Atherosclerosis 239 (2015) 483–495

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

New insights into the pathophysiology of dyslipidemia in type 2 diabetes

Marja-Riitta Taskinen [a,*], Jan Borén [b,**]

[a] Heart and Lung Centre, Helsinki University Hospital and Research Programs' Unit, Diabetes & Obesity, University of Helsinki, Finland
[b] Department of Molecular and Clinical Medicine, University of Gothenburg and Sahlgrenska University Hospital, Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 30 December 2014
Received in revised form
28 January 2015
Accepted 30 January 2015
Available online 7 February 2015

Keywords:
Type 2 diabetes
Dyslipidemia
Triglycerides
Fatty liver
β-oxidation
De novo lipogenesis (DNL)
CVD

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.

© 2015 Elsevier Ireland Ltd. All rights reserved.

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

* Corresponding author. Biomedicum Helsinki, Haartamaninkatu 8, 00290 Helsinki, Finland.
** Corresponding author. Wallenberg Laboratory, Sahlgrenska University Hospital, Gothenburg, Sweden.
E-mail addresses: marja-riitta.taskinen@helsinki.fi (M.-R. Taskinen), jan.boren@wlab.gu.se (J. Borén).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.01.039
0021-9150/© 2015 Elsevier Ireland Ltd. All rights reserved.

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

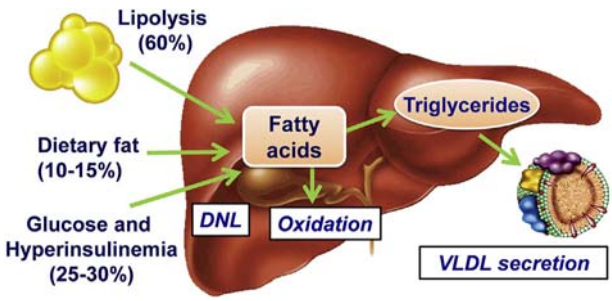

Fig. 1. Contributions of various metabolic pathways to liver steatosis in humans. Reductions in fatty acid oxidation and triglyceride export seem to have only minor roles in hepatic triglyceride deposition. By contrast, the increased availability of fatty acids from the adipose tissue through unabated 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].

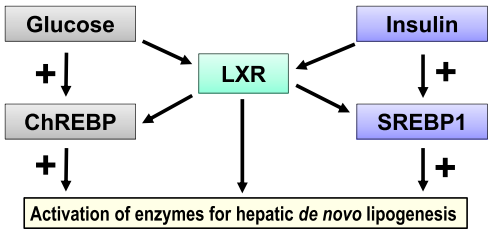

Fig. 2. The disturbed metabolic setting in diabetes involves activation of transcription factors enhancing DNL in the liver. The pathway activity for lipogenesis is coordinated by key transcription factors; sterol regulatory element binding protein 1 (SREBP-1), carbohydrate response element binding protein (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.

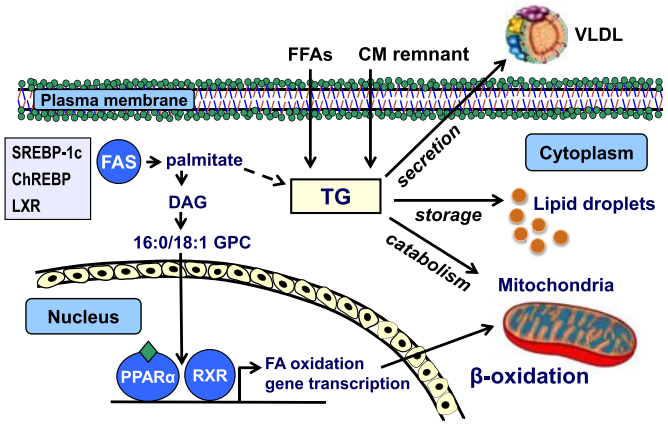

Fig. 3. FAS as a regulator of hepatic triglyceride metabolism. Fatty acid synthase controls fatty acid catabolism through the synthesis of a ligand for PPARα, which activates fatty acid oxidation genes. FAS makes a minor contribution of lipids to stored and secreted triglycerides, with the major contributions coming from plasma FFAs and dietary fats from chylomicron remnants. 16:0/18:1 GPC, 16:0/18:1-glycerophos phocholine; 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, hypertriglyceridemia 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

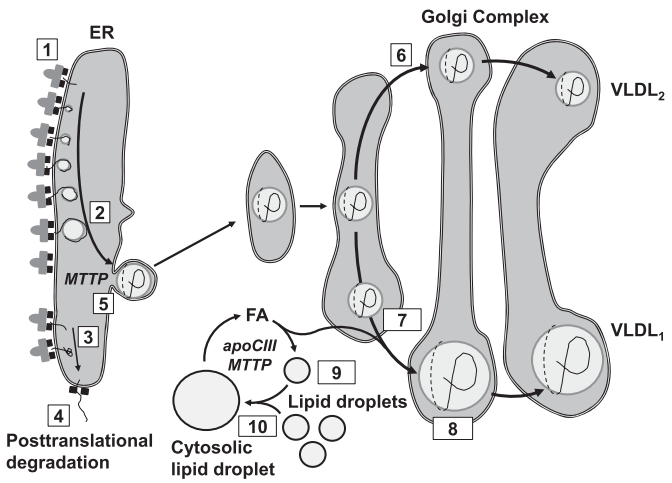

Fig. 4. Assembly and secretion of apoB100-containing lipoproteins. ApoB is synthesized and translocated into the lumen of the endoplasmic reticulum (ER) (1). The growing apoB molecule is co-translationally lipidated by MTTP to form the primordial VLDL particle (pre-VLDL) (2). Alternatively, apoB fails 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 droplets, 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 resistance 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 insulin 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 overproduction 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 development 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 coenzyme 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.

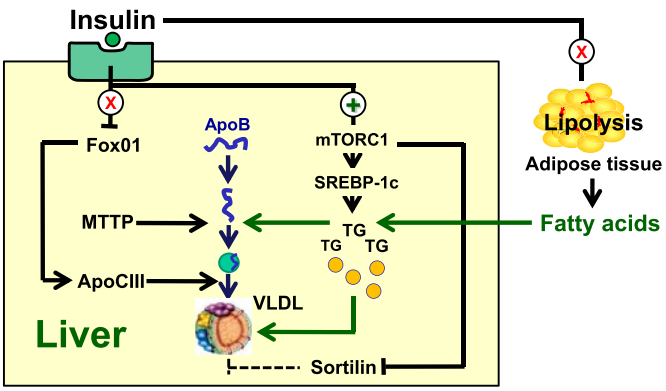

Fig. 5. Regulation of VLDL secretion by insulin signaling. Type 2 diabetes is characterized by selective insulin resistance: insulin fails to suppress lipolysis in the adipose tissue and FoxO1 in the liver leading to increased fatty acid flux and increased expression of MTTP and apoCIII, thereby promoting 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].

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

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 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-endosulfatase (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].

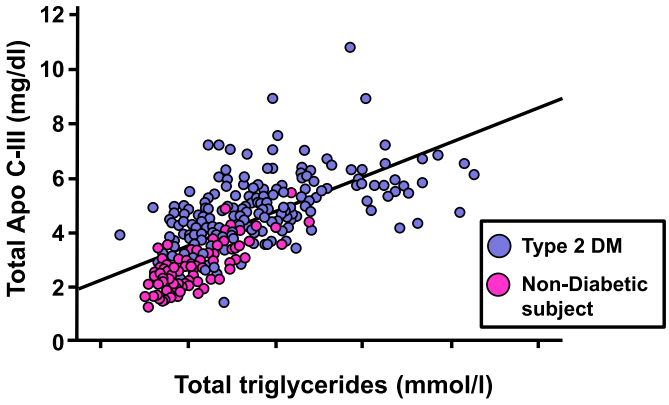

Fig. 6. Relationship between serum apoCIII and triglyceride levels. ApoCIII concentration in plasma is increased in subjects with type 2 diabetes and correlates with serum triglyceride levels. n = 313, r = 0.71; p < 0.001. Figure modified from Hiukka et al. [30].

