Review

New insights into the pathophysiology of dyslipidemia in type 2 diabetes

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ABSTRACT

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality for patients with type 2 diabetes, despite recent significant advances in management strategies to lessen CVD risk factors. A major cause is the atherogenic dyslipidemia, which consists of elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol. The different components of diabetic dyslipidemia are not isolated abnormalities but closely linked to each other metabolically. The underlying disturbances are hepatic overproduction and delayed clearance of TRLs. Recent results have unequivocally shown that triglyceride-rich lipoproteins and their remnants are atherogenic. To develop novel strategies for the prevention and treatment of dyslipidaemia, it is essential to understand the pathophysiology of dyslipoproteinaemia in humans. Here, we review recent advances in our understanding of the pathophysiology of diabetic dyslipidemia.

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1. Introduction

In recent decades, the world has seen an unprecedented rise in the prevalence of diabetes, and it is predicted that the number of people with type 2 diabetes will increase from about 350 million today to 592 million by 2035 [1,2]. Between 2010 and 2030, the number of adults with diabetes is expected to increase by 20% in developed countries and by 69% in developing countries [3,4]. These escalating rates of diabetes worldwide represent a heavy disease burden at the population and individual level as well as for the total health care system.

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality for patients with type 2 diabetes, despite recent significant advances in management strategies to lessen CVD risk factors [5]. It has been estimated that diabetes will shorten the life of a 50-year-old person by on average six years, and about 58% of this effect is due to increased vascular disease [6]. The difference in CVD risk between individuals with and without diabetes has narrowed substantially in recent decades, but strong associations between diabetes and vascular outcomes remain [7–9]. Recent data indicate that diabetes per se increases CVD risk about two-fold on average but the risk varies widely depending on the population [10]. Importantly, those with diabetes and coronary heart disease are at substantially higher risk of future CVD events [6,11,12].

The excess CVD risk in individuals with diabetes is due to several risk factors including both unmodifiable factors (age, gender and genetics) and traditional risk factors such as hypertension, lipids, hyperglycemia and smoking. The overall cardiometabolic risk is driven by a complex interplay between these factors and the components of the metabolic syndrome commonly associated with type 2 diabetes. A major cause is the atherogenic dyslipidemia, which consists of elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol. Importantly, statins fail to adequately correct these features of dyslipidemia and several recent trials have failed

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to show benefits from fibrates or niacin when added to statins [13,14]. This review aims to summarize recent advances in our understanding of the pathophysiology of diabetic dyslipidemia.

1.1. Prevalence of dyslipidemia in type 2 diabetes

Lipid abnormalities are common in people with Type 2 diabetes but the prevalence varies between different populations, the presence of the metabolic syndrome and the variable definition of the cut off levels for serum triglycerides [15,16]. The Botnia study reported the prevalence of dyslipidemia (TG > 1.7 mmol/L and HDL chol < 0.9 mmol/L in men and <1.15 mmol/L in women) to be 54% in men and 56% in women [17]. In the FIELD study about 38% of recruited subjects had both high triglycerides (>1.7 mmol/L) and low HDL cholesterol (<1.03 mmol/L in men and <1.29 mmol/L in women) [18]. A large population based registry of 75,048 patients with type 2 diabetes in Sweden reported that about 37–38% had elevated triglycerides (>1.7 mmol/L but < 4.0 mmol/L) with or without low HDL cholesterol [19]. Recent studies have consistently reported high prevalence (about 35–50%) of dyslipidemia also in T2D subjects treated with statins leaving the subjects at high residual risk [20–22].

2. Disturbed metabolism of triglyceride-rich lipoproteins in diabetes

2.1. Distribution of TRL species

Plasma TRLs are a mixture of lipoprotein species characterized by different densities and apoprotein composition and are derived either from the intestine (chylomicrons) or the liver [very low-density lipoprotein (VLDL)]. TRLs consist of a core of neutral lipids (mainly triglycerides but also some cholesteryl esters) surrounded by a monolayer of phospholipids, free cholesterol and proteins. Each TRL particle contains one molecule of apolipoprotein B (apoB) [23–25]. ApoB exists in two forms, apoB100 and apoB48, which are coded by the same gene. ApoB48, which is formed in the intestine, is present on chylomicrons and chylomicron remnants, whereas apoB100 exists on VLDL, intermediate-density lipoprotein (IDL) and LDL.

Dietary lipids are hydrolyzed in the intestinal lumen and products are taken up by enterocytes (reviewed in Ref. [26]). The lipids are assembled into chylomicron particles using apoB48 as a scaffolding protein. Chylomicrons are secreted into lymphatic vessels originating in the villi of the small intestine. They enter into the bloodstream at the thoracic duct's connection with the left subclavian vein. Alternatively, dietary lipids are stored in the cytosol as lipid droplets [26,27]. The cytosolic lipid droplets are subsequently mobilized and secreted during fasting state in enterocytes. Mobilization involves hydrolysis of triglycerides, mobilization of FFAs to the endoplasmic reticulum (ER), and resynthesis of triglycerides at the ER and subsequent secretion with lipoproteins. Their accumulation may provide a mechanism for the storage of fat during meal consumption and to mobilize it at a later time. The mobilization of fat from these stores might contribute to plasma triglyceride increases seen just before the digestion of food [28]. In addition to chylomicrons, recent studies indicate that HDL assembly and secretion by the intestine also plays a role in lipid absorption [26,29].

VLDL particles are commonly separated into two main classes: large triglyceride-rich VLDL$_1$ particles [Svedberg flotation rate (Sf) 60–400] and smaller more dense VLDL$_2$ particles (Sf 20–60). Large VLDL$_1$ particles seem to be the major determinant for the variation of plasma triglycerides between healthy subjects and individuals with type 2 diabetes, and we have reported that the concentration

of VLDL$_1$ particles is markedly increased in type 2 diabetic subjects [30]. Once in the circulation, VLDL is exposed to lipoprotein lipase (LPL), which catalyzes the removal of triglycerides from VLDL for storage or energy production in adipose tissue, cardiac muscle and skeletal muscle. When triglycerides are removed from large VLDL$_1$ particles via LPL-mediated lipolysis, their density increases and they become VLDL$_2$ particles. The activity of LPL determines the residence time of circulating VLDL$_1$ and VLDL$_2$ particles.

