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Review

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Pathophysiology of Diabetic Dyslipidemia

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Accumulating clinical evidence has suggested serum triglyceride (TG) is a leading predictor of atherosclerotic cardiovascular disease, comparable to low-density lipoprotein (LDL)-cholesterol (C) in populations with type 2 diabetes, which exceeds the predictive power of hemoglobinA1c. Atherogenic dyslipidemia in diabetes consists of elevated serum concentrations of TG-rich lipoproteins (TRLs), a high prevalence of small dense low-density lipoprotein (LDL), and low concentrations of cholesterol-rich high-density lipoprotein (HDL)2-C. A central lipoprotein abnormality is an increase in large TG-rich very-low-density lipoprotein (VLDL)1, and other lipoprotein abnormalities are metabolically linked to increased TRLs. Insulin critically regulates serum VLDL concentrations by suppressing hepatic VLDL production and stimulating VLDL removal by activation of lipoprotein lipase. It is still debated whether hyperinsulinemia compensatory for insulin resistance is causally associated with the overproduction of VLDL. This review introduces experimental and clinical observations revealing that insulin resistance, but not hyperinsulinemia stimulates hepatic VLDL production. LDL and HDL consist of heterogeneous particles with different size and density. Cholesterol-depleted small dense LDL and cholesterol-rich HDL2 subspecies are particularly affected by insulin resistance and can be named "Metabolic LDL and HDL," respectively. We established the direct assays for quantifying small dense LDL-C and small dense HDL(HDL3)-C, respectively. Subtracting HDL3-C from HDL-C gives HDL2-C. I will explain clinical relevance of measurements of LDL and HDL subspecies determined by our assays. Diabetic kidney disease (DKD) substantially worsens plasma lipid profile thereby potentiated atherogenic risk. Finally, I briefly overview pathophysiology of dyslipidemia associated with DKD, which has not been so much taken up by other review articles.

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

Introduction

Diabetes is a disease of hyperglycemia due to deficiency of insulin actions, but serum lipids are also strongly affected by insulin. Serum lipid abnormalities (dyslipidemia) are commonly seen in diabetic populations irrespective of insulin deficiency or insulin resistance[1, 2]. It is no doubt that low-density lipoprotein (LDL)-cholesterol (C) is the most important risk factor for atherosclerotic cardiovascular disease (CVD) such as coronary artery diseases. However, severe hypercholesterolemia is not frequently observed in diabetic populations, rather hypertriglyceridemia and low high-density lipoprotein (HDL-C) are more common. A representative cohort study for Japanese populations with type 2 diabetic has revealed that the serum triglyceride (TG) levels are a leading predictor of CVD, comparable to LDL-C, which exceeded the predictive power of hemoglobinA1c[3]. This observation simply implies that dyslipidemia is more powerful CVD risk than hyperglycemia even in diabetic populations whose blood glucose levels are substantially high. Thus, it is important to understand the pathophysiology of dyslipidemia based on the deficiency of insulin action. This review will firstly discuss the mechanisms of hypertriglyceridemia, a central lipid abnormality in diabetes. It is still matter of debate whether hyperinsulinemia compensatory for insulin resistance is causally associated with the overproduction of very-low-density lipoprotein (VLDL). I will explain the distinct role of insulin and insulin resistance in TG-rich lipoprotein (TRL) metabolism based on basic and clinical obser-

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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[4]. 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 type 2 diabetes have relative insulin deficiency, and the elevated FFA levels increase hepatic VLDL-TG secretion. In absolute insulin-deficient patients with type 1 diabetes, however, elevated FFA levels do not stimulate hepatic VLDL-TG secretion because the livers cannot respond to the increased FFA flux under severe insulin deficiency. The hypertriglyceridemia in patients with type 1 diabetes is primarily due to defect in the removal of VLDL-TG. This proposal provides important fundamental knowledge for understanding diabetic hypertriglyceridemia. However, one point remains questionable: Does hyperinsulinemia increase hepatic VLDL production? I will discuss this important issue later.

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[21]. 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[21]. 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[22]. In the presence of low levels of hepatic lipids, much of the synthesized apoB is degraded intracellularly[22, 23]. When hepatic TG is increased, degradation of apoB is reduced, and VLDL production is facilitated[23]. 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[24].