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

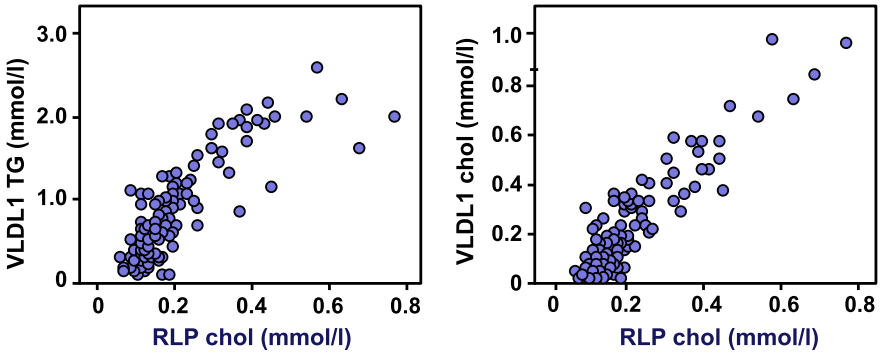

Fig. 7. Remnant-like particle cholesterol (RLP-chol) is linked with elevation of $VLDL_1$-triglyceride (TG) in type 2 diabetes. Correlations between RLP-cholesterol and $VLDL_1$-TG [$r = 0.80$; $p < 0.001$] and $VLDL_1$-cholesterol [$r = 0.81$; $p < 0.0019$]. From Hiukka et al. Unpublished.

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.

Acknowledgments

This work was funded by EU-project RESOLVE (Nr. 305707), Leducq Foundation (11 CVD 03), the Helsinki University Central Hospital Research Foundation (TYH2012134), Swedish Research Council, the Sigrid Juselius Foundation, Novo Nordisk Foundation, Swedish Diabetes Foundation, Diabetes Wellness, the Swedish Heart-Lung Foundation, and the Sahlgrenska University Hospital ALF Research Grants.

References

[1] L. Guariguata, D.R. Whiting, I. Hambleton, et al., Global estimates of diabetes prevalence for 2013 and projections for 2035, Diabetes Res. Clin. Pract. 103 (2014) 137–149.
[2] P.Z. Zimmet, D.J. Magliano, W.H. Herman, et al., Diabetes: a 21st century challenge, Lancet Diabetes Endocrinol. 2 (2014) 56–64.
[3] D.R. Whiting, L. Guariguata, C. Weil, et al., IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030, Diabetes Res. Clin. Pract. 94 (2011) 311–321.
[4] J.E. Shaw, R.A. Sicree, P.Z. Zimmet, Global estimates of the prevalence of diabetes for 2010 and 2030, Diabetes Res. Clin. Pract. 87 (2010) 4–14.
[5] J.J. Joseph, S.H. Golden, Type 2 diabetes and cardiovascular disease: what next? Curr. Opin. Endocrinol. Diabetes Obes. 21 (2014) 109–120.

