MEDWIN PUBLISHERS
Committed to create value for Researchers

Diabetes and Obesity International Journal
ISSN: 2574-7770

Hypertriglyceridemia and Non-Alcoholic Fatty Liver Disease in Metabolic Syndrome and Type 2 Diabetes

Tangvarasittichai S*

Chronic Diseases Research Unit, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Thailand

***Corresponding author**: Dr. Surapon Tangvarasittichai, Chronic Diseases Research Unit, Department of Medical Technology, Faculty of Allied Health Sciences, Naresuan University, Phitsanulok 65000, Thailand, Tel: 66055966276; Email: surapon14t@yahoo.com

Review Article

Volume 3 Issue 4

Received Date: September 24, 2018

Published Date: October 29, 2018

DOI: 10.23880/doij-16000188

Abstract

Metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) are associated with artherogenic dyslipidemia and abnormal postprandial lipoprotein metabolism which consists with elevated fasting and postprandial triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol as cardiovascular disease risk factors. These abnormal lipids concentrations can result from alterations in the production, conversion, or catabolism of lipoprotein particles. Whereas the liver is the central organ in lipogenesis, gluconeogenesis and cholesterol metabolism and the intestine is also a major role in lipoprotein production. However, many research studies demonstrated a variety of pathological conditions focused on the metabolic functions within the liver. As observed in the world population, increase in the prevalence of MetS and T2DM promotes pathophysiological from atherogenic dyslipidemia and cause non-alcoholic fatty liver disease (NAFLD). Alterations in insulin activity, response and signaling are held accountable for these alterations in lipid storage, transport andβ-oxidation. This review focuses on dysfunctions and alterations in increased lipoprotein production prolongs dyslipidemia, hepatic lipid uptake, storage and metabolism in the clinical of NAFLD in MetS and T2DM patients, and may directly contribute to cause atherogenesis in these patients.

Keywords: Metabolic Syndrome; Type 2 Diabetes Mellitus; Insulin Resistance; Adipose Tissue; Dyslipidemia; β-Oxidation; De Novo Lipogenesis; Non-Alcoholic Fatty Liver Disease

Abbreviations: MetS: Metabolic Syndrome; T2DM: Type 2 Diabetes Mellitus; TRLs: Triglyceride-Rich Lipoproteins; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; NAFLD: Non-Alcoholic Fatty Liver Disease

Introduction

Obesity is increasing dramatically in the world with consequences important pathological of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1]. About 350 million cases global incidence of T2DM is projected to 592 million by 2035, with estimated to reach $132 billion to diabetes in the United States [2] 20% number of adults with diabetes are in developed countries and by 69% in developing countries [3]. These increasing rates of T2DM worldwide represent the important disease burden to the world population as well as for the total health care system. In general of classical perception, adipose tissue as an organ of fatty acids storage, has been known and replaced over the last few years by the research knowledge that adipose tissue has the central role in lipid and glucose metabolism and also produces a large number of adipokines and hormones, e.g. leptin, adiponectin, interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1) [4]. Excessive visceral obesity, referred as metabolic syndrome (MetS) is associated with the increasing incidence of CVD and T2DM [5]. There are several CVD risk factors including (i) age, gender and genetics as un-modifiable factors and (ii) traditional risk factors as hypertension, dyslipidemia, hyperglycemia and smoking. This cardiometabolic risk is driven by the interplay between these factors and the components of MetS associated with T2DM. The association of atherogenic dyslipidemia with MetS and T2DM is characterized by a cluster of interrelated in abnormalities of lipoprotein metabolism, which consists of elevated plasma triglyceride (TG)-rich lipoproteins (TRLs) of both fasting and postprandial state, reduced high-density lipoprotein (HDL) cholesterol and small dense low-density lipoprotein (sdLDL).