ApoB48- and apoB100-containing particles are cleared from the circulation by common pathways and, therefore, compete for clearance [31]. Increased secretion of VLDL from the liver is an important predictor of postprandial accumulation of chylomicrons and chylomicron remnants [32]. Thus, the serum triglyceride concentration reflects the balance between the secretion and removal of TRLs.

2.2. Disturbed metabolism of intestinal TRLs in type 2 diabetes

The human intestine efficiently absorbs dietary fat predominantly in the form of triglycerides. After eating a meal, triglycerides are hydrolyzed by lipase to yield fatty acids, which are then absorbed into the enterocytes and: (1) used for synthesis of cholesteryl esters or phospholipids; (2) oxidized; (3) re-esterified to form triglycerides for incorporation into chylomicrons; or (4) stored as triglycerides in cytoplasmic lipid droplets. The multistep assembly of chylomicrons within the enterocyte is not as well characterized as the assembly process of VLDL in the liver, but it is presumed that these processes are similar and dependent on the microsomal triglyceride transfer protein (MTTP) for lipidation of apoB [28,33–36].

In humans, insulin acutely inhibits the production rate of apoB48 and secretion of chylomicrons [36]. It has also been speculated that chronic intestinal overproduction of apoB48 may package intestinal fat more efficiently and contribute significantly to both liver lipids and postprandial lipemia [36–38]. Although about 80% of the increase in triglycerides after a fat-load meal comes from apoB48-containing lipoproteins [39], approximately 80% of the increase in particle number is accounted for by apoB100-containing VLDL particles [40]. Recent findings have further expanded our understanding of the regulation of chylomicron particle secretion by the human intestine (reviewed in Ref. [38]). In addition to ingested lipid, which remains the major regulator of chylomicron secretion [28], a number of systemic and luminal factors have been shown to regulate intestinal lipoprotein secretion [38]. The intestinally derived incretin hormone GLP-1 may directly, in addition to indirectly through modulation of pancreatic hormones, inhibit chylomicron secretion [41]. DPP-4 inhibitors suppress chylomicron production, predominantly by a GLP-1 effect [38]. Another intestinal hormone GLP-2 may not stimulate chylomicron synthesis per se; instead, it may promote rapid release of preformed and stored chylomicron particles from the enterocytes [42,43]. Enteral glucose and fructose promote lipid-induced chylomicron production [44]. The polyphenol resveratrol [45] is capable of suppressing chylomicron particle production. Intestinal cholesterol and bile acid metabolism [38,46] and gut microbiota modulate lipid homeostasis [47]; however, their potential roles in mediating intestinal lipoprotein secretion remain less identified.

2.3. Regulators of VLDL synthesis and secretion

Recently we reported that overproduction of large VLDL$_1$ particles is a key factor determining the concentration of serum triglycerides in subjects with type 2 diabetes [48]. The increased secretion of VLDL$_1$ particles is due to the overproduction of both VLDL$_1$-triglyceride and VLDL$_1$-apoB resulting in an increased

number of VLDL$_1$ particles that are similar in size and composition to those of non-diabetic subjects. The available data suggest that hepatic lipid metabolism is severely dysregulated in type 2 diabetes [49–52].

2.4. Dysregulation of triglyceride synthesis in type 2 diabetes

Hepatic lipid homeostasis is regulated by the balance between the import and export of lipids, and an imbalance between these processes leads to increased VLDL secretion or lipid accumulation in hepatocytes as seen in non-alcoholic fatty liver disease (NAFLD), a common finding in subjects with type 2 diabetes [48,53–56]. The secretion of VLDL has been extensively studied but mainly in cultured hepatoma cell lines and primary hepatocytes from animals. The synthesis and secretion of VLDL particles is dependent on substrate availability (i.e., triglyceride and apoB100) and is regulated by insulin and other hormones [57–60]. It should be recognized that triglycerides in hepatocytes and in VLDL particles are derived from multiple processes including triglyceride synthesis from FFA re-esterification, de novo lipogenesis (DNL) and uptake of remnant particles (Fig. 1) [61].

The dynamics of FFA metabolism play a critical role in triglyceride synthesis in hepatocytes and also in the pathogenesis of liver fat accumulation [62–67]. Importantly, the contribution of visceral lipolysis to the FFA pool increases as a function of visceral fat volume, averaging about 30–45% of FFA uptake in the postprandial phase [68,69]. Furthermore, upper-body subcutaneous fat is the dominant contributor to circulating FFAs and the source of the excess FFA release in upper-body obesity [70]. Fatty acid transport proteins (FATPs) and CD36 transporters regulate the cellular uptake and intracellular trafficking of fatty acids and also the formation of fatty acyl-CoAs [71]. Notably the FA sources for the liver fat and released VLDL particles are closely similar [72]. Overall the delivery of FFAs from the adipose tissue depots is increased in obesity and type 2 diabetes.

2.5. Genetic susceptibility to developing NAFLD

Genetic susceptibility is a significant contributor to NAFLD [73–75] and the group by Hobbs and coworkers have made critical advances in this field. First they identified a missense variant in patatin-like phospholipase domain-containing 3 (*PNPLA3*) that is strongly associated with hepatic triglyceride content [76]. Subsequent genome-wide association studies (GWAS) found other common SNPs associated with liver fat content [77,78], including two sequence variants in *PNPLA3* (rs738409 and rs2281135) and one in *TM6SF2* (rs58542926) [79]. The precise function of PNPLA3 is unclear, but it appears to be involved with acylglycerol synthesis and also hydrolysis [80]. Neither ablation nor overexpression of wild-type PNPLA3 affects liver fat content in mice [81], whereas hepatic overexpression of the human 148M transgene causes steatosis [82]. These data indicate that physiological expression of PNPLA3 148M variant causes NAFLD, and that the accumulation of catalytically inactive PNPLA3 on the surfaces of lipid droplets is associated with the accumulation of TG in the liver [82]. Interestingly, the PNPLA3 148M has also been shown to promote intracellular lipid accumulation in the liver by reducing the lipidation of VLDL [83].