[6] Emerging Risk Factors Collaboration, S.R. Seshasai, S. Kaptoge, A. Thompson, et al., Diabetes mellitus, fasting glucose, and risk of cause-specific death, N Engl J Med. 364 (2011) 829–841.
[7] E.W. Gregg, Y. Li, J. Wang, et al., Changes in diabetes-related complications in the United States, 1990–2010, N. Engl. J. Med. 370 (2014) 1514–1523.
[8] K. Faerch, B. Carstensen, T.P. Almdal, et al., Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002–2010), J. Clin. Endocrinol. Metab. 99 (2014) E642–E646.
[9] Emerging Risk Factors Collaboration, N. Sarwar, P. Gao, et al., Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies, Lancet 375 (2010) 2215–2222.
[10] N. Sattar, Revisiting the links between glycaemia, diabetes and cardiovascular disease, Diabetologia 56 (2013) 686–695.
[11] S. Vilbergsson, G. Sigurdsson, H. Sigvaldason, et al., Coronary heart disease mortality amongst non-insulin-dependent diabetic subjects in Iceland: the independent effect of diabetes. The Reykjavik Study 17-year follow up, J. Intern. Med. 244 (1998) 309–316.
[12] S.M. Haffner, S. Lehto, T. Ronnemaa, et al., Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabettic subjects with and without prior myocardial infarction, N. Engl. J. Med. 339 (1998) 229–234.
[13] W.E. Boden, J.L. Probstfield, T. Anderson, et al., Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy, N. Engl. J. Med. 365 (2011) 2255–2267.
[14] H.T.C. Group, M.J. Landray, R. Haynes, et al., Effects of extended-release niacin with laropiprant in high-risk patients, N. Engl. J. Med. 371 (2014) 203–212.
[15] M.R. Taskinen, Type 2 diabetes as a lipid disorder, Curr. Mol. Med. 5 (2005) 297–308.
[16] M.J. Chapman, H.N. Ginsberg, P. Amarenco, et al., Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management, Eur. Heart J. 32 (2011) 1345–1361.
[17] B. Isomaa, P. Almgren, T. Tuomi, et al., Cardiovascular morbidity and mortality associated with the metabolic syndrome, Diabetes Care 24 (2001) 683–689.
[18] R. Scott, M. Donoghoe, G.F. Watts, et al., Impact of metabolic syndrome and its components on cardiovascular disease event rates in 4900 patients with type 2 diabetes assigned to placebo in the FIELD randomised trial, Cardiovasc. Diabetol. 10 (2011) 102.
[19] M. Eriksson, B. Zethelius, K. Eeg-Olofsson, et al., Blood lipids in 75,048 type 2 diabetic patients: a population-based survey from the Swedish National Diabetes Register, Eur. J. Cardiovasc. Prev. Rehabil. Off. J. Eur. Soc. Cardiol. 18 (2011) 97–105. Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology.
[20] M. Feher, M. Greener, N. Munro, Persistent hypertriglyceridemia in statin-treated patients with type 2 diabetes mellitus, Diabetes Metab. Syndr. Obes. 6 (2013) 11–15.
[21] L.A. Leiter, P. Lundman, P.M. da Silva, et al., Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study, Diabet. Med. 28 (2011) 1343–1351.
[22] Z. Reiner, D. De Bacquer, K. Kotseva, et al., Treatment potential for dyslipidaemia management in patients with coronary heart disease across Europe: findings from the EUROASPIRE III survey, Atherosclerosis 231 (2013) 300–307.
[23] S.O. Olofsson, J. Boren, Apolipoprotein B: a clinically important apolipoprotein which assembles atherogenic lipoproteins and promotes the development of atherosclerosis, J. Intern. Med. 258 (2005) 395–410.
[24] X. Wang, V. Chauhan, A.T. Nguyen, et al., Immunochemical evidence that human apoB differs when expressed in rodent versus human cells, J. Lipid Res. 44 (2003) 547–553.
[25] J.P. Segrest, M.K. Jones, V.K. Mishra, et al., Apolipoprotein B-100: conservation of lipid-associating amphipathic secondary structural motifs in nine species of vertebrates, J. Lipid Res. 39 (1998) 85–102.
[26] M.M. Hussain, Intestinal lipid absorption and lipoprotein formation, Curr. Opin. Lipidol. 25 (2014) 200–206.
[27] S. Demignot, F. Beilstein, E. Morel, Triglyceride-rich lipoproteins and cytosolic lipid droplets in enterocytes: key players in intestinal physiology and metabolic disorders, Biochimie 96 (2014) 48–55.
[28] J.E. Lambert, E.J. Parks, Postprandial metabolism of meal triglyceride in humans, Biochim. Biophys. Acta 1821 (2012) 721–726.
[29] J. Iqbal, M.M. Hussain, Evidence for multiple complementary pathways for efficient cholesterol absorption in mice, J. Lipid Res. 46 (2005) 1491–1501.
[30] A. Hiukka, J. Fruchart-Najib, E. Leinonen, et al., Alterations of lipids and apolipoprotein CIII in very low density lipoprotein subspecies in type 2 diabetes, Diabetologia 48 (2005) 1207–1215.
[31] J.D. Brunzell, W.R. Hazzard, D. Porte Jr., et al., Evidence for a common, saturable, triglyceride removal mechanism for chylomicrons and very low density lipoproteins in man, J. Clin. Investig. 52 (1973) 1578–1585.
[32] M. Adiels, N. Matikainen, J. Westerbacka, et al., Postprandial accumulation of chylomicrons and chylomicron remnants is determined by the clearance capacity, Atherosclerosis 222 (2012) 222–228.
[33] J. Boren, M.R. Taskinen, S.O. Olofsson, et al., Ectopic lipid storage and insulin resistance: a harmful relationship, J. Intern. Med. 274 (2013) 25–40.
[34] S.O. Olofsson, J. Boren, Apolipoprotein B secretory regulation by degradation, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1334–1338.
[35] N.A. Abumrad, N.O. Davidson, Role of the gut in lipid homeostasis, Physiol. Rev. 92 (2012) 1061–1085.
[36] C. Xiao, G.F. Lewis, Regulation of chylomicron production in humans, Biochim. Biophys. Acta 1821 (2012) 736–746.
[37] A. Veilleux, E. Grenier, P. Marceau, et al., Intestinal lipid handling: evidence and implication of insulin signaling abnormalities in human obese subjects, Arterioscler. Thromb. Vasc. Biol. 34 (2014) 644–653.
[38] C. Xiao, S. Dash, C. Morgantini, et al., New and emerging regulators of intestinal lipoprotein secretion, Atherosclerosis 233 (2014) 608–615.
[39] J.S. Cohn, E.J. Johnson, J.S. Millar, et al., Contribution of apoB-48 and apoB-100 triglyceride-rich lipoproteins (TRL) to postprandial increases in the plasma concentration of TRL triglycerides and retinyl esters, J. Lipid Res. 34 (1993) 2033–2040.
[40] F. Karpe, M. Bell, J. Bjorkegren, et al., Quantification of postprandial triglyceride-rich lipoproteins in healthy men by retinyl ester labeling and simultaneous measurement of apolipoproteins B-48 and B-100, Arterioscler. Thromb. Vasc. Biol. 15 (1995) 199–207.
[41] C. Xiao, R.H. Bandsma, S. Dash, et al., Exenatide, a glucagon-like peptide-1 receptor agonist, acutely inhibits intestinal lipoprotein production in healthy humans, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1513–1519.
[42] S. Dash, C. Xiao, C. Morgantini, et al., Glucagon-like peptide-2 regulates release of chylomicrons from the intestine, Gastroenterology 147 (2014), 1275–1284.e1274.
[43] S. Dash, C. Xiao, C. Morgantini, et al., Glucagon-like peptide-2 acutely stimulates chylomicron release in healthy humans, Diabetes 62 (2013) A76–A77.
[44] C. Xiao, S. Dash, C. Morgantini, et al., Novel role of enteral monosaccharides in intestinal lipoprotein production in healthy humans, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 1056–1062.
[45] S. Dash, C. Xiao, C. Morgantini, et al., High-dose resveratrol treatment for 2 weeks inhibits intestinal and hepatic lipoprotein production in overweight/obese men, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 2895–2901.
[46] A.J. Tremblay, B. Lamarche, J.C. Hogue, et al., Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia, J. Lipid Res. 50 (2009) 1463–1471.
[47] P.D. Cani, S. Possemiers, T. Van de Wiele, et al., Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability, Gut 58 (2009) 1091–1103.
[48] M. Adiels, M.R. Taskinen, C. Packard, et al., Overproduction of large VLDL particles is driven by increased liver fat content in man, Diabetologia 49 (2006) 755–765.
[49] B. Verges, Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes, Atherosclerosis 211 (2010) 353–360.
[50] V.A. Zammit, Hepatic triacylglycerol synthesis and secretion: DGAT2 as the link between glycaemia and triglyceridaemia, Biochem. J. 451 (2013) 1–12.
[51] R.J. Perry, V.T. Samuel, K.F. Petersen, et al., The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes, Nature 510 (2014) 84–91.
[52] Z. Sun, M.A. Lazar, Dissociating fatty liver and diabetes, Trends Endocrinol. Metab. 24 (2013) 4–12.
[53] M.R. Taskinen, M. Adiels, J. Westerbacka, et al., Dual metabolic defects are required to produce hypertriglyceridemia in obese subjects, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2144–2150.
[54] J. Boren, M.R. Taskinen, M. Adiels, Kinetic studies to investigate lipoprotein metabolism, J. Intern Med. 271 (2012) 166–173.
[55] M. Adiels, J. Westerbacka, A. Soro-Paavonen, et al., Acute suppression of VLDL1 secretion rate by insulin is associated with hepatic fat content and insulin resistance, Diabetologia 50 (2007) 2356–2365.
[56] M. Adiels, M.R. Taskinen, J. Boren, Fatty liver, insulin resistance, and dyslipidemia, Curr. Diabetes Rep. 8 (2008) 60–64.
[57] J.D. Sparks, C.E. Sparks, K. Adeli, Selective hepatic insulin resistance, VLDL overproduction, and hypertriglyceridemia, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2104–2112.
[58] E. Fisher, E. Lake, R.S. McLeod, Apolipoprotein B100 quality control and the regulation of hepatic very low density lipoprotein secretion, J. Biomed. Res. 28 (2014) 178–193.
[59] M.E. Haas, A.D. Attie, S.B. Biddinger, The regulation of ApoB metabolism by insulin, Trends Endocrinol. Metab. 24 (2013) 391–397.
[60] M.P. Czech, M. Tencerova, D.J. Pedersen, et al., Insulin signalling mechanisms for triacylglycerol storage, Diabetologia 56 (2013) 949–964.
[61] Y.F. Otero, J.M. Stafford, O.P. McGuinness, Pathway-selective insulin resistance and metabolic disease: the importance of nutrient flux, J. Biol. Chem. 289 (2014) 20462–20469.
[62] G.F. Lewis, K.D. Uffelman, L.W. Szeto, et al., Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans, J. Clin. Investig. 95 (1995) 158–166.
[63] M.T. Timlin, B.R. Barrows, E.J. Parks, Increased dietary substrate delivery alters hepatic fatty acid recycling in healthy men, Diabetes 54 (2005) 2694–2701.
[64] S. Nielsen, F. Karpe, Determinants of VLDL-triglycerides production, Curr. Opin. Lipidol. 23 (2012) 321–326.
[65] A. Tchernof, J.P. Despres, Pathophysiology of human visceral obesity: an update, Physiol. Rev. 93 (2013) 359–404.
[66] V.A. Zammit, Role of insulin in hepatic fatty acid partitioning: emerging

