with the progression of DKD. Plasma lipid profiles change substantially as the
DKD advances. Overt proteinuria/hypoaalbuminemia markedly increases LDL-C, and kidney dysfunction increases remnants and decreases HDL-C. We found that patients with DKD exhibited remarkable post-prandial hypertriglyceridemia and hyper-apoB48, a marker of chylomicrons. Hypertriglyceridemia was developed even in early stage of DKD. We studied a possible mechanism behind the hypertriglyceridemia in early stage of DKD. Plasma von Willebrand factor (vWF) is widely used as a surrogate marker for vascular endothelial damage. VWF was significantly elevated in albuminuric diabetes, whereas it remained normal in nondiabetic patients with kidney disease. These results suggest that albuminuria in diabetes implies not only kidney damage but also widespread vascular endothelial damage. Microalbuminuric diabetic patients had lower heparin-releasable LPL mass and higher vWF levels, and the LPL mass was inversely related to vWF. We speculate that the generalized endothelial damage decreases the functional LPL mass anchored on the endothelium, which is reflected by increased plasma vWF levels.

ApoC1 and apoC3 are inhibitors of the lipolysis and particle uptake of TRLs. Especially TRL-apoC3 levels were significantly elevated in both diabetic and nondiabetic CKD. The molecular mechanisms of upregulation of apoC3 remain unknown; however, we found that PPAR-alpha gene expression was remarkably diminished in animal model of CKD. PPAR-alpha is a target molecule of TG-lowering agent, fibrates, and inversely regulates the production of apoC3. Hepatic TG lipase, a key enzyme for hydrolysis of intermediate-density lipoprotein (IDL), is markedly decreased in advanced CKD irrespective of nondiabetes or diabetes, which may explain the substantial increase of remnant lipoproteins. ApoA5 has been the focus of significant attention as a potential modulator of plasma TG in spite of its very low plasma concentration. Measured apoA5 levels were markedly reduced in both diabetic and nondiabetic HD patients, suggesting that reduced apoA5 might play an important role in the development of hypertriglyceridemia in some HD populations. Angiopoietin-like 4 has been considered a candidate molecule by which hypertriglyceridemia is developed in nephrotic syndrome. It remains to be determined whether angiopoietin-like 4 plays a pivotal role in the development of dyslipidemia associated with DKD.

Conclusion

Diabetes is a disease of insulin which strictly regulates both glucose and lipid metabolism. The effect of insulin on TRL metabolism is a key for understanding diabetic dyslipidemia. FFA/TRL/sdLDL particle is an atherogenic axis. In addition, the progression of DKD should be taken into account as an exacerbated factor for diabetic dyslipidemia. I wish this review helps to understand the pathophysiology of lipid abnormalities, a leading cause of CVD in diabetes populations.

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Conflicts of Interests

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