Two common (SNPs) in the promoter region of the APOC3 gene have also been associated with the occurrence of NAFLD [84]. However, subsequent studies in Hispanic, European American, African American and European subjects have failed to confirm the association of APOC3 variants and with NAFLD [85–88]. A meta-analysis of combined GWAS datasets identified four other SNPs associated with liver fat content and other aspects of the NAFLD

phenotype [77]. These were localized in or near the genes neurocan (NCAN, SNP rs2228603), protein phosphatase 1, regulatory (inhibitor) subunit 3B (PPP1R3B, SNP rs4240624), glucokinase regulator (GCKR, SNP rs780094) and lysophospholipase-like 1 (LYPLAL1, SNP rs12137855) [77].

2.6. Dysregulation of DNL in hepatocytes in type 2 diabetes

Elevated de novo lipogenesis (DNL) [89] (i.e., the process by which acetyl-CoA, an intermediate stage in the metabolism of simple sugar, is converted to fatty acids) is increasingly recognized as an important contributor to hepatic triacylglycerol concentrations in NAFLD [72,90] and other states of insulin resistance [89,91–93], thus igniting clinical interest in DNL as a potential therapeutic target [61,94,95]. DNL allows conversion of carbohydrates to fatty acids through an interplay between glycolysis, biosynthesis of saturated fatty acids and their desaturation mediated by stearoyl-CoA desaturase (SCD)-1, re-esterification into triacylglycerols and packaging into VLDL particles to export triglycerides. The pathways are dependent on nutritional status and regulated by several transcription factors and nuclear receptors under hormonal and genetic control [96–100]. Sterol regulatory element binding protein 1 (SREBP1) and carbohydrate element binding protein (ChREBP) are master regulators of DNL driving the upregulation of regulatory enzymes: acetyl CoA carboxylase (ACC), fatty acid synthase (FAS), SCD and elongation of very long-chain fatty acids protein 6 (Elovl6). As SREBP-1 is activated by insulin and ChREBP by glucose, hyperinsulinemia together with hyperglycemia will promote DNL as SREBP-1 and ChREBP act synergistically to stimulate DNL (Fig. 2) [98].

FAS is the rate-limiting enzyme for DNL; it acts as a house keeper protein for energy balance as it lies at the cross step of FFA partitioning to oxidation and different lipid pathways (Fig. 3) [101]. FAS is regulated by both nutrients (including glucose and dietary fat) and hormones. Nutrient excess is associated with elevated levels of insulin, which are known to stimulate FAS. In contrast, dietary fats suppress FAS expression leading to decreased DNL [101]. Interestingly, FAS action is also linked to activation of the peroxisome proliferator-activated receptor (PPAR)α pathway regulating fatty acid oxidation in mitochondria in the liver [101].

2.7. The coordinate control of DNL, elongation, and desaturation

There is evidence to suggest that DNL-derived fatty acids, mainly palmitate (16:0) and oleate (18:0), are preferentially channeled into pathways of elongation and desaturation in hepatocytes
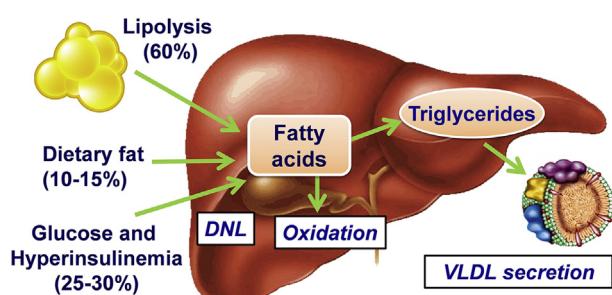

Fig. 1. Contributions of various metabolic pathways to liver steatosis in humans. Reductions in fatty acid oxidation and triglyceride export seem to have only minor roles in hepatic triglyceride deposition. By contrast, the increased availability of fatty acids from the adipose tissue through unabated lipolysis and de novo lipogenesis (DNL) from glucose are major providers of lipids in steatotic livers. Figure modified from Ferre P and Foutelle F [98].

[102]. The enzyme SCD1 is rate-limiting in the desaturation of palmitate and oleate to monounsaturated palmitoleic acid (16:1) and oleic acid (18:1), which are key substrates for the formation of triglycerides [103]. Interestingly, there is parallel upregulation of expression of genes involved in DNL and in fatty acid elongation and desaturation, suggesting coordinated control of expression. Therefore, the fatty acid ratios 16:1/16:0 and 18:1/18:0 have been used as a surrogate marker for DNL [104]. Lee et al. have also proposed that VLDL-TG 16:1n-7 M percentage functions as a biomarker for elevated liver fat when isotope use is not feasible [105]. Thus, along with quantitative contributions to liver TGs [72], the DNL pathway has qualitative implications whereby the principal fatty acid products of DNL are saturated [106], which can have negative consequences on cellular functions such as insulin signaling [107].

SCD1-deficient mice are lean and protected from diet-induced obesity and insulin resistance, but it is somewhat counterintuitive for the reduction of unsaturated fatty acids to be beneficial. Moreover, 16:1 n-7, a product of *scd1* action, has been proposed to act as a beneficial 'lipokine' in an animal model [108]. Furthermore, *scd1* deficiency is associated with cellular stress and therefore SCD1 has been referred to as a 'double-edged sword' [109]. In humans, high SCD1 activity has been reported with insulin resistance, fatty liver, the metabolic syndrome and type 2 diabetes [110]. However, the reported data on SCD1 activity in fatty liver disease are conflicting and need further investigation [111–113].

2.8. Contribution of DNL to liver fat and postprandial TRL particles

Although the contribution of DNL to liver fat is trivial (about 5%) in healthy subjects, its contribution in NAFLD increases to up to 15–25% [72]. Recently the significant contribution of DNL to fat in hepatocytes in NAFLD has been demonstrated in humans [114]. Our recent data suggest that augmented fasting and postprandial DNL associate with decrease in rate of lipid oxidation and accumulation of postprandial TRL particles [115]. The rate of DNL was not related to liver fat and could therefore not direct palmitate to intracellular TG. The imbalance between hepatic TG production and oxidation was closely linked to aberrant TRL metabolism, which contributes to postprandial dyslipidemia and predisposes to CVD. Thus, these data indicate that DNL also contributes to lipids in postprandial TRL particles [115]. Furthermore, the contribution of DNL to liver fat may have been overlooked and needs to be re-evaluated in particular when it comes to diabetes where the co-existence of hyperinsulinemia and hyperglycemia would synergistically promote DNL [116].