concepts, Biochem. J. 314 (Pt 1) (1996) 1–14.
[67] L. Hodson, K.N. Frayn, Hepatic fatty acid partitioning, Curr. Opin. Lipidol. 22 (2011) 216–224.
[68] R.J. Havel, J.P. Kane, E.O. Balasse, et al., Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans, J. Clin. Investig. 49 (1970) 2017–2035.
[69] S. Nielsen, Z. Guo, C.M. Johnson, et al., Splanchnic lipolysis in human obesity, J. Clin. Invest. 113 (2004) 1582–1588.
[70] C. Koutsari, M.D. Jensen, Thematic review series: patient-oriented research. Free fatty acid metabolism in human obesity, J. Lipid Res. 47 (2006) 1643–1650.
[71] L. Rui, Energy metabolism in the liver, Compr. Physiol. 4 (2014) 177–197.
[72] K.L. Donnelly, C.I. Smith, S.J. Schwarzenberg, et al., Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease, J. Clin. Invest. 115 (2005) 1343–1351.
[73] S.W. Koppe, Obesity and the liver: nonalcoholic fatty liver disease, Transl. Res. 164 (2014) 312–322.
[74] M.E. Rinella, A.J. Sanyal, NAFLD in 2014: genetics, diagnostics and therapeutic advances in NAFLD, Nat. Rev. Gastroenterol. Hepatol. 2 (2015) 65–66.
[75] Q.M. Anstee, C.P. Day, The genetics of NAFLD, Nat. Rev. Gastroenterol. Hepatol. 10 (2013) 645–655.
[76] S. Romeo, J. Kozlitina, C. Xing, et al., Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease, Nat. Genet. 40 (2008) 1461–1465.
[77] E.K. Speliotes, L.M. Yerges-Armstrong, J. Wu, et al., Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits, PLoS Genet. 7 (2011) e1001324.
[78] R.G. Victor, R.W. Haley, D.L. Willett, et al., The Dallas Heart Study: a population-based probability sample for the multidisciplinary study of ethnic differences in cardiovascular health, Am. J. Cardiol. 93 (2004) 1473–1480.
[79] J. Kozlitina, E. Smagris, S. Stender, et al., Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease, Nat. Genet. 46 (2014) 352–356.
[80] M. Kumari, G. Schoiswohl, C. Chitraju, et al., Adiponutrin functions as a nutritionally regulated lysophosphatidic acid acyltransferase, Cell. Metab. 15 (2012) 691–702.
[81] M.K. Basantani, M.T. Sitnick, L. Cai, et al., Pnpla3/Adiponutrin deficiency in mice does not contribute to fatty liver disease or metabolic syndrome, J. Lipid Res. 52 (2011) 318–329.
[82] E. Smagris, S. BasuRay, J. Li, et al., Pnpla3I148M knockin mice accumulate PNPLA3 on lipid droplets and develop hepatic steatosis, Hepatology 61 (2015) 108–118.
[83] C. Pirazzi, M. Adiels, M.A. Burza, et al., Patatin-like phospholipase domain-containing 3 (PNPLA3) I148M (rs738409) affects hepatic VLDL secretion in humans and in vitro, J. Hepatol. 57 (2012) 1276–1282.
[84] K.F. Petersen, S. Dufour, A. Hariri, et al., Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease, N. Engl. J. Med. 362 (2010) 1082–1089.
[85] J. Kozlitina, E. Boerwinkle, J.C. Cohen, et al., Dissociation between APOC3 variants, hepatic triglyceride content and insulin resistance, Hepatology 53 (2011) 467–474.
[86] L. Valenti, V. Nobili, A. Al-Serri, et al., The APOC3 T-455C and C-482T promoter region polymorphisms are not associated with the severity of liver damage independently of PNPLA3 I148M genotype in patients with nonalcoholic fatty liver, J. Hepatol. 55 (2011) 1409–1414.
[87] F. Sentinelli, S. Romeo, C. Maglio, et al., Lack of effect of apolipoprotein C3 polymorphisms on indices of liver steatosis, lipid profile and insulin resistance in obese Southern Europeans, Lipids Health Dis. 10 (2011) 93.
[88] A. Peter, K. Kantartzis, F. Machicao, et al., Visceral obesity modulates the impact of apolipoprotein C3 gene variants on liver fat content, Int. J. Obes. Lond 36 (2012) 774–782.
[89] A. Vedala, W. Wang, R.A. Neese, et al., Delayed secretory pathway contributions to VLDL-triglycerides from plasma NEFA, diet, and de novo lipogenesis in humans, J. Lipid Res. 47 (2006) 2562–2574.
[90] F. Diraison, P. Moulin, M. Beylot, Contribution of hepatic de novo lipogenesis and reesterification of plasma non esterified fatty acids to plasma triglyceride synthesis during non-alcoholic fatty liver disease, Diabetes Metab. 29 (2003) 478–485.
[91] J.M. Schwarz, P. Linfoot, D. Dare, et al., Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets, Am. J. Clin. Nutr. 77 (2003) 43–50.
[92] M.S. Wilke, M.A. French, Y.K. Goh, et al., Synthesis of specific fatty acids contributes to VLDL-triacylglycerol composition in humans with and without type 2 diabetes, Diabetologia 52 (2009) 1628–1637.
[93] I. Marques-Lopes, D. Ansorena, I. Astiasaran, et al., Postprandial de novo lipogenesis and metabolic changes induced by a high-carbohydrate, low-fat meal in lean and overweight men, Am. J. Clin. Nutr. 73 (2001) 253–261.
[94] A.L. Birkenfeld, G.I. Shulman, Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes, Hepatology 59 (2014) 713–723.
[95] A. Berlanga, E. Guiu-Jurado, J.A. Porras, et al., Molecular pathways in nonalcoholic fatty liver disease, Clin. Exp. Gastroenterol. 7 (2014) 221–239.
[96] X. Xu, J.S. So, J.G. Park, et al., Transcriptional control of hepatic lipid metabolism by SREBP and ChREBP, Semin. Liver Dis. 33 (2013) 301–311.
[97] P. Karagianni, I. Talianidis, Transcription factor networks regulating hepatic fatty acid metabolism, Biochim. Biophys. Acta 1851 (2015) 2–8.
[98] P. Ferre, F. Foufelle, Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c, Diabetes Obes. Metab. 12 (Suppl. 2) (2010) 83–92.
[99] I.J. Lodhi, X. Wei, C.F. Semenkovich, Lipoexpediency: de novo lipogenesis as a metabolic signal transmitter, Trends Endocrinol. Metab. 22 (2011) 1–8.
[100] C. Postic, J. Girard, Contribution of de novo fatty acid synthesis to hepatic steatosis and insulin resistance: lessons from genetically engineered mice, J. Clin. Investig. 118 (2008) 829–838.
[101] A.P. Jensen-Urstad, C.F. Semenkovich, Fatty acid synthase and liver triglyceride metabolism: housekeeper or messenger? Biochim. Biophys. Acta 1821 (2012) 747–753.
[102] J.K. Yee, C.S. Mao, H.S. Hummel, et al., Compartmentalization of stearoyl-coenzyme A desaturase 1 activity in HepG2 cells, J. Lipid Res. 49 (2008) 2124–2134.
[103] J. Gong, H. Campos, S. McGarvey, et al., Adipose tissue palmitoleic acid and obesity in humans: does it behave as a lipokine? Am. J. Clin. Nutr. 93 (2011) 186–191.
[104] L. Hodson, B.A. Fielding, Stearoyl-CoA desaturase: rogue or innocent bystander? Prog. Lipid Res. 52 (2013) 15–42.
[105] J.J. Lee, J.E. Lambert, Y. Hovhannisyan, et al., Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis, Am. J. Clin. Nutr. 101 (2015) 34–43.
[106] A. Aarsland, R.R. Wolfe, Hepatic secretion of VLDL fatty acids during stimulated lipogenesis in men, J. Lipid Res. 39 (1998) 1280–1286.
[107] C.J. Field, E.A. Ryan, A.B. Thomson, et al., Diet fat composition alters membrane phospholipid composition, insulin binding, and glucose metabolism in adipocytes from control and diabetic animals, J. Biol. Chem. 265 (1990) 11143–11150.
[108] H. Cao, K. Gerhold, J.R. Mayers, et al., Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism, Cell 134 (2008) 933–944.
[109] H. Sampath, J.M. Ntambi, The role of stearoyl-CoA desaturase in obesity, insulin resistance, and inflammation, Ann. N. Y. Acad. Sci. 1243 (2011) 47–53.
[110] J. Kroger, M.B. Schulze, Recent insights into the relation of Delta5 desaturase and Delta6 desaturase activity to the development of type 2 diabetes, Curr. Opin. Lipidol. 23 (2012) 4–10.
[111] A. Kotronen, T. Seppanen-Laakso, J. Westerbacka, et al., Hepatic stearoyl-CoA desaturase (SCD)-1 activity and diacylglycerol but not ceramide concentrations are increased in the nonalcoholic human fatty liver, Diabetes 58 (2009) 203–208.
[112] N. Stefan, A. Peter, A. Cegan, et al., Low hepatic stearoyl-CoA desaturase 1 activity is associated with fatty liver and insulin resistance in obese humans, Diabetologia 51 (2008) 648–656.
[113] G. Silbernagel, M. Kovarova, A. Cegan, et al., High hepatic SCD1 activity is associated with low liver fat content in healthy subjects under a lipogenic diet, J. Clin. Endocrinol. Metab. 97 (2012) E2288–E2292.
[114] J.E. Lambert, M.A. Ramos-Roman, J.D. Browning, et al., Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease, Gastroenterology 146 (2014) 726–735.
[115] N. Matikainen, M. Adiels, S. Soderlund, et al., Hepatic lipogenesis and a marker of hepatic lipid oxidation, predict postprandial responses of triglyceride-rich lipoproteins, Obesity Silver Spring 22 (2014) 1854–1859.
[116] F. Ameer, L. Scandiuzzi, S. Hasnain, et al., De novo lipogenesis in health and disease, Metabolism 63 (2014) 895–902.
[117] D.G. Mashek, Hepatic fatty acid trafficking: multiple forks in the road, Adv. Nutr. 4 (2013) 697–710.
[118] J. Lopez-Miranda, E. Vilella, F. Perez-Jimenez, et al., Low-density lipoprotein metabolism in rats treated with cyclosporine, Metabolism 42 (1993) 678–683.
[119] N. Stefan, H.U. Haring, The metabolically benign and malignant fatty liver, Diabetes 60 (2011) 2011–2017.
[120] N. Gruben, R. Shiri-Sverdlov, D.P. Koonen, et al., Nonalcoholic fatty liver disease: a main driver of insulin resistance or a dangerous liaison? Biochim. Biophys. Acta 1842 (2014) 2329–2343.
[121] Y. Jin, P.J. McFie, S.L. Banman, et al., Diacylglycerol acyltransferase-2 (DGAT2) and monoacylglycerol acyltransferase-2 (MGAT2) interact to promote triacylglycerol synthesis, J. Biol. Chem. 289 (2014) 28237–28248.
[122] M. Pagadala, T. Kasumov, A.J. McCullough, et al., Role of ceramides in nonalcoholic fatty liver disease, Trends Endocrinol. Metab. 23 (2012) 365–371.
[123] F. Magkos, X. Su, D. Bradley, et al., Intrahepatic diacylglycerol content is associated with hepatic insulin resistance in obese subjects, Gastroenterology 142 (2012), 1444–1446.e1442.
[124] T.L. Innerarity, J. Boren, S. Yamanaka, et al., Biosynthesis of apolipoprotein B48-containing lipoproteins. Regulation by novel post-transcriptional mechanisms, J. Biol. Chem. 271 (1996) 2353–2356.
[125] M. Adiels, S.O. Olofsson, M.R. Taskinen, et al., Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1225–1236.
[126] J. Boren, L. Graham, M. Wettesten, et al., The assembly and secretion of ApoB 100-containing lipoproteins in Hep G2 cells. ApoB 100 is cotranslationally integrated into lipoproteins, J. Biol. Chem. 267 (1992) 9858–9867.