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 organellar where apoB is degraded in the hepatocytes[25]. FFA such as oleic acid-albumin complex rapidly enhances apo B secretion by hepatocytes because of the suppression of apoB degradation in ER[22, 26]. However, high doses of FFA for a long period inhibit apo B secretion in association with induction of ER stress, which induces steatohepatitis[27]. 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[28]. 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[29].

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[30]. However, the contribution of TRL remnants flux to newly produced VLDL-TG is estimated to be far small compared with that of FFA[24]. 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[31].

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[32]. 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[33]. 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 responsive element binding protein[34]. DNL is stimulated by insulin through insulin receptor substrate 1 (IRS1); however, IRS-1 is not downregulated by hyperinsulinemia[35]. 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[36]. 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[37]. 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[38].

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[39-41]. The suppressive effects of insulin on VLDL production requires phosphoinositide 3-kinase activity, a downstream of insulin signaling[41]. 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[42] and suppression of forkhead box protein O1 (FOXO1) phosphorylation[43]. Thus, insulin resistance stimulates MTP activity and thereby enhances VLDL assembly. Lewis *et al.*[5] 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[5]. Similar to exogenous insulin, sulfonylurea suppressed VLDL-TG production and reduced serum TG levels[44], 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[45]. Taken together, there is no evidence that hyper-

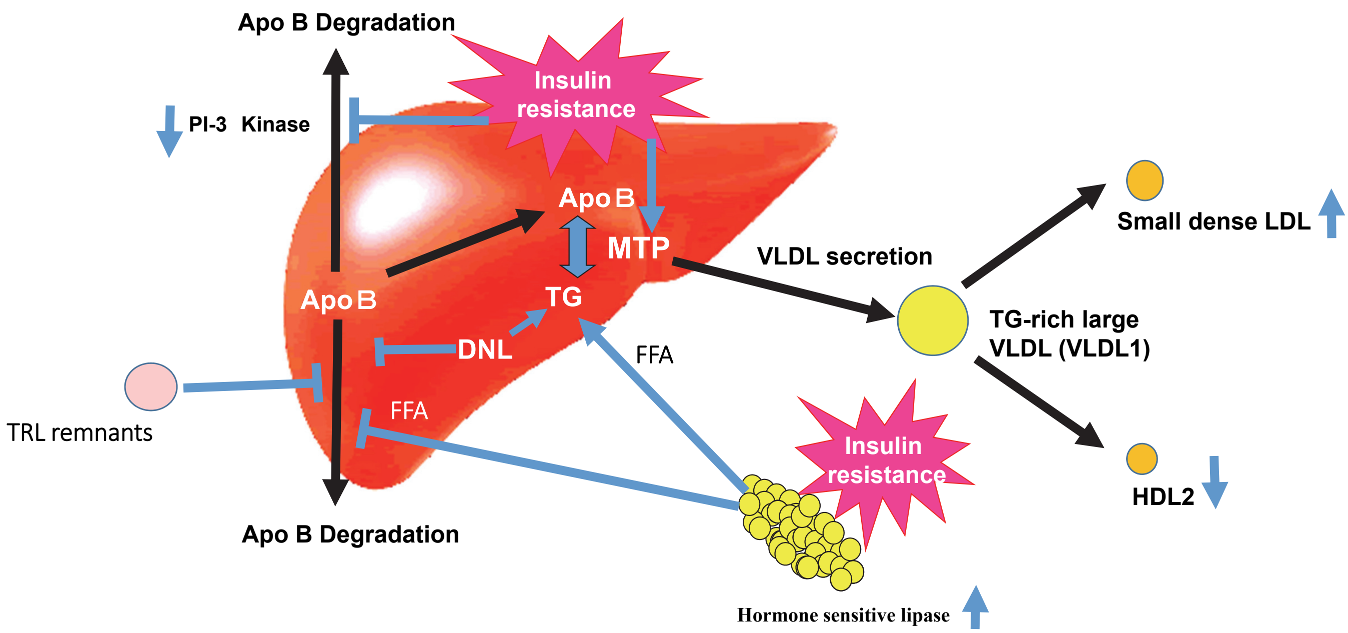

Fig. 1. Pathogenesis of insulin resistance on VLDL overproduction and its related changes in other lipoproteins.