Nonalcoholic fatty liver disease (NAFLD) is the liver disorders ranging from a simple steatosis to nonalcoholic steatohepatitis and cirrhosis (as advanced pathologies). The central obesity associated with insulin resistance is the major cause of hepatic steatosis which is characterized by over triglyceride-rich lipid accumulation in the liver. The evidence of triglyceride-rich lipid accumulation supports by dysregulation of adipose lipolysis and liver de novo lipogenesis (DNL) plays a major role in hepatic steatosis. This review aims to summarize the understanding of the pathophysiology of adipose tissue metabolism, which is altered by central obesity and T2DM, causes insulin resistance in the liver and skeletal muscle. The contribution of the alterations in hepatic glucoseandlipid metabolism by disturbing theinsulin signalling pathways through fatty acids in circulation causing lipid overload and lipotoxicity and are linked to NAFLD pathogenesis [6].

Distribution of Triglyceride (TG)-Rich Lipoproteins

Dietary lipids are hydrolyzed and taken up by enterocytes in the intestinal lumen [7]. The lipids are assembled into the chylomicron particles by using apolipoprotein (apo) B-48. Then, these chylomicrons are secreted into lymphatic vessels originating from the villi of the small intestine and enter into bloodstream at the thoracic duct's connection with the left subclavian vein. TRLs consist with a core neutral lipids (mainly triglycerides and some of cholesteryl esters) surrounded by a monolayer of phospholipids, free cholesterol and proteins. Each TRL particle contains one molecule of apoB. Plasma TRLs are the mixture of lipoprotein species and derived from the intestine (chylomicrons) or the liver [very low density lipoprotein (VLDL)] [7, 8]. ApoB exists in two major forms, apoB-48 and apoB-100, both are coded by the same gene. ApoB-48, which is formed in the intestine and is present on chylomicrons and chylomicron remnants, while apoB-100 presents on VLDL, intermediate-density lipoprotein (IDL) and low density lipoprotein (LDL). VLDL in the circulation is exposed and catalyzed by lipoprotein lipase (LPL) to remove triglycerides for storage or energy production in adipose tissue, cardiac muscle and skeletal muscle. After triglycerides were removed from large VLDL1 by LPL, they increases density and become to VLDL2 particles. The activity of LPL determines for the residence time forVLDL1 and VLDL2 particles in circulation.

VLDL particles can be separated into two classes: (i) VLDL1, a large triglyceride-rich particle [Svedberg flotation rate (Sf) 60-400] and (ii) VLDL2, a smaller, denser particle (Sf 20-60). Large VLDL1 particles were used as the major determinant for plasma triglycerides variation of between healthy subjects and T2DM patients, and have been reported elevated VLDL1 particles in T2DM subjects [9]. Increased secretion of VLDL from the liver is the major determinant of postprandial dyslipidemia (elevation of chylomicrons and chylomicron remnants) [10]. Thus, the plasma triglyceride concentration may reflect the balance between the secretion and removal of TRLs. In normal physiology, insulin inhibits the production of apoB-48 and also inhibits chylomicrons secretion [11]. Thus, insulin resistance may cause chronic intestinal apoB-48

overproduction to cause more efficiency of intestinal fat packaging and contribute to liver lipids and postprandial lipidemia [11,12]. About 80% of elevated triglycerides after a fat-load meal come from apoB-48-containing chylomicronsparticles [13], and approximately 80% of the increase in another particle is accounted from apoB-100-containing VLDL particles [14].