[127] J.R. Wetterau, D.B. Zilversmit, Purification and characterization of microsomal triglyceride and cholesteryl ester transfer protein from bovine liver microsomes, Chem. Phys. Lipids 38 (1985) 205–222.
[128] A.C. Rutledge, Q. Su, K. Adeli, Apolipoprotein B100 biogenesis: a complex array of intracellular mechanisms regulating folding, stability, and lipoprotein assembly, Biochem. Cell. Biol. 88 (2010) 251–267.
[129] S.O. Olofsson, O. Wiklund, J. Boren, Apolipoproteins A-I and B: biosynthesis, role in the development of atherosclerosis and targets for intervention against cardiovascular disease, Vasc. Health Risk Manag. 3 (2007) 491–502.
[130] P. Stillemark-Billton, C. Beck, J. Boren, et al., Relation of the size and intracellular sorting of apoB to the formation of VLDL 1 and VLDL 2, J. Lipid Res. 46 (2005) 104–114.
[131] Z. Yao, H. Zhou, D. Figeys, et al., Microsome-associated lumenal lipid droplets in the regulation of lipoprotein secretion, Curr. Opin. Lipidol. 24 (2013) 160–170.
[132] I. Ramasamy, Recent advances in physiological lipoprotein metabolism, Clin. Chem. Lab. Med. 52 (2014) 1695–1727.
[133] K. Bostrom, M. Wettesten, J. Boren, et al., Pulse-chase studies of the synthesis and intracellular transport of apolipoprotein B-100 in Hep G2 cells, J. Biol. Chem. 261 (1986) 13800–13806.
[134] S.O. Olofsson, J. Boren, Apolipoprotein B secretory regulation by degradation, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1334–1338.
[135] E.A. Fisher, H.N. Ginsberg, Complexity in the secretory pathway: the assembly and secretion of apolipoprotein B-containing lipoproteins, J. Biol. Chem. 277 (2002) 17377–17380.
[136] E.A. Fisher, M. Pan, X. Chen, et al., The triple threat to nascent apolipoprotein B. Evidence for multiple, distinct degradative pathways, J. Biol. Chem. 276 (2001) 27855–27863.
[137] M. Pan, A.I. Cederbaum, Y.L. Zhang, et al., Lipid peroxidation and oxidant stress regulate hepatic apolipoprotein B degradation and VLDL production, J. Clin. Investig. 113 (2004) 1277–1287.
[138] J.L. Brodsky, E.A. Fisher, The many intersecting pathways underlying apolipoprotein B secretion and degradation, Trends Endocrinol. Metab. 19 (2008) 254–259.
[139] E.A. Fisher, K.J. Williams, Autophagy of an oxidized, aggregated protein beyond the ER: a pathway for remarkably late-stage quality control, Autophagy 4 (2008) 721–723.
[140] J. Joven, E. Vilella, S. Ahmad, et al., Lipoprotein heterogeneity in end-stage renal disease, Kidney Int. 43 (1993) 410–418.
[141] D. Wiggins, G.F. Gibbons, The lipolysis/esterification cycle of hepatic triacylglycerol. Its role in the secretion of very-low-density lipoprotein and its response to hormones and sulphonylureas, Biochem. J. 284 (1992) 457–462.
[142] A.M. Salter, D. Wiggins, V.A. Sessions, et al., The intracellular triacylglycerol/fatty acid cycle: a comparison of its activity in hepatocytes which secrete exclusively apolipoprotein (apo) B100 very-low-density lipoprotein (VLDL) and in those which secrete predominantly apoB48 VLDL, Biochem. J. 332 (Pt 3) (1998) 667–672.
[143] G.F. Gibbons, K. Islam, R.J. Pease, Mobilisation of triacylglycerol stores, Biochim. Biophys. Acta 1483 (2000) 37–57.
[144] M. Sundaram, Z. Yao, Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion, Nutr. Metab. Lond. 7 (2010) 35.
[145] S.-O. Olofsson, G. Bjursell, K. Boström, et al., Apolipoprotein B: structure, biosynthesis and role in the lipoprotein assembly process, Atherosclerosis 68 (1987) 1–17.
[146] D.J. Murphy, J. Vance, Mechanisms of lipid-body formation, Trends Biochem. Sci. 24 (1999) 109–115.
[147] D.A. Brown, Lipid droplets: proteins floating on a pool of fat, Curr. Biol. 11 (2001) R446–R449.
[148] Y. Wang, K. Tran, Z. Yao, The activity of microsomal triglyceride transfer protein is essential for accumulation of triglyceride within microsomes in McA-RH7777 cells. A unified model for the assembly of very low density lipoproteins, J. Biol. Chem. 274 (1999) 27793–27800.
[149] Z. Yao, Human apolipoprotein C-III – a new intrahepatic protein factor promoting assembly and secretion of very low density lipoproteins, Cardiovasc. Hematol. Disord. Drug Targets 12 (2012) 133–140.
[150] Z. Yao, Y. Wang, Apolipoprotein C-III and hepatic triglyceride-rich lipoprotein production, Curr. Opin. Lipidol. 23 (2012) 206–212.
[151] M. Sundaram, S. Zhong, M.B. Khalil, et al., Expression of apolipoprotein C-III in McA-RH7777 cells enhances VLDL assembly and secretion under lipid-rich conditions, J. Lipid Res. 51 (2010) 150–161.
[152] W. Qin, M. Sundaram, Y. Wang, et al., Missense mutation in APOC3 within the C-terminal lipid binding domain of human ApoC-III results in impaired assembly and secretion of triacylglycerol-rich very low density lipoproteins: evidence that ApoC-III plays a major role in the formation of lipid precursors within the microsomal lumen, J. Biol. Chem. 286 (2011) 27769–27780.
[153] M. Sundaram, S. Zhong, M.B. Khalil, et al., Functional analysis of the missense APOC3 mutation Ala23Thr associated with human hypotriglyceridemia, J. Lipid Res. 51 (2010) 1524–1534.
[154] G. Musso, R. Gambino, M. Cassader, Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD), Prog. Lipid Res. 48 (2009) 1–26.