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 inhibit 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.

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[46].

VLDL Subspecies

VLDL particles are separated into two main classes: large TG-rich VLDL1 particles and smaller more dense VLDL2 particles[47]. VLDL particle is either secreted from the liver as VLDL2 or further lipidated to form a mature, TG-rich VLDL (i.e., VLDL1)[36, 48]. 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[49]. The reverse is true in the insulin-resistant state; VLDL1 production is preferentially increased without affecting VLDL2 production[50]. 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[51]. Fig. 1 depicts the pathogenesis of insulin resistance on VLDL overproduction and its related changes in other lipoproteins.

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[13]. Since 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[52, 53]. ApoC3 deficient mice were hypotriglyceridemic by enhanced VLDL-TG removal, and never developed hypertriglyceridemia even if obesity[54] or diabetes[55] were induced. Insulin sup-

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

Metabolic abnormalities	insulin	Insulin resistance	VLDL metabolism
FFA flux into the liver	↓	↑	Increase VLDL secretion
Intracellular degradation of apoB	↑	↓	Increase VLDL secretion
de novo lipogenesis (DNL)	↑	↑ indirect	Enlarge VLDL particle size
Microsomal triglyceride transfer protein (MTP)	↓	↑	Stimulate VLDL assembly
Lipoprotein lipase (LPL)	↑	↓	Decrease VLDL catabolism
Apolipoprotein C3	↓	↑	Decrease VLDL catabolism

presses apoC3 expression in the liver through downregulation of FOXO1[56]. Insulin resistance conversely stimulates apoC3 production by FOXO1 activation. ApoA5[57] and angiopoietin-like proteins[58] play an important role in regulating LPL activity and thereby TRL catabolism. It remains largely unknown how insulin/ insulin resistance affects these key molecules affecting TRL catabolism. Table 1 lists the comparison of insulin versus insulin resistance on major metabolic abnormalities of VLDLs.

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[59]. We examined the effect of pioglitazone on VLDL-TG metabolism in rats with severe insulin resistance[60]. 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[61]. Unexpectedly, pioglitazone did not suppress VLDL-TG overproduction. Nagashima *et al.*[62] 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[63]. 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[64]. RLP-C is highly correlated with plasma TG levels, and subjects with metabolic syndrome and type 2 diabetes have higher levels[65]. 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.

SdLDL

Unlike nephrotic syndrome or hypothyroidism, diabetes is not a representative disease exhibiting severe hypercholesterolemia. However, LDL-C is the best predictor of CVD[66], and LDL lowering by statin treatments dramatically reduced the incidence of CVD in diabetes populations[67]. Why do LDL-C concentrations strongly affect CVD outcomes in diabetic patients. This is because the nature of LDL particles in diabetic patients are changed to more atherogenic than those in nondiabetic patients. LDL particles are not created equally[68]. Austin and Krauss discovered that individuals with small sized LDL particles (pattern B) had substantially higher prevalence of CVD than those with large-buoyant LDL particles (pattern A) determined by the gel electrophoresis[69]. SdLDL particles are thought to be more atherogenic than large-buoyant LDL parti-