VLDL Synthesis, Secretion and Dysregulation

Recently research studied report the overproduction of large VLDL1 particles from liver, is a major factor of the of serum triglycerides concentration in T2DM patients [15]. This overproduction and secretion of large VLDL1 particles is due to the overproduction of both VLDL1-triglyceride and VLDL1-apoB to cause increased concentration of VLDL1 particles that are similar in size and composition to those of all subjects. Many research data demonstrated that hepatic lipid metabolism is severely dysregulated in T2DM [15,16]. The liver plays a central role of lipid metabolism. Hepatic lipid homeostasis is the balance between the import and export of lipids while an imbalance dysregulated the import and export of lipids, these processes leads to increased VLDL secretion or increased lipid accumulation in hepatocytes to cause hepatic steatosis or non-alcoholic fatty liver disease (NAFLD), common occurred in MetS and T2DM [16,17]. The synthesis and secretion of VLDL particles has been studied in hepatoma cell lines and hepatocytes from animals, which is dependent on triglyceride and apoB-100 substrates availability and is regulated by insulin and hormones [18]. In general, free fatty acids (FFAs) were used for hepatic TG formation are derived from three major sources: (i) diet, (ii) de novo lipogenesis (DNL), and (iii) adipose tissue lipolysis. Donnelly, et al. demonstrated that in the livers of NAFLD patients, 60% of hepatic TG accumulation is derived from FFAs mobilized from peripheral adipose tissue, 25%from hepatic DNL, and 15% from dietary lipids [19]. This evidence indicates that dysregulation of adipose lipolysis and hepatic DNL plays major roles of TG accumulation in liver and progression of NAFLD pathogenesis. In normal physiology, DNL is stimulated by increased plasma glucose and insulin that occurs at postprandial state while lipolysis occurs at fasting state that is induced by catecholamines, natriuretic peptides, and glucagon but suppressed by insulin [20]. Therefore, disorder in endocrine system can also directly contribute to the development and progression of NAFLD.

Metabolism of dynamics FFAplaysthe major role in hepatocytes triglyceride synthesis and the TGaccumulation in liver [21,22]. In fasting state, declined insulin level stimulates TG hydrolysis in adipocyte to mobilize FFAs for non-adipose tissue using such as the liver. However, in insulin resistant state, which is associated with central obesity or T2DM condition, adipocyte lipolysis increases regardless of nutritional fluctuations, leading to cause abundant FFAs released into the blood circulation [19]. Overall the FFAs delivery from the adipose tissue is increased in obesity and T2DM. There are many membrane-bound proteins in the liver, which are responsible for circulating FFAs transportation into hepatocytes, such as fatty acid transporter protein (FATP)-2, FATP-5 [23], fatty acid translocase (FAT/CD36) [24], fatty acid binding proteins (FABP)-1, FABP-4, FABP-5 [25], and caveolins [26]. Up-regulation of many FFA transporters is associated with insulin resistant state and increased hepatic steatosis in NAFLD patients [27]. The expression of these FFA transporters is regulated by insulin and nuclear receptors, such as liver X receptor (LXR) [28], farnesoid X receptor (FXR) [29], pregnane X receptor (PXR) [30], peroxisome proliferator-activated receptor (PPAR)-α, and PPAR-γ [31]. Therefore, the targeting of these nuclear receptors is attractive receptors for NAFLD prevention. Notably the FA sources for the liver fat and the released VLDL particles are the same [32].

Hepatic De Novo Lipogenesis

Increased levels of FFAs in circulation play an important role of hepatic steatosis in obese and T2DM.

De novo lipogenesis, locally synthesized FFAs from glucose also contribute about one-third proportion of the total TGs accumulation in the livers of NAFLD patients [19]. In normal physiological, DNL postprandial increases which is mediated by the two transcriptional factors: (i) Sterol regulatory element binding protein-1c(SREBP-1c) [33], which is activated by insulin; and (ii) Carbohydrate response element binding protein (ChREBP), which is activated by glucose [34]. During carbohydrate feeding, insulin induces SREBP-1c activation, which involves by two mechanisms: (i) Transcriptional up-regulation and (ii) Proteolytic cleavage activation of SREBP-1c precursor [35]. SREBP-1c precursor localized at the endoplasmic reticulum (ER) membrane, where it interacts with SREBP cleavageactivating protein (SCAP) [35,36]. SCAP interacts with insulin-induced gene (INSIG) protein, which retains the SREBP-1c/SCAP complex in the ER when cellular cholesterol is high [37]. SCAP will dissociate from INSIG, and the SREBP-1c/SCAP complex is transported into the Golgi apparatus as coat protein II vesicles when cholesterol depletion or presence of insulin [38]. In Golgi apparatus, SREBP-1c precursor is cleaved by two