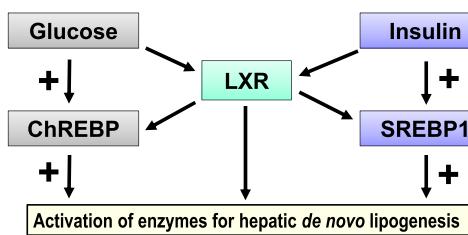Emerging data indicate that increased DNL leads to the accumulation of lipid metabolites, including diacylglycerol (DAG). DAG is an important branch point in glycerolipid synthesis, because it can be further acylated by sn-1,2-diacylglycerol acyltransferase (DGAT) to form triacylglycerol, or phosphoethanolamine or phosphocholine head groups can be added to form phosphatidylethanolamine and phosphatidylcholine, respectively [117,118]. DAG activates protein kinase C (PKC) isoforms, which have been shown to phosphorylate serine residues in insulin receptor substrate (IRS)-1/2, thereby inhibiting insulin signal transduction leading to hepatic insulin resistance and ultimately further increasing hepatic glucose production [94,119,120].

The DGAT2 activity seems to be critical for channeling DAGs produced by the DNL pathway into VLDL assembly and secretion [121]. This metabolic routing is proposed to favor the accumulation of "good" fat and prevent accumulation of lipotoxic species (DAGs, ceramides) [122]. Ceramides are lipid species that act as metabolic modulators in several processes including oxidative stress, inflammation and apoptosis coupled with insulin resistance. Interestingly, recent observations have confirmed that DAG concentrations in human liver biopsy specimens correlate with parameters of hepatic insulin sensitivity in obese subjects with NAFLD [123].

2.9. Assembly and secretion of VLDL particles

The disposal of lipids from the liver is maintained by secretion of triglyceride-rich VLDL [124]. The formation of VLDL in the liver is a complex and highly regulated process (Fig. 4). It starts with the synthesis of apoB100 in the endoplasmic reticulum of the cell [125]. ApoB100 co-translationally associates with lipids to form partially lipidated nascent VLDL particles [126]. These are further lipidated to triglyceride-poor VLDL$_2$ particles by the action of MTTP, which catalyzes the transfer of triglycerides, cholesteryl ester, and phosphatidylcholine from membranes to the nascent VLDL particle [33,34,125,127–129]. The VLDL$_2$ particles are either secreted from the cell or act as precursors to larger, triglyceride-rich VLDL$_1$ particles [57,130]. The conversion of VLDL$_2$ to VLDL$_1$ requires a bulk addition of triglycerides and thus differs from the stepwise lipidation of apoB100 to form the partially lipidated precursor VLDL particles [130,131].
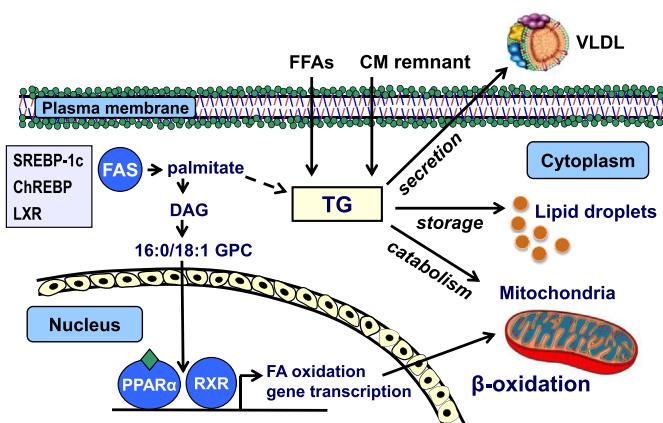
Fig. 2. The disturbed metabolic setting in diabetes involves activation of transcription factors enhancing DNL in the liver. The pathway activity for lipogenesis is coordinated by key transcription factors; sterol regulatory element binding protein 1 (SREBP-1), carbohydrate response element binding protein (ChREBP), and liver X receptor (LXR). SREBP-1 and ChREBP are master regulators of lipogenesis driving the upregulation of regulatory enzymes. As SREBP-1 is activated by insulin and ChREBP by glucose, hyperinsulinemia together with hyperglycemia will promote hepatic DNL and consequently VLDL production.

Fig. 3. FAS as a regulator of hepatic triglyceride metabolism. Fatty acid synthase controls fatty acid catabolism through the synthesis of a ligand for PPARα, which activates fatty acid oxidation genes. FAS makes a minor contribution of lipids to stored and secreted triglycerides, with the major contributions coming from plasma FFAs and dietary fats from chylomicron remnants. 16:0/18:1 GPC, 16:0/18:1-glycerophosphocholine; DAG, diacylglycerol; FAS, fatty acid synthase; FFA, free fatty acid; PPARα, peroxisome proliferator-activated receptor alpha; RXR, retinoid X receptor; TG, triglyceride; VLDL, very low-density lipoprotein. Figure modified from Jensen-Urstad APL et al. [101].

The formation of VLDL is highly regulated by the availability of lipids: if apoB100 fails to be lipidated and is incorrectly folded it will be sorted to posttranslational degradation [34,59,132]. Degradation of apoB100 is accomplished by both proteasomal and non-proteasomal pathways and each pathway is regulated by one or more metabolic factors [133–140]. Studies indicate that the fatty acids used for the biosynthesis of VLDL-triglycerides are derived from triglycerides stored in cytosolic lipid droplets [131,141–143]. However, it is still unclear how the lipid droplets are added to the VLDL core lipids [131,144–147], but it has been shown that the formation of cytoplasmic lipid droplets requires MTTP [148] and apoCIII.

2.10. Intracellular roles of apoC-III for VLDL secretion

ApoC-III is a small protein and a component of VLDL and HDL particles. In a series of publications, Yao and coworkers have unraveled an intracellular role of apo-CIII in promoting hepatic $VLDL_1$ secretion [144,149,150]. Feeding *apoCIII* deficient mice with a high fat diet failed to stimulate $VLDL_1$ production *in vivo*. In contrast, reconstitution of apoC-III expression using adenovirus encoding human apoC-III resulted in robust formation and secretion of $VLDL_1$ particles. The stimulatory effect of human apoC-III on the assembly and secretion of $VLDL_1$ was recapitulated ex vivo in McA-RH7777 cells cultured in lipid-rich media [151]. Metabolic labeling experiments have shown that apoCIII also plays a central role in the formation of cytosolic lipid droplets, and in promoting bulk triglyceride incorporation during $VLDL_1$ assembly [149]. Structure–function analysis of naturally occurring apoC-III variants (Ala23Thr and Lys58Glu) has defined two functional domains that play respective roles in lipid droplet formation and $VLDL_1$ assembly [152,153].