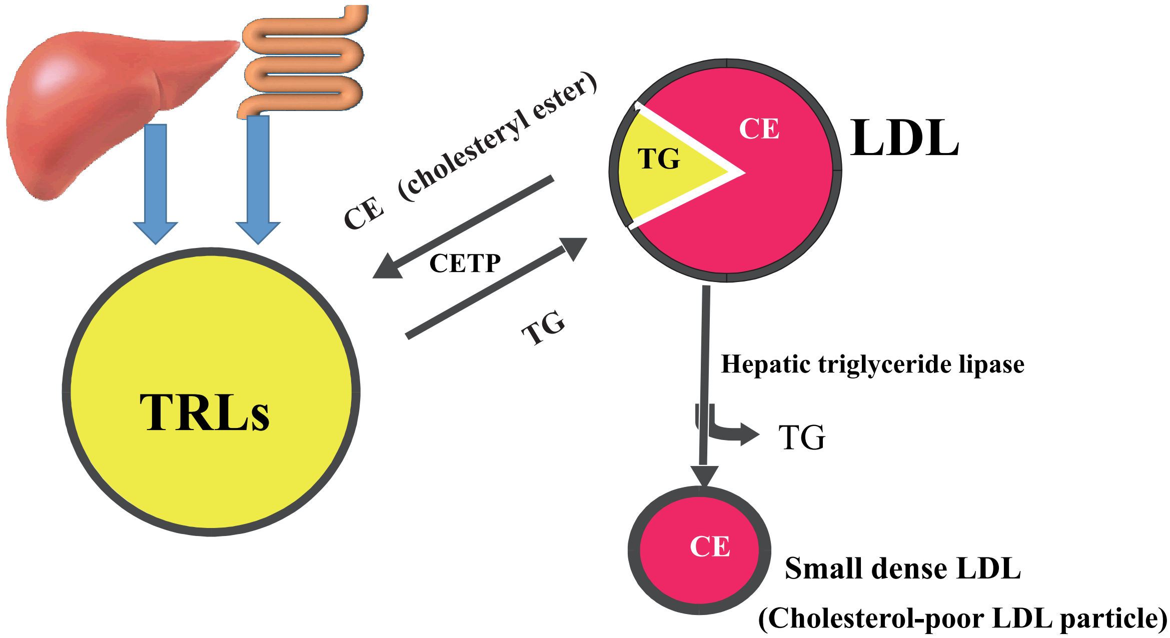

Fig. 2. Overproduction of TG-rich lipoproteins creates small dense LDL.

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).

cles as a result of their better penetration of the arterial wall, lower binding affinity for the LDL receptor, longer plasma half-life, and weaker resistance to oxidative stress[70]. Several studies have reported a 2- to 3-fold increase in the risk of CVD in patients with pattern B LDL particles[69, 71]. LDL size became smaller, and the incidence of the pattern B were higher in diabetic patients[70]. The formation of sdLDL is closely associated with insulin resistance and hypertriglyceridemia[70], and VLDL1-TG level is the major predictor of LDL size[48, 51, 70]. The mechanisms for formation of sdLDL are estimated as follows: 1) Cholesteryl ester transfer protein (CETP) facilitates the transfer of TGs from TRLs to LDL, 2) the resulting TG-rich LDL is a preferred substrate for hepatic lipase; and 3) increased lipolysis of TG-rich LDL results in the formation of cholesterol-poor LDL, that is, sdLDL[72] (**Fig. 2**). In metabolic syndrome, LDL-C levels are usually normal, but LDL particle size becomes small and the number of LDL particles is increased[73]. Abdominal fat volume measured by CT scan was positively associated with sdLDL-C but inversely associated with large-buoyant LDL-C[74]. Therefore, we can call sdLDL as "Metabolic LDL."

LDL size is negatively regulated by serum TG levels, and LDL size is significantly reduced in hypertriglyceridemic subjects. However, individuals with severe hypertriglyceridemia, such as chylomicronemia, have only modest increase in CVD risk[75]. 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-analyzer[76]. 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 IIb)[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 controls[80]. SdLDL-C levels are highly ($r = 0.94$) correlated with sdLDL-apoB levels[81], 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