proteases, (i) S1P and (ii) S2P, releasing its N terminus as the active form of the transcription factor. Then, enter the nucleus to activate the lipogenic gene expression [39]. In the insulin-resistant liver, lipogenesis is selectively enhanced even resistance to insulin-mediated suppression of gluconeogenesis [39]. These evidences suggest that ER stress activates the cleavage of insulin-independent SREBP-1c [40]. In obese animal model, the ER stress inhibition decreases SREBP-1c activation and lipogenesisto improve hepatic steatosis and insulin sensitivity [40]. The transcriptional factors, ChREBP when cellular glucose is low, it localizes in the cytoplasm, when cellular glucose is high, it enters into the nucleus [34]. Glucose activates ChREBP expression, regulated its translocation from the cytoplasm to the nucleus, and promoting its binding with carbohydrate responsive element (ChoRE) [34,41]. ChoRE is present at the promoters of glycolytic and lipogenic genes, including acetyl-CoA carboxylase 1, fatty acid synthase (FAS), and stearoyl-CoA desaturase 1 (SCD-1) [34,42]. ChREBP activation mediated the lipogenic genes expression may increase TG synthesis. Consistently within the NAFLD patients demonstrate increased hepatic enzyme activities for TG synthesis, such as glycerol-3-phosphate acyltransferase, 1-acylglycerol-3-phosphate acyltransferase, and diacylglycerolacyltransferase [42,43]. Under fasting condition in NAFLD patients, DNL is not further increase postprandially suggested that the liver of these patients may have reached the maximal capacity in DNL [19,44].

Altered Hepatic TG Secretion

Hepatic TGs were packaged as a constituent of very low density lipoprotein (VLDL) for secretion into the blood circulation. VLDL particles assembly occurs in the ER, this process involves the interactions of lipids and apoB-100 [45]. This process is mediated by microsomal TG transfer protein (MTP), that has apoB100 binding activity and lipid transfer activity [46]. The VLDL secretion rate depends on the availability of hepatic TG lipids and the overall hepatocytes capacity for VLDL assembly. When TGs are unavailable, lipid-free apoB100 is degraded via proteasomal and non-proteasomal pathways [47]. Insulin plays the major role in regulation of the capacity for VLDL assembly. For the response of insulin action, apoB-100 is degraded [47], while MTP expression is suppressed [48]. Then, impaired VLDL assembly and secretion can cause the excessive lipid accumulation in the liver, as found in the hypobetalipoproteinemiapatients that caused from apoB mutation [49] or in the abetalipoproteinemia that caused from MTP mutations [50]. However, NAFLD is characterized by increased expression of hepatic apoB-100 and MTP [51], and also characterized by VLDL particles overproduction, which may enhance lipid availability from fat lipolysis and hepatic DNL and the failure of insulin to suppress VLDL production. VLDL overproduction and secretion may be the compensatory mechanism to protect the liver from steatos is under over nutritional conditions. However, under prolonged over nutrition condition, this mechanism may fail to counter-balance to cause chronic increases in liver TG synthesis, resulting in hepatic steatosis. These observations may demonstrate the disorder stimulation of lipogenesis in insulin resistant liver.

Hepatic TG hydrolysis, Fatty Acid Oxidation and Autophagyin Fatty liver

Hepatic TGs hydrolysis and fatty acid β-oxidation is the other metabolic pathway for the hepatic TGs disposal in mitochondria. All of the excessive TGs are stored in cytosolic LDs and have to be hydrolyzed to release FFAs for utilization by using functional hydrolases. Wu, et al. reported that the deletion of adipose triglyceride lipase (ATGL) induces hepatic steatosis [52]. This ATGL enzyme requires comparative gene identification-58 (CGI-58) as a co-activator for the full activation. [This CGI-58 also known as α/β-hydrolase domain-containing 5 (Abhd5)] [53]. The deletion of CGI-58 in liver relative to ATGL causes more advanced TG accumulation in liver to cause NAFLD, NASH and hepatic fibrosis [54], while the deletion of ATGL knockout mice develop only simple steatosis but not NASH or fibrosis [52]. This suggests that the CGI-58 plays an essential role in NAFLD development and progression.