[155] V. Ratziu, S. Bellentani, H. Cortez-Pinto, et al., A position statement on NAFLD/NASH based on the EASL 2009 special conference, J. Hepatol. 53 (2010) 372–384.
[156] A.H. Kissebah, S. Alfarsi, D.J. Evans, et al., Integrated regulation of very low density lipoprotein triglyceride and apolipoprotein-B kinetics in non-insulin-dependent diabetes mellitus, Diabetes 31 (1982) 217–225.
[157] L. Duvillard, F. Pont, E. Florentin, et al., Metabolic abnormalities of apolipoprotein B-containing lipoproteins in non-insulin-dependent diabetes: a stable isotope kinetic study, Eur. J. Clin. Investig. 30 (2000) 685–694.
[158] K. Ouguerram, T. Magot, Y. Zair, et al., Effect of atorvastatin on apolipoprotein B100 containing lipoprotein metabolism in type-2 diabetes, J. Pharmacol. Exp. Ther. 306 (2003) 332–337.
[159] M.H. Cummings, G.F. Watts, A.M. Umpleby, et al., Increased hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 in NIDDM, Diabetologia 38 (1995) 959–967.
[160] X. Wu, K.J. Williams, NOX4 pathway as a source of selective insulin resistance and responsiveness, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1236–1245.
[161] A. Aravinthan, B. Challis, N. Shannon, et al., Selective insulin resistance in hepatocyte senescence, Exp. Cell Res. 331 (2015) 38–45.
[162] A. Kamagate, H.H. Dong, FoxO1 integrates insulin signaling to VLDL production, Cell. Cycle 7 (2008) 3162–3170.
[163] M. Wan, K.F. Leavens, D. Saleh, et al., Postprandial hepatic lipid metabolism requires signaling through Akt2 independent of the transcription factors FoxA2, FoxO1, and SREBP1c, Cell. Metab. 14 (2011) 516–527.
[164] K.F. Leavens, M.J. Birnbaum, Insulin signaling to hepatic lipid metabolism in health and disease, Crit. Rev. Biochem. Mol. Biol. 46 (2011) 200–215.
[165] A. Kamagate, S. Qu, G. Perdomo, et al., FoxO1 mediates insulin-dependent regulation of hepatic VLDL production in mice, J. Clin. Investig. 118 (2008) 2347–2364.
[166] D. Ai, J.M. Baez, H. Jiang, et al., Activation of ER stress and mTORC1 suppresses hepatic sortilin-1 levels in obese mice, J. Clin. Investig. 122 (2012) 1677–1687.
[167] A. Strong, Q. Ding, A.C. Edmondson, et al., Hepatic sortilin regulates both apolipoprotein B secretion and LDL catabolism, J. Clin. Investig. 122 (2012) 2807–2816.
[168] L. Andersson, P. Bostrom, J. Ericson, et al., PLD1 and ERK2 regulate cytosolic lipid droplet formation, J. Cell. Sci. 119 (2006) 2246–2257.
[169] M. Adiels, J. Boren, M.J. Caslake, et al., Overproduction of VLDL1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 1697–1703.
[170] M.R. Taskinen, Diabetic dyslipidaemia: from basic research to clinical practice, Diabetologia 46 (2003) 733–749.
[171] R. Malmstrom, C.J. Packard, T.D. Watson, et al., Metabolic basis of hypotriglyceridemic effects of insulin in normal men, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 1454–1464.
[172] G.F. Lewis, K.D. Uffelman, L.W. Szeto, et al., Effects of acute hyperinsulinemia on VLDL triglyceride and VLDL apoB production in normal weight and obese individuals, Diabetes 42 (1993) 833–842.
[173] M.H. Cummings, G.F. Watts, A.M. Umpleby, et al., Acute hyperinsulinemia decreases the hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 in NIDDM, Diabetes 44 (1995) 1059–1065.
[174] E. Sondergaard, L.P. Sorensen, I. Rahbek, et al., Postprandial VLDL-triacylglycerol secretion is not suppressed in obese type 2 diabetic men, Diabetologia 55 (2012) 2733–2740.
[175] E. Fabbrini, F. Magkos, B.S. Mohammed, et al., Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 15430–15435.
[176] L.P. Sorensen, E. Sondergaard, B. Nellemann, et al., Increased VLDL-triglyceride secretion precedes impaired control of endogenous glucose production in obese, normoglycemic men, Diabetes 60 (2011) 2257–2264.
[177] N. Sahini, J. Borlak, Recent insights into the molecular pathophysiology of lipid droplet formation in hepatocytes, Prog. Lipid Res. 54 (2014) 86–112.
[178] K. Begriche, J. Massart, M.A. Robin, et al., Mitochondrial adaptations and dysfunctions in nonalcoholic fatty liver disease, Hepatology 58 (2013) 1497–1507.
[179] N.B. Ruderman, D. Dean, Malonyl CoA, long chain fatty acyl CoA and insulin resistance in skeletal muscle, J. Basic Clin. Physiol. Pharmacol. 9 (1998) 295–308.
[180] R.L. Veech, The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism,, Prostagl. Leukot. Essent. Fat. Acids 70 (2004) 309–319.
[181] M.T. Nakamura, B.E. Yudell, J.J. Loor, Regulation of energy metabolism by long-chain fatty acids, Prog. Lipid Res. 53 (2014) 124–144.
[182] L.P. Bechmann, R.A. Hannivoort, G. Gerken, et al., The interaction of hepatic lipid and glucose metabolism in liver diseases, J. Hepatol. 56 (2012) 952–964.
[183] S. Fu, S.M. Watkins, G.S. Hotamisligil, The role of endoplasmic reticulum in hepatic lipid homeostasis and stress signaling,, Cell. Metab. 15 (2012) 623–634.
[184] S. Mandard, M. Muller, S. Kersten, Peroxisome proliferator-activated receptor alpha target genes, Cell. Mol. Life Sci. 61 (2004) 393–416.
[185] M. Rakhshandehroo, B. Knoch, M. Muller, et al., Peroxisome proliferator-activated receptor alpha target genes, PPAR Res. (2010) 2010.
[186] S. Crunkhorn, Metabolic disorders: FGF21 analogue shows promise in the clinic, Nat. Rev. Drug Discov. 12 (2013) 825.
[187] M. Straczkowski, M. Karczewska-Kupczewska, A. Adamska, et al., Serum