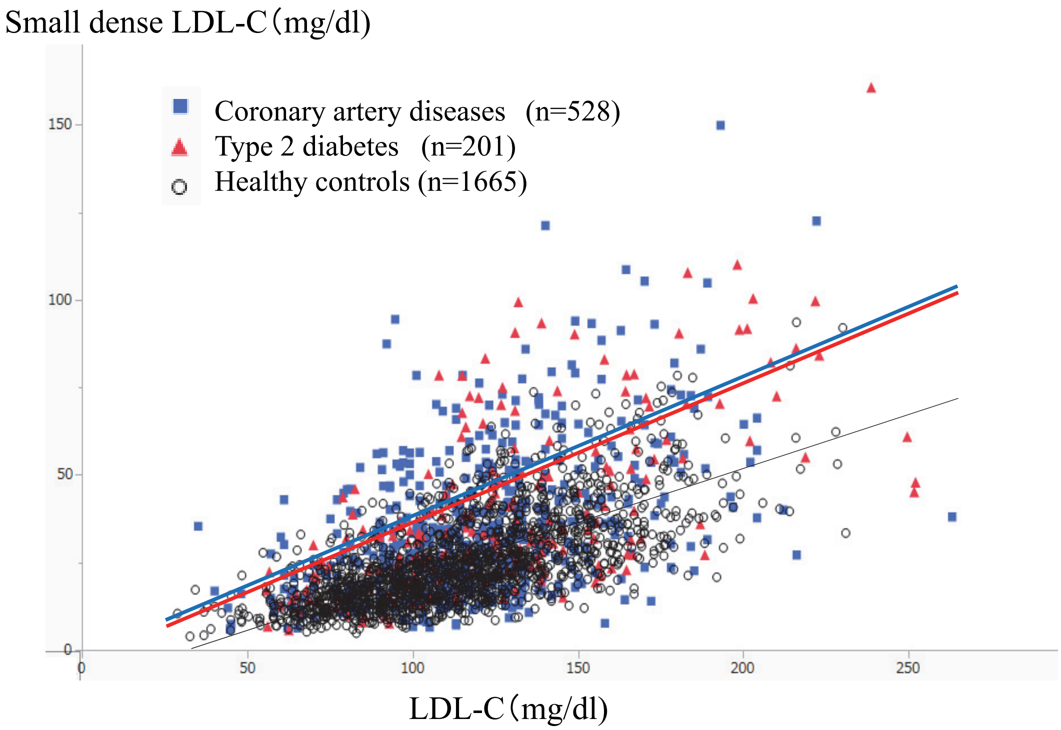

Fig. 3. Relationship between LDL-C and small dense LDL-C concentrations in healthy controls, patients with type 2 diabetes without coronary heart diseases (CAD), and patients with CAD including diabetes.

SdLDL-C levels corresponding to LDL-C levels are higher in patients with diabetes or CAD than in healthy controls. This figure is made based on our original data published in reference (80).

predictor of CVD. Hence, increased HDL levels may protect against the development of CVD because of the ability of HDL to mediate reverse cholesterol transport from peripheral tissues, such as large vessels to the liver. However, therapeutic interventions aimed at increasing plasma HDL-C (niacin and CETP inhibitors) have failed to show efficacy in outcome trials[82, 83]. Furthermore, human genetic variants associated with HDL-C levels have failed to support the causal role of HDL-C in the pathology of CVD[84]. Nonetheless, it is no doubt that low HDL-C is a sensitive biomarker for CVD. HDL has subspecies, namely HDL2 and HDL3. Large, cholesterol-rich HDL2 is inversely associated with serum TG levels and insulin resistance, whereas small, cholesterol-poor HDL3 is not[85]. We established a homogeneous assay for the direct measurement of cholesterol in HDL3[86]. Subtracting HDL3-C from HDL-C gives HDL2-C. We found that HDL2-C was more closely inversely correlated than HDL-C with body weight, fasting glucose and insulin, 2 h glucose, index of insulin resistance, and C-reactive protein, whereas HDL3-C was not correlated with these factors[87]. Okazaki *et al*. also reported that large HDL-C levels were inversely associated with visceral fat area[74]. 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[88]. 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[89]; 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[90]. Hyperglycemia-induced advanced glycation end products, oxidative stress, and low-grade inflammation are possible mechanisms for promoting HDL dysfunction[90].

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/hypoalbuminemia markedly increases LDL-C, and kidney dysfunction increases remnants and decreases HDL-C[91]. We found that patients with DKD exhibited remarkable postprandial hypertriglyceridemia and hyper-apoB48, a marker of chylomicrons[92]. Hypertriglyceridemia was developed even in early stage of DKD[91]. 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[93]. 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[94]. 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[95]. 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[96]. 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[97], 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[98]. Measured apoA5 levels were markedly reduced in both diabetic and nondiabetic HD patients[99], 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[100]. 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

Tsutomu Hirano has received clinical research grants from Denka Seiken, AstraZeneka, MSD, and Takeda Pharmaceutical Co., and has received lecture honoraria from Kowa Pharmaceutical Co, AstraZeneka, MSD, and Takeda Pharmaceutical Co. The funding agencies had no role in the preparation of the manuscript.

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