Since the formation of VLDL is regulated by the availability of hepatic lipids, it is not surprising that hepatic lipid accumulation is linked to overproduction of large $VLDL_1$ particles [48]. The most common form of liver steatosis is NAFLD [154,155]. This is related to insulin resistance and type 2 diabetes, and probably explains (at least partly) the dyslipidaemia that is observed in subjects with insulin resistance and type 2 diabetes [156–159].

2.11. Mechanisms leading to overproduction of VLDL in type 2 diabetes

As discussed above, insulin promotes lipogenesis, hyper-triglyceridemia and hepatic steatosis [61,160]. It has long been a mystery how these pathways remain insulin-responsive in type 2 diabetes when insulin-dependent regulation of glucose metabolism is impaired. To explain the elevation in plasma and tissue lipids, investigators have suggested the presence of pathway-selective insulin resistance [61,160,161]. In this model, insulin signaling to glucose metabolism is impaired, but insulin signaling to lipid metabolism is intact. Results from several groups have clarified at a molecular level how type 2 diabetes drives VLDL secretion through multiple pathways, identifying several control points and signaling events that are major targets for insulin action in hepatocytes [57,59–61]. Thus, insulin fails to suppress lipolysis in the adipose tissue and FoxO1 activity in the liver [162], but is still able to activate mammalian target of rapamycin complex 1 (mTORC1) [163,164]. The disinhibition of FoxO1 leads to increased expression of MTTP and apoCIII, thereby promoting VLDL formation (Fig. 5) [59,165]. At the same time, the stimulation of mTORC1 in the liver leads to the activation of SREBP-1c and increased lipogenesis and also to the suppression of sortilin [166]. Because sortilin increases apoB degradation, the suppression of sortilin further promotes apoB secretion [167]. Finally, the increased DNL, coupled
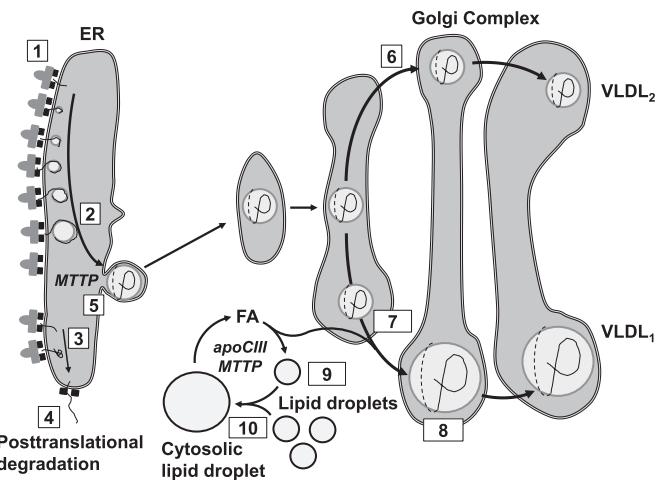

Fig. 4. Assembly and secretion of apoB100-containing lipoproteins. ApoB is synthe-sized and translocated into the lumen of the endoplasmic reticulum (ER) (1). The growing apoB molecule is co-translationally lipidated by MTTP to form the primordial VLDL particle (pre-VLDL) (2). Alternatively, apoB fails to be lipidated and is incorrectly folded (3) and sorted to proteasomal degradation (4). Late in the ER compartment, the pre-VLDL particle is converted to a triglyceride-poor $VLDL_2$ particle (5). The $VLDL_2$ particle is either transported through the secretory pathway and then secreted (6), or further lipidated (7) to form a triglyceride-rich VLDL ($VLDL_1$) particle, which is then secreted (8). The formation of triglyceride-rich VLDL is highly dependent on the accumulation of triglycerides in cytosolic lipid droplets. These lipid droplets are formed as small primordial droplets from microsomal membranes (9) and increase in size by fusion (10). The triglycerides within the droplets undergo lipolysis and are re-esterified before they lipidate the triglyceride-poor $VLDL_2$ to form triglyceride-rich $VLDL_1$. ApoCIII and MTTP play a central role in the formation of cytosolic lipid drop-lets, and in promoting bulk triglyceride incorporation during $VLDL_1$ assembly.

with increased flux of FFAs to the liver, expands the cytoplasmic pool of triglycerides available to lipidate apoB [168], thus, driving the formation of large triglyceride-rich $VLDL_1$. The overall result is an increased secretion of apoB in the form of $VLDL_1$ particles in type 2 diabetes. Thus, the increased level of plasma triglycerides in type 2 diabetes is achieved mainly by an increased $VLDL_1$-triglyceride pool that is the effect of an increased number of particles rather than an increased particle size [125,169].

The molecular mechanisms in pathway-selective insulin resis-tance are still unclear and further studies are needed to delineate the mechanisms involved, including the role of NAD(P)H oxidase 4 (NOX4) as inhibition of NOX4 in cultured hepatocytes seems to recapitulate the entire complicated pattern of pathway-selective insulin resistance [160].

2.12. Impaired suppression of $VLDL_1$ secretion by insulin is associated with NAFLD and insulin resistance

We and others have proposed that a physiological action of in-sulin is to directly suppress production of large VLDL particles in the liver in analogy to the suppression of glucose production [170–173]. We have demonstrated that this action of insulin is defective in subjects with type 2 diabetes resulting in the over-production of large $VLDL_1$ particles [55,171]. This fundamental defect of acute insulin action on $VLDL_1$ production has been demonstrated also in obese insulin-resistant subjects [62,174] as well as in those with high liver fat (NAFLD) [55,175]. Interestingly, this impaired action of insulin to downregulate VLDL secretion is observed to precede the development of hepatic suppression of endogenous glucose production in obese men [176]. This finding suggests that this defect is an early phenomenon in the develop-ment of hepatic insulin resistance and dysregulation of hepatic lipid metabolism. Interestingly, data from animal studies suggest

that loss of the inhibitory action of insulin on apoB100 secretion may be the initial step leading to the hypersecretion of VLDL particles [57]. Although liver fat, visceral fat, glucose, insulin and HOMA-IR index correlated with VLDL production rate in a univariate analysis, only hepatic fat and glucose content remained significant in multivariate analyses [169]. These observations strongly suggest that liver fat content and hyperglycemia seem to be the driving forces of the overproduction of VLDL$_1$ particles in people with type 2 diabetes.