fibroblast growth factor 21 in human obesity: regulation by insulin infusion and relationship with glucose and lipid oxidation, Int. J. Obes. 37 (2013) 1386–1390.
[188] W.S. Chow, A. Xu, Y.C. Woo, et al., Serum fibroblast growth factor-21 levels are associated with carotid atherosclerosis independent of established cardiovascular risk factors, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 2454–2459.
[189] G. Gaich, J.Y. Chien, H. Fu, et al., The effects of LY2405319, an FGF21 analog, in obese human subjects with type 2 diabetes, Cell. Metab. 18 (2013) 333–340.
[190] Y. Li, K. Wong, A. Giles, et al., Hepatic SIRT1 attenuates hepatic steatosis and controls energy balance in mice by inducing fibroblast growth factor 21, Gastroenterology 146 (2014), 539–549 e537.
[191] T. Coskun, H.A. Bina, M.A. Schneider, et al., Fibroblast growth factor 21 corrects obesity in mice, Endocrinology 149 (2008) 6018–6027.
[192] Y. Zhang, T. Lei, J.F. Huang, et al., The link between fibroblast growth factor 21 and sterol regulatory element binding protein 1c during lipogenesis in hepatocytes, Mol. Cell. Endocrinol. 342 (2011) 41–47.
[193] I.C. Gaemers, J.M. Stallen, C. Kunne, et al., Lipotoxicity and steatohepatitis in an overfed mouse model for non-alcoholic fatty liver disease, Biochim. Biophys. Acta 1812 (2011) 447–458.
[194] G.M. Dallinga-Thie, R. Franssen, H.L. Mooij, et al., The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight, Atherosclerosis 211 (2010) 1–8.
[195] F. Willecke, D. Scerbo, P. Nagareddy, et al., Lipolysis, and not hepatic lipogenesis, is the primary modulator of triglyceride levels in streptozotocin-induced diabetic mice, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 102–110.
[196] S. Kersten, Physiological regulation of lipoprotein lipase, Biochim. Biophys. Acta 1841 (2014) 919–933.
[197] C. Marcoux, M. Tremblay, A. Fredenrich, et al., Lipoprotein distribution of apolipoprotein C-III and its relationship to the presence in plasma of triglyceride-rich remnant lipoproteins, Metabolism 50 (2001) 112–119.
[198] H. Campos, D. Perlov, C. Khoo, et al., Distinct patterns of lipoproteins with apoB defined by presence of apoE or apoC-III in hypercholesterolemia and hypertriglyceridemia, J. Lipid Res. 42 (2001) 1239–1249.
[199] A. Hiukka, M. Stahlman, C. Pettersson, et al., ApoCIII-enriched LDL in type 2 diabetes displays altered lipid composition, increased susceptibility for sphingomyelinase, and increased binding to biglycan, Diabetes 58 (2009) 2018–2026.
[200] S.D. Proctor, D.F. Vine, J.C. Mamo, Arterial retention of apolipoprotein B(48)- and B(100)-containing lipoproteins in atherogenesis, Curr. Opin. Lipidol. 13 (2002) 461–470.
[201] A. Varbo, M. Benn, G. Davey Smith, et al., Remnant cholesterol, low-density lipoprotein cholesterol, and blood pressure as mediators from obesity to ischemic heart disease, Circ. Res. (2014 Nov 19) pii: CIRCRESAHA.114.304846. [Epub ahead of print].
[202] B.G. Nordestgaard, A. Varbo, Triglycerides and cardiovascular disease, Lancet 384 (2014) 626–635.
[203] K. Nakajima, T. Saito, A. Tamura, et al., Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunoaffinity mixed gels, Clin. Chim. Acta 223 (1993) 53–71.
[204] Y. Fujioka, Y. Ishikawa, Remnant lipoproteins as strong key particles to atherogenesis, J. Atheroscler. Thromb. 16 (2009) 145–154.
[205] J.R. McNamara, P.K. Shah, K. Nakajima, et al., Remnant-like particle (RLP) cholesterol is an independent cardiovascular disease risk factor in women: results from the Framingham Heart Study, Atherosclerosis 154 (2001) 229–236.
[206] K. Kugiyama, H. Doi, K. Takazoe, et al., Remnant lipoprotein levels in fasting serum predict coronary events in patients with coronary artery disease, Circulation 99 (1999) 2858–2860.
[207] A. Varbo, M. Benn, A. Tybjaerg-Hansen, et al., Remnant cholesterol as a causal risk factor for ischemic heart disease, J. Am. Coll. Cardiol. 61 (2013) 427–436.
[208] A.B. Jorgensen, R. Frikke-Schmidt, A.S. West, et al., Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction, Eur. Heart J. 34 (2013) 1826–1833.
[209] A. Varbo, M. Benn, A. Tybjaerg-Hansen, et al., Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation, Circulation 128 (2013) 1298–1309.
[210] M. Thomsen, A. Varbo, A. Tybjaerg-Hansen, et al., Low nonfasting triglycerides and reduced all-cause mortality: a mendelian randomization study, Clin. Chem. 60 (2014) 737–746.
[211] Triglyceride Coronary Disease Genetics Collaboration, Emerging Risk Factors Collaboration, N. Sarwar, et al., Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies, Lancet 375 (2010) 1634–1639.
[212] T.M. Teslovich, K. Musunuru, A.V. Smith, et al., Biological, clinical and population relevance of 95 loci for blood lipids, Nature 466 (2010) 707–713.
[213] R. Do, C.J. Willer, E.M. Schmidt, et al., Common variants associated with plasma triglycerides and risk for coronary artery disease, Nat. Genet. 45 (2013) 1345–1352.
[214] B.G. Nordestgaard, A. Langsted, J.J. Freiberg, Nonfasting hyperlipidemia and cardiovascular disease, Curr. Drug Targets 10 (2009) 328–335.
[215] J.R. Moreton, Atherosclerosis and alimentary hyperlipemia, Science 106 (1947) 190–191.
[216] J.R. Moreton, Physical state of lipids and foreign substances producing atherosclerosis, Science 107 (1948) 371–373.
[217] D.C. Chan, G.F. Watts, T.G. Redgrave, et al., Apolipoprotein B-100 kinetics in visceral obesity: associations with plasma apolipoprotein C-III concentration, Metabolism 51 (2002) 1041–1046.
[218] G.F. Watts, P.H. Barrett, J. Ji, et al., Differential regulation of lipoprotein kinetics by atorvastatin and fenofibrate in subjects with the metabolic syndrome, Diabetes 52 (2003) 803–811.
[219] N. Mero, R. Malmstrom, G. Steiner, et al., Postprandial metabolism of apolipoprotein B-48- and B-100-containing particles in type 2 diabetes mellitus: relations to angiographically verified severity of coronary artery disease, Atherosclerosis 150 (2000) 167–177.
[220] H.C. Hassing, R.P. Surendran, H.L. Mooij, et al., Pathophysiology of hypertriglyceridemia, Biochim. Biophys. Acta 1821 (2012) 826–832.
[221] M.R. Taskinen, Lipoprotein lipase in diabetes, Diabetes Metab. Rev. 3 (1987) 551–570.
[222] K.J. Williams, K. Chen, Recent insights into factors affecting remnant lipoprotein uptake, Curr. Opin. Lipidol. 21 (2010) 218–228.
[223] K. Chen, M.L. Liu, L. Schaffer, et al., Type 2 diabetes in mice induces hepatic overexpression of sulfatase 2, a novel factor that suppresses uptake of remnant lipoproteins, Hepatology 52 (2010) 1957–1967.
[224] H.C. Hassing, H. Mooij, S. Guo, et al., Inhibition of hepatic sulfatase-2 in vivo: a novel strategy to correct diabetic dyslipidemia, Hepatology 55 (2012) 1746–1753.
[225] N. Matikainen, M.A. Burza, S. Romeo, et al., Genetic variation in SULF2 is associated with postprandial clearance of triglyceride-rich remnant particles and triglyceride levels in healthy subjects, PLoS One 8 (2013) e79473.
[226] H.C. Hassing, R.P. Surendran, B. Derudas, et al., SULF2 strongly prediposes to fasting and postprandial triglycerides in patients with obesity and type 2 diabetes mellitus, Obesity (Silver Spring) 22 (2014) 1309–1316.
[227] A.T. Wong, D.C. Chan, J. Pang, et al., Plasma apolipoprotein B-48 transport in obese men: a new tracer kinetic study in the postprandial state, J. Clin. Endocrinol. Metab. 99 (2014) E122–E126.
[228] A.T. Wong, D.C. Chan, P.H. Barrett, et al., Effect of omega-3 fatty acid ethyl esters on apolipoprotein B-48 kinetics in obese subjects on a weight-loss diet: a new tracer kinetic study in the postprandial state, J. Clin. Endocrinol. Metab. 99 (2014) E1427–E1435.
[229] F. Sun, M. Stolinski, F. Shojaee-Moradie, et al., A novel method for measuring intestinal and hepatic triacylglycerol kinetics, Am. J. Physiol. Endocrinol. Metab. 305 (2013) E1041–E1047.
[230] F.M. Riches, G.F. Watts, R.P. Naoumova, et al., Hepatic secretion of very-low-density lipoprotein apolipoprotein B-100 studied with a stable isotope technique in men with visceral obesity, Int. J. Obes. Relat. Metab. Disord. 22 (1998) 414–423.
[231] F. Pont, L. Duvillard, E. Florentin, et al., Early kinetic abnormalities of apoB-containing lipoproteins in insulin-resistant women with abdominal obesity, Arterioscler. Thromb. Vasc. Biol. 22 (2002) 1726–1732.
[232] A.H. Kissebah, S. Alfarsi, D.J. Evans, et al., Plasma low density lipoprotein transport kinetics in noninsulin-dependent diabetes mellitus, J. Clin. Investig. 71 (1983) 655–667.
[233] B. Verges, New insight into the pathophysiology of lipid abnormalities in type 2 diabetes, Diabetes Metab. 31 (2005) 429–439.
[234] M. Stahlman, H.T. Pham, M. Adiels, et al., Clinical dyslipidaemia is associated with changes in the lipid composition and inflammatory properties of apolipoprotein-B-containing lipoproteins from women with type 2 diabetes, Diabetologia 55 (2012) 1156–1166.
[235] C.J. Packard, Triacylglycerol-rich lipoproteins and the generation of small, dense low-density lipoprotein, Biochem. Soc. Trans. 31 (2003) 1066–1069.
[236] A.M. Georgieva, M.M. van Greevenbroek, R.M. Krauss, et al., Subclasses of low-density lipoprotein and very low-density lipoprotein in familial combined hyperlipidemia: relationship to multiple lipoprotein phenotype, Arterioscler. Thromb. Vasc. Biol. 24 (2004) 744–749.
[237] K.R. Feingold, C. Grunfeld, M. Pang, et al., LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes, Arterioscler. Thromb. 12 (1992) 1496–1502.
[238] C. Baynes, A.D. Henderson, V. Anyaoku, et al., The role of insulin insensitivity and hepatic lipase in the dyslipidaemia of type 2 diabetes,, Diabet. Med. 8 (1991) 560–566.
[239] E.A. Nikkila, J.K. Huttunen, C. Ehnholm, Postheparin plasma lipoprotein lipase and hepatic lipase in diabetes mellitus. Relationship to plasma triglyceride metabolism, Diabetes 26 (1977) 11–21.
[240] M.A. Austin, M.-C. King, K.M. Vranizan, et al., Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk, Circulation 82 (1990) 495–506.
[241] B. Lamarche, A. Tchernof, S. Moorjani, et al., Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study, Circulation 95 (1997) 69–75.
[242] C.D. Gardner, S.P. Fortmann, R.M. Krauss, Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women, J. Am. Med. Assoc. 276 (1996) 875–881.
[243] J. Vakkilainen, G. Steiner, J.C. Ansquer, et al., Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS), Circulation 107 (2003) 1733–1737.