Autophagy is a catabolic process of basal turnover of the constituents of damaged cell, organelles, lipids and LDs to lysosomes for degradation in normal physiological conditions. Autophagic turnover increases in prolonged starvation to maintain the cellular energy homeostasis. Singh et al. have demonstrated the downregulation of lipid-specific macroautophagy in the liver of genetic and dietary obese mice, promotes steatosis [55]. This also found decreased hepatic autophagy in obese mice [56]. There are many mechanisms that account for the autophagy decline [55]: (i) Elevated autophagy-related gene-7 degradation by the obesity-induced calcium-dependent protease calpain-2 [56], (ii) Increased amino acid flux into hepatocytes in overnutrition state to cause hyper-activation of rapamycin signaling, an autophagy inhibitory pathway [57], (iii) reduction in lysosomal

acidification and cathepsin L to cause impairs substrate degradation in autolysosomes [58]. Fukuo, et al. demonstrated that the expression of cathepsin B, D, and L levels is decreased in the liver of NAFLD patients [59]. The alterations of AMPK and PI3K signaling pathways may also regulate autophagy to influence NAFLD development and progression in obese. Schematic of these processes were summarized in Fig 1.

Genetic and NAFLD Development

The etiology of hepatic steatosis is multifactorial, genetic involvement [60] and life style or environmental factors, including over nutrition, alcohol consumption, virus infection, drugs, or altered immune function. Hepatic steatosis is an early and simple form of fatty liver disease, which is characterized by triglyceride (TG)-rich lipid droplets (LDs) accumulation in the hepatocytes, but without hepatic inflammation or liver injury. Hepatic steatosis is diagnosed when present hepatic TG content exceeds the 95th percentile for healthy individuals (>55 mg per g of liver) or present cytoplasmic LDs more than 5% of hepatocytes [60]. Nonalcoholic fatty liver disease (NAFLD) is the common fatty liver disease and covers the full spectrum of liver pathologies, such as hepatic steatosis, nonalcoholic steatohepatitis (NASH) and cirrhosis. Hepatic steatosis is benign. However, some of these steatosis patients may develop to NASH and may progress to hepatic fibrosis, cirrhosis or cancer [61]. The prevalence of fatty liver disease is estimated to be 20%–30% in Western countries and 5%-18% in Asia [62,63]. Genetic is a significantly contributor to cause NAFLD [64]. According to the advances study in this field as: (i) Identified a missense variant in patatin-like phospholipase domain-containing 3 (PNPLA3),it's strongly associated with hepatic TG levels [65], (ii) Identifieda common SNPs associated with hepatic TG levels [66],(iii) Including two variants in PNPLA3(rs738409 and rs2281135) and TM6SF2 (rs58542926) [67]. The PNPLA3 function is involved with acylglycerol synthesis and hydrolysis [68]. Neither depletion nor over expression of wild-type PNPLA3 affects hepatic TG levels in mice [69], whereas hepatic over expression of PNPLA3 148M causes steatosis [70].PNPLA3 I148M has also been shown reduction of VLDL lipidation to promote lipid accumulation intracellular of the liver without affecting the body mass, dyslipidemia, or insulin resistance [71],(iv) Two SNPs in the promoter region of the APOC3 gene have been associated with NAFLD [72],but this APOC3 variants have failed to confirm with NAFLD in Hispanic, European American, African American and European subjects [73].

Conclusion

Obese, MetS and T2DM patients have the higher risk for CVD than normal subjects. As the results of these metabolisms and signaling pathways that try to compensate for these dysregulation metabolism, including insulin resistance and NAFLD. The evidence that raised the concentration of VLDL and TG, is the major CVD risk factor and all-cause mortality. This failure includes lipotoxicity-associated disturbance in insulin activity and signaling, mitochondrial dysfunction, oxidative stress, and dysregulation of lipid transport and metabolism in adipose tissue and liver. This supported by the research studies in genetic and epidemiology evidences. The crosslink between fat transportation, metabolism and the liver is obvious. Prevention and therapeutic approaches should highlight on integrated pathophysiology of organ-organ fat communications, transportation and accumulation. Hopefully, these results may lead to the new treatment that target on this hepatic dysregulation of large VLDL, TRLs clearance and postprandial hyperlipidemia.