2.13. Lipid export from the liver

The amount of hepatic triglycerides is controlled by the export pathways that dispose triglycerides either by lipid oxidation and/or secretion of VLDL particles. If these pathways are not able to compensate for an excess synthesis of hepatic triglycerides, the lipids will be packed in lipid droplets [177]. Physiologically, the liver does not serve as a storage place for fat and, therefore, the export pathways are critical to prevent net lipid accumulation in hepatocytes when lipid input is increased. Thus, β-oxidation and VLDL output serve as tools to cope with lipid overload in hepatocytes and to alleviate the lipotoxicity associated with excess DAG and ceramides.

2.14. Fatty acid oxidation

The partition of fatty acids between esterification and β-oxidation is a critical step in hepatic lipid metabolism and is controlled by nutritional status, insulin and other hormones [178]. The critical branching point is the formation of acetyl-Co-A that can be channeled to either esterification or β-oxidation in mitochondria. Interestingly, increased DNL leads to a decreased rate of β-oxidation since malonyl-CoA (produced during the DNL) inhibits the activity of carnitine palmitoyltransferase (CPT1). The carnitine palmitoyltransferase system is an essential step in the β-oxidation of long-chain fatty acids. This transfer system is necessary because, while fatty acids are activated (in the form of a thioester linkage to co-enzyme A) on the outer mitochondrial membrane, the activated fatty acids must be oxidized within the mitochondrial matrix. Unlike short- and medium-chain fatty acids, long-chain fatty acids such as palmitoyl-CoA cannot freely diffuse through the mitochondrial inner membrane, and require a shuttle system to be transported to the mitochondrial matrix [179]. Thus, malonyl-CoA acts like a molecular switch between fatty acid synthesis and

oxidation, explaining why increased DNL decreases the rate of β-oxidation by reducing fatty acid entry to mitochondria.

Mitochondrial β-oxidation is coupled with energy production and generation of ketone bodies [180]. Fatty acid oxidation is regulated by various PPARs but PPARα seems to be a master regulator of fatty acid β-oxidation [97]. PPARα upregulates several genes involved in the mitochondrial fatty acid oxidation. Importantly, PGC-1α, a co-activator of PPARα, enhances lipid oxidation through complex processes including SIRT1 and hepatic Lipin-1 as well mTORC-1 [71,178,181–183]. Potential mechanisms that may upregulate mitochondrial fatty acid oxidation include high FFA concentrations and increased concentrations of fibroblast growth factor 21 (FGF21), leptin and interleukin 6 (IL-6) via activation of PPARα [184,185]. FGF21 has been recently identified as a hepatokine that is upregulated in liver during fasting [186]. As FGF21 plays a significant role in both glucose and lipid metabolism, it has rapidly gained interest as a metabolic regulator of energy balance by modulating lipid oxidation [178,187]. Interestingly, FGF21 has been reported to associate with carotid atherosclerosis in a recent cohort study [188], and to improve dyslipidemia in obese subjects with type 2 diabetes [189]. Thus, FGF21 has emerged as a novel regulator of hepatic lipid metabolism [190–193].

3. Regulation of TRL clearance

The clearance of TRLs from the circulation is a complex process and includes both the hydrolysis of triglycerides and removal of remnant particles by the liver. After secretion of TRLs from the intestine and liver, triglycerides are removed from the lipoproteins by LPL allowing the delivery of FFAs to muscle and adipose tissue. The key regulator of LPL activity is insulin, which stimulates the expression of LPL in endothelial cells [194]. Interestingly, insulin deficiency in mice leads to increased triglyceride levels and defective removal of postprandial triglycerides, indicating that significant hypertriglyceridemia in insulin-dependent diabetes is primarily because of changes in lipolysis and not changes in hepatic insulin signaling [195]. LPL is also regulated also by several apoproteins including apoCII, apoCIII, angiopoietin-like 3 (ANGPTL-3) and ANGPTL-4 [196]. Much interest has focused on apoCIII since it is elevated in type 2 diabetic subjects and correlates with serum triglyceride levels (Fig. 6) [30,197–199].

As triglycerides are removed and density increases [194], chylomicrons become chylomicron remnants, and large triglyceride-rich VLDL$_1$ particles become smaller VLDL$_2$ and subsequently IDL. IDL can be further hydrolyzed by hepatic lipase to LDL, which is catabolized mainly by hepatic uptake of LDL through LDL receptors. Since the TRLs contain a substantial amount of cholesteryl esters, the smaller remnant particles formed by triglyceride hydrolysis are enriched in cholesteryl esters [194]. Because of their size, most remnant particles cannot cross the endothelium as efficiently as smaller LDL particles [200]. However, since remnant particles contain approximately 40 times higher levels of cholesteryl esters per particle compared with LDL [200], elevated levels of remnants may lead to accelerated atherosclerosis and CVD [201,202].

Remnant-like particles (RLP) can be isolated from serum samples by the immune adsorption method with monoclonal antibodies to apoAI and apoB [203], and measurement of fasting RLP-cholesterol may be used as a surrogate to estimate circulating remnant particles [204]. In a subset of 1567 women from the Framingham Heart study, RLP-cholesterol was independently associated with prevalent coronary artery disease (CAD) [205]. Furthermore, high levels of RLP-cholesterol were predictive for future events independently of other risk factors in a Japanese population with CAD [206]. Importantly, we found a strong correlation between RLP-cholesterol and VLDL$_1$-triglyceride in type 2
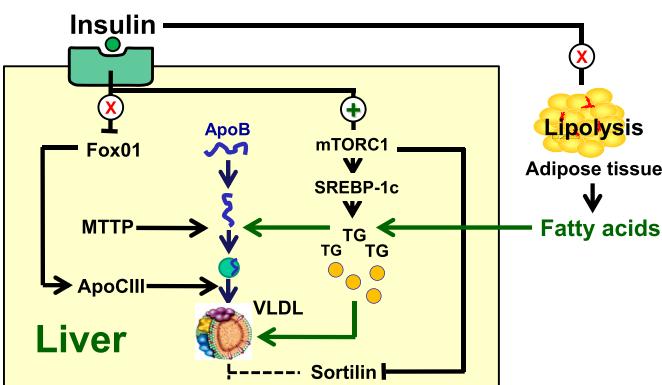

Fig. 5. Regulation of VLDL secretion by insulin signaling. Type 2 diabetes is characterized by selective insulin resistance: insulin fails to suppress lipolysis in the adipose tissue and FoxO1 in the liver leading to increased fatty acid flux and increased expression of MTTP and apoCIII, thereby promoting apoB secretion. The stimulation of mTORC1 activity leads to activation of SREBP-1c and enhanced DNL. The overall result is VLDL overproduction. Figure modified from Haas et al. [59].

diabetes (Fig. 7).