[244] F.M. Sacks, H. Campos, Clinical review 163: cardiovascular endocrinology: low-density lipoprotein size and cardiovascular disease: a reappraisal, J. Clin. Endocrinol. Metab. 88 (2003) 4525–4532.
[245] A.T. Lada, L.L. Rudel, Associations of low density lipoprotein particle composition with atherogenicity, Curr. Opin. Lipidol. 15 (2004) 19–24.
[246] S. Rashid, T. Watanabe, T. Sakaue, et al., Mechanisms of HDL lowering in insulin resistant, hypertriglyceridemic states: the combined effect of HDL triglyceride enrichment and elevated hepatic lipase activity, Clin. Biochem. 36 (2003) 421–429.
[247] M. Stahlman, B. Fagerberg, M. Adiels, et al., Dyslipidemia, but not hyperglycemia and insulin resistance, is associated with marked alterations in the HDL lipidome in type 2 diabetic subjects in the DIWA cohort: Impact on small HDL particles, Biochim. Biophys. Acta 1831 (2013) 1609–1617.
[248] J. Borén, M.R. Taskinen, S.O. Olofsson, M. Levin, Ectopic lipid storage and insulin resistance: a harmful relationship, J Intern Med. 274 (1) (2013 Jul) 25–40.
[249] M. Adiels, S.O. Olofsson, M.R. Taskinen, et al., Diabetic dyslipidaemia, Curr. Opin. Lipidol. 17 (2006) 238–246.
[250] G.F. Watts, E.M. Ooi, D.C. Chan, Demystifying the management of hypertriglyceridaemia, Nat. Rev. Cardiol. 10 (2013) 648–661.