Conflict of Interest: The author has no conflict of interest to report.

Acknowledgement: We sincerely thank all co-workers, technical assistance and Asst. Prof. Dr. Ronald A. Markwardt, Burapha University, for his critical reading and correcting of the manuscript.

References

1. Flier JS (2004) Obesity wars: molecular progress confronts an expanding epidemic. Cell 116(2): 337-350.

2. Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, et al. (2014) Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res ClinPract 103(2): 137-149.

3. Whiting DR, Guariguata L, Weil C, Shaw J (2011) IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 94(3): 311-321.

4. Winkler G, Winkler G, Kiss S, Keszthelyi L, Sápi Z, et al. (2003) Expression of tumor necrosis factor (TNF)-alpha protein in the subcutaneous and visceral adipose tissue in correlation with adipocyte cell

volume, serum TNF-alpha, soluble serum TNF-receptor-2 concentrations and C-peptide level. Eur J Endocrinol 149(2): 129-135.

5. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, et al. (2005) Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet 366(9497): 1640-1649.

6. Unger RH (200) Lipotoxic diseases. Annu Rev Med 53: 319-336.

7. Hussain MM (2014) Intestinal lipid absorption and lipoprotein formation. Curr Opin Lipidol 25(3): 200-206.

8. Olofsson SO, Borèn J (2005) Apolipoprotein B: a clinically important apolipoprotein which assembles atherogenic lipoproteins and promotes the development of atherosclerosis. J Intern Med 258(5): 395-410.

9. Hiukka A, Fruchart-Najib J, Leinonen E, Hilden H, Fruchart JC, et al. (2005) Alterations of lipids and apolipoprotein CIII in very low density lipoprotein subspecies in type 2 diabetes. Diabetologia 48(6): 1207-1215.

10. Adiels M, Matikainen N, Westerbacka J, Söderlund S, Larsson T, et al. (201) Postprandial accumulation of chylomicrons and chylomicron remnants is determined by the clearance capacity. Atherosclerosis 222(1): 222-228.

11. Xiao C, Lewis GF (2012) Regulation of chylomicron production in humans. Biochim Biophys Acta 1821(5): 736-746.

12. Xiao C, Dash S, Morgantini C, Lewis GF (2014) New and emerging regulators of intestinal lipoprotein secretion. Atherosclerosis 233(2): 608-615.

13. Cohn JS, Johnson EJ, Millar JS, Cohn SD, Milne RW, et al. (1993) 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(12): 2033-2040.

14. Karpe F, Bell M, Björkegren J, Hamsten A (1995) 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(2): 199-207.

15. Verges B (2010) Abnormal hepatic apolipoprotein B metabolism in type 2 diabetes. Atherosclerosis 211(2): 353-360.

16. Perry RJ, Samuel VT, Petersen KF, Shulman GI (2014) The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature 510(7503): 84-91.

17. Adiels M, Westerbacka J, Soro-Paavonen A, Häkkinen AM, Vehkavaara S, et al. (2007) Acute suppression of VLDL1 secretion rate by insulin is associated with hepatic fat content and insulin resistance. Diabetologia 50(11): 2356-2365.

18. Sparks JD, Sparks CE, Adeli K (2012) Selective hepatic insulin resistance, VLDL overproduction, and hypertriglyceridemia. Arterioscler Thromb Vasc Biol 32(9): 2104-2112.

19. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, et al. (2005) Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115(5): 1343-1351.

20. Nielsen TS, Jessen N, Jørgensen JO, Møller N, Lund S (2014) Dissecting adipose tissue lipolysis: molecular regulation and implications for metabolic disease. J Mol Endocrinol 52(3): R199-R222.