3.1. Genetic evidence for a causative role of remnant particles for developing CVD

Thus, these and other studies have suggested that raised concentrations of triglycerides and remnant cholesterol predispose an individual to cardiovascular disease. However, large-scale evidence for this has been lacking [202], but it is now clarified that lifelong raised triglycerides and remnant cholesterol are causally associated with low-grade inflammation, cardiovascular disease, and all-cause mortality [207–211]. A doubling of genetically raised remnant cholesterol concentrations due to *APOA5* genetic variants was associated with a 2.2-times increased risk of myocardial infarction [208]. With use of genetic variants in *LPL*, a 1 mmol/L increase in triglycerides was shown to associate with a 2.0-times increased risk of all-cause mortality [210]. Genome-wide association studies (GWAS) have likewise contributed information that suggests a causal association between raised triglycerides and cardiovascular disease [212,213]. Taken together, genetic studies strongly support the theory that high concentrations of triglyceride-rich lipoproteins or remnant cholesterol are causal risk factors for cardiovascular disease and all-cause mortality, and that low HDL cholesterol is probably an innocent bystander. Low HDL cholesterol might merely be a long-term marker of raised triglycerides and remnant cholesterol, similar to raised HbA1c concentrations that mark long-term, raised glucose concentrations [214]. Or perhaps, HDL cholesterol might be a marker of cardiovascular health but is non-causal in the process.

The importance of postprandial lipoproteins for the development of atherosclerosis was initially proposed by Moreton in 1947 who wrote "the lipid particles must be assumed to be retained and deposited from the plasma-derived nutrient lymph stream which normally passes from the lumen through the intramural structures toward the adventitial venules and lymphatics. It may be theorized that the increased particle size of the lipids in sustained or alimentary hyperlipemia is the stimulus to the phagocytosis in the intima by macrophages and the formation of the typical foam cells" [215,216]. It is now clear that Moreton's work has not received the attention it deserves.

3.2. Mechanisms for prolonged residence time of TRLs

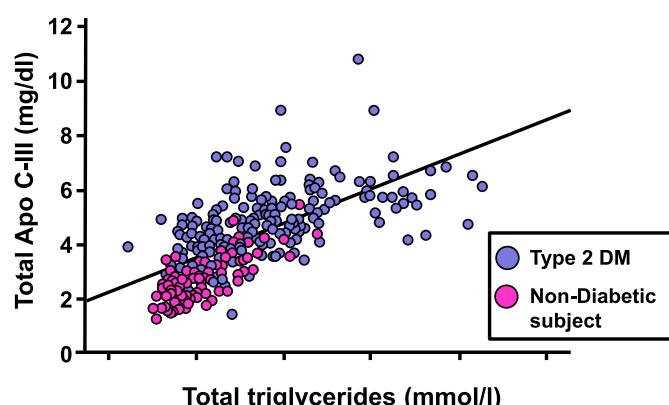Postprandial hyperlipidemia is highly prevalent in diabetic

Fig. 6. Relationship between serum apoCIII and triglyceride levels. ApoCIII concentration in plasma is increased in subjects with type 2 diabetes and correlates with serum triglyceride levels. n = 313, r = 0.71; p < 0.001. Figure modified from Hiukka et al. [30].

patients, and the long residence time of TRL remnants has thus been highlighted as an inherent feature of diabetic dyslipidemia [217,218]. This is likely caused by several mechanisms [132,219,220]. First, LPL activity has been shown to be decreased in insulin resistance and type 2 diabetes [221]. The mechanism for delayed postprandial hyperlipidemia also involves decreased hepatic clearance of TRL remnants, which is mediated by the heparan sulfate proteoglycan (HSPG) syndecan-1 and the LDL receptor [222]. The importance of the HSPG pathway has been questioned, but recent results demonstrate that dysfunction of syndecan-1 in animal models disrupts defective hepatic remnant clearance [222]. Furthermore, in mice with type 2 diabetes, uptake of remnant lipoproteins is suppressed by accelerated degradation of HSPG owing to the hepatic induction of heparan sulfate 6-O-endo-sulfatase (SULF2) [223,224]. Two recent studies have confirmed these results in humans by showing that genetic variation in SULF2 is associated with impaired postprandial clearance of TRLs and triglyceride levels in healthy subjects [225], and strongly predisposes to increased fasting and postprandial triglycerides in patients with obesity and type 2 diabetes mellitus [226].

3.3. Kinetic studies to elucidate the pathophysiology of impaired postprandial lipoprotein metabolism

Several groups have performed kinetic studies to further our understanding of the pathophysiology of impaired postprandial lipoprotein metabolism. Nielsen and workers used a VLDL-TG tracer to assess postprandial VLDL-TG kinetics in type 2 diabetic men, and demonstrated an abolition of postprandial suppression of VLDL-TG secretion in type 2 diabetic men [174]. Moreover, the VLDL-TAG clearance rate was significantly reduced postprandially in lean men, but remained unchanged in type 2 diabetic men. However, a significant difference in the change in clearance could not be demonstrated between the two groups. Wong et al. developed a kinetic model, which describes the non-steady-state postprandial metabolism of apoB48, and showed that postprandial hypertriglyceridemia in central obesity relates to an overproduction and impaired catabolism of apoB-48-containing lipoproteins [227]. The obese men also had significantly higher secretion rates of apoB-48 in the fasted state (145%) as well as at 3–8 h (approx. 70%) in response to a fat load. This was associated with a greater number of apoB48-containing particles secreted in the obese men, compared with lean men (125%). The fractional catabolic rate of apoB-48 was significantly lower in the obese men compared with the lean men (33%). The same group showed that addition of-3 FAEE supplementation to a moderate weight-loss diet in obese subjects significantly improved chylomicron metabolism by independently decreasing the secretion of apoB-48 [228].