21. Lewis GF, Uffelman KD, Szeto LW, Weller B, Steiner G (1995) Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans. J Clin Investig 95(1): 158-166.

22. Hodson L, Frayn KN (2011) Hepatic fatty acid partitioning. Curr Opin Lipidol 22(3): 216-224.

23. Falcon A, Doege H, Fluitt A, Tsang B, Watson N, et al. (2010) FATP2 is a hepatic fatty acid transporter and peroxisomal very long-chain acyl-CoA synthetase. Am J Physiol Endocrinol Metab 299(3): E384-E393.

24. Xu S, Jay A, Brunaldi K, Huang N, Hamilton JA (2013) CD36 enhances fatty acid uptake by increasing the rate of intracellular esterification but not transport across the plasma membrane. Biochemistry 52(41): 7254-7261.

25. Queipo-Ortuño MI, Escoté X, Ceperuelo-Mallafré V, Garrido-Sanchez L, Miranda M, et al. (2012) FABP4 dynamics in obesity: discrepancies in adipose tissue and liver expression regarding circulating plasma levels. PLoS ONE 7(11): e48605.

26. Mastrodonato M, Calamita G, Rossi R, Mentino D, Bonfrate L, et al. (2011) Altered distribution of caveolin-1 in early liver steatosis. Eur J Clin Invest 41(6): 642-651.

27. Berk PD (2008) Regulatable fatty acid transport mechanisms are central to the pathophysiology of obesity, fatty liver, and metabolic syndrome. Hepatology 48(5): 1362-1376.

28. Lima-Cabello E, García-Mediavilla MV, Miquilena-Colina ME, Vargas-Castrillón J, Lozano-Rodríguez T, et al. (2011) Enhanced expression of pro-inflammatory mediators and liver X-receptor-regulated lipogenic genes in non-alcoholic fatty liver disease and hepatitis C. Clin Sci (Lond) 120(6): 239-250.

29. Yang ZX, Shen W, Sun H (2010) Effects of nuclear receptor FXR on the regulation of liver lipid metabolism in patients with non-alcoholic fatty liver disease. Hepatol Int 4(4): 741-748.

30. Zhou J, Febbraio M, Wada T, Zhai Y, Kuruba R, et al. (2008) Hepatic fatty acid transporter Cd36 is a common target of LXR, PXR, and PPARgamma in promoting steatosis. Gastroenterology 134(2): 556-567.

31. Memon RA, Tecott LH, Nonogaki K, Beigneux A, Moser AH, et al. (2000) Up-regulation of peroxisome proliferator-activated receptors (PPAR-α) and PPAR-γ messenger ribonucleic acid expression in the liver in murine obesity: troglitazone induces expression of PPAR-γ-responsive adipose tissue-specific genes in the liver of obese diabetic mice. Endocrinology 141(11): 4021-4031.

32. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, et al. (2005) Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. J Clin Invest 115(5): 1343-1351.

33. Foretz M, Guichard C, Ferré P, Foufelle F (1999) Sterol regulatory element binding protein-1c is a major mediator of insulin action on the hepatic expression of glucokinase and lipogenesis-related genes. Proc Natl Acad Sci USA 96(22): 12737-12742.

34. Ishii S, Iizuka K, Miller BC, Uyeda K (2004) Carbohydrate response element binding protein directly promotes lipogenic enzyme gene transcription. Proc Natl Acad Sci USA 101(44): 15597-15602.

35. Shimomura I, Bashmakov Y, Ikemoto S, Horton JD, Brown MS, et al. (1999) Insulin selectively increases SREBP-1c mRNA in the livers of rats with streptozotocin-induced diabetes. Proc Natl Acad Sci USA 96(24): 13656-13661.

36. Nohturfft A, DeBose-Boyd RA, Scheek S, Goldstein JL, Brown MS (1999) Sterols regulate cycling of SREBP cleavage-activating protein (SCAP) between endoplasmic reticulum and Golgi. Proc Natl Acad Sci USA 96(20): 11235-11240.