Sun et al. developed an immunoaffinity method that completely separated hepatic and intestinal lipoproteins [229]. Using a continuous feeding protocol and an intravenous glycerol tracer in healthy volunteers the authors showed that the FCR of VLDL$_1$ and VLDL$_2$ in the fasted state did not differ from the equivalent fraction in a fed state in healthy subjects. The study also measured VLDL and chylomicron TG production rate for the first time in a separate study during a continuous feeding protocol and showed that 47% of total TG production in the Sf > 60 fraction was from chylomicrons.

4. Consequences of VLDL overproduction on LDL and HDL metabolism

In subjects with type 2 diabetes, hepatic uptake of VLDL, IDL and LDL is decreased, resulting in increased plasma residence time of these lipoproteins [217,218,230] and thus further contributing to the increased TRL levels in circulation. There are also reports of
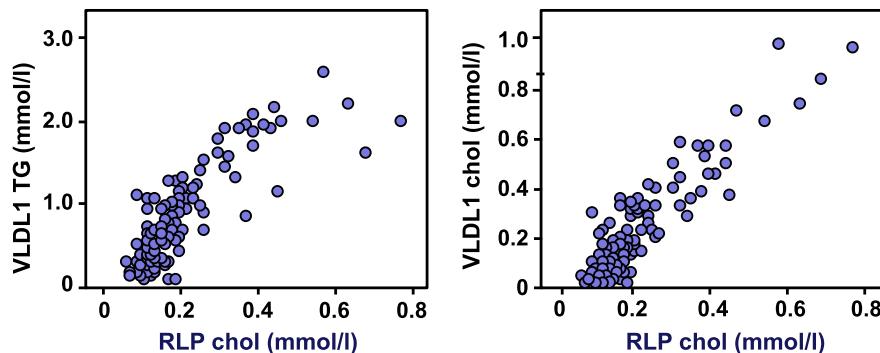
Fig. 7. Remnant-like particle cholesterol (RLP-chol) is linked with elevation of VLDL$_1$-triglyceride (TG) in type 2 diabetes. Correlations between RLP-cholesterol and VLDL$_1$-TG [r = 0.80; p < 0.001] and VLDL$_1$-cholesterol [r = 0.81; p < 0.0019]. From Hiukka et al. Unpublished.

increased production of IDL and LDL in insulin-resistant women without diabetes [231], and in men with mild but not severe diabetes [232].

The formation of small dense LDL is closely associated with insulin resistance and hypertriglyceridemia [233,234], and the VLDL$_1$-triglyceride level is the major predictor of LDL size in individuals with or without type 2 diabetes [16,48,170,235,236]. The mechanism that leads to the formation of small dense LDL is well elaborated, and both cholesteryl ester transfer protein (CETP) and hepatic lipase are involved: (1) CETP facilitates the transfer of triglycerides from VLDL$_1$ to LDL; (2) the resulting triglyceride-rich LDL is a preferred substrate for hepatic lipase; and (3) increased lipolysis of triglyceride-rich LDL results in the formation of small dense LDL [170,233]. Thus, it seems that the presence of large triglyceride-rich VLDL$_1$ particles is a prerequisite for small dense LDL formation, and such correlations have been observed [48,235,236]. However, small dense LDL are also observed in patients with type 2 diabetes and insulin resistance with close to normal triglyceride levels [237]. This might be explained by increased hepatic lipase activity commonly seen in patients with type 2 diabetes [238,239]. Several studies have shown that the presence of small dense LDL particles is associated with increased cardiovascular risk [240–243]. However, it is still under debate if small dense LDL levels add independent information on risk assessment over standard risk factors [244,245].

Increased levels of VLDL$_1$ also alter the composition of HDL through the actions of CETP and hepatic lipase, leading to the formation of small dense HDL and increased catabolism of these particles [16,246,247]. Recent results show that dyslipidemia is required in addition to insulin resistance in order to induce modifications with potentially functional implications in the HDL lipidome in type 2 diabetic subjects. Such modifications are notably focused on small HDL particles. Thus, such modifications in the lipidome appear to constitute integral features of functionally deficient, inflammatory HDL in type 2 diabetes [247]. This explains why there is an inverse correlation between HDL and liver fat [48].

Taken together, the overproduction of VLDL$_1$ particles initiates a sequence of events that results in the atherogenic lipid triad consisting of elevated plasma concentrations of fasting and postprandial TRLs, small dense LDL and low HDL cholesterol. Therefore, it is not unexpected that liver fat content correlates with the different components of the atherogenic dyslipidemia. Furthermore, the strong correlation between overproduction of VLDL$_1$ and liver fat likely explains why liver fat content in obesity seems to be a better marker of metabolic derangement and CVD risk than visceral obesity per se.

5. Summary

Patients with diabetes have an approximately two-fold increased risk of CVD compared with patients who do not have diabetes. The evidence that raised concentrations of remnant cholesterol, marked by raised triglycerides, is a causal risk factor for CVD and all-cause mortality is strong and supported by both genetic and epidemiological studies. However, randomized intervention trial evidence is urgently needed, that triglyceride-lowering reduces cardiovascular disease in patients with raised triglycerides. The different components of the dyslipidemia are not isolated abnormalities but closely linked to each other metabolically [170,248]. The underlying disturbances are hepatic overproduction of large triglyceride-rich VLDL$_1$ and delayed clearance of TRLs [170,249]. Evidence from genetic studies suggests potential drug targets for triglyceride reduction. Indeed, several new drugs with properties for lowering triglycerides are being developed or are already being tested in clinical trials [250], including some that are specifically aimed at reducing triglycerides. These drugs include among others n-3 fatty acids and apoC3 inhibitors. Hopefully, these results will lead to novel treatment focusing on the hepatic overproduction of large VLDL$_1$, delayed clearance of TRLs and postprandial hyperlipidemia. This is critical since efficient treatment of diabetic dyslipidemia must be based on the underlying mechanisms.

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