37. Yang T, Espenshade PJ, Wright ME, Yabe D, Gong Y, et al. (2002) Crucial step in cholesterol homeostasis: sterols promote binding of SCAP to INSIG-1, a membrane protein that facilitates retention of SREBPs in ER. Cell 110(4): 489-500.

38. Yellaturu CR, Deng X, Cagen LM, Wilcox HG, Mansbach CM 2nd, et al. (2009) Insulin enhances post-translational processing of nascent SREBP-1c by promoting its phosphorylation and association with COPII vesicles. J Biol Chem 284(12): 7518-7532.

39. Horton JD, Goldstein JL, Brown MS (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. J Clin Invest 109(9): 1125-1131.

40. Kammoun HL, Chabanon H, Hainault I, Luquet S, Magnan C, et al. (2009) GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. J Clin Invest 119(5): 1201-1215.

41. Uyeda K, Repa JJ (2006) Carbohydrate response element binding protein, ChREBP, a transcription factor coupling hepatic glucose utilization and lipid synthesis. Cell Metab 4(2): 107-110.

42. Ma L, Robinson LN, Towle HC (2006) ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. J Biol Chem 281(39): 28721-28730.

43. Lindén D, William-Olsson L, Ahnmark A, Ekroos K, Hallberg C, et al. (2006) Liver-directed overexpression of mitochondrial glycerol-3-phosphate acyltransferase results in hepatic steatosis, increased triacylglycerol secretion and reduced fatty acid oxidation. FASEB J 20(3): 434-443.

44. Diraison F, Moulin P, Beylot M (2003) 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(5): 478-485.

45. Gibbons GF, Wiggins D, Brown AM, Hebbachi AM (2004) Synthesis and function of hepatic very-low-density lipoprotein. Biochem Soc Trans 32(Pt 1): 59-64.

46. Hussain MM, Shi J, Dreizen P (2003) Microsomal triglyceride transfer protein and its role in apoB-lipoprotein assembly. J Lipid Res 44(1): 22-32.

47. Ginsberg HN, Fisher EA (2009) The ever-expanding role of degradation in the regulation of apolipoprotein B metabolism. J Lipid Res 50S: S162-S166.

48. Lindén D, William-Olsson L, Ahnmark A, Ekroos K, Hallberg C, et al. (2006) Liver-directed overexpression of mitochondrial glycerol-3-phosphate acyltransferase results in hepatic steatosis, increased triacylglycerol secretion and reduced fatty acid oxidation. FASEB J 20(3): 434-443.

49. Tanoli T, Yue P, Yablonskiy D, Schonfeld G (2004) Fatty liver in familial hypobetalipoproteinemia: roles of the APOB defects, intraabdominal adipose tissue, and insulin sensitivity. J Lipid Res 45(5): 941-947.

50. Berriot-Varoqueaux N, Aggerbeck LP, Samson-Bouma M, Wetterau JR (2000) The role of the microsomal triglygeride transfer protein in abetalipoproteinemia. Annu Rev Nutr 20(1): 663-697.

51. Higuchi N, Kato M, Tanaka M, Miyazaki M, Takao S, et al. (2011) Effects of insulin resistance and hepatic lipid accumulation on hepatic mRNA expression levels of apoB, MTP and L-FABP in non-alcoholic fatty liver disease. ExpTher Med 2(6): 1077-1081.

52. Wu JW, Wang SP, Alvarez F, Casavant S, Gauthier N, et al. (2011) Deficiency of liver adipose triglyceride lipase in mice causes progressive hepatic steatosis. Hepatology 54(1): 122-132.

53. Lass A, Zimmermann R, Haemmerle G, Riederer M, Schoiswohl G, et al. (2006) Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin-Dorfman syndrome. Cell Metab 3(5): 309-319.

54. Guo F, Ma Y, Kadegowda AK, Betters JL, Xie P, et al. (2013) Deficiency of liver comparative gene identification-58 causes steatohepatitis and fibrosis in mice. J Lipid Res 54(8): 2109-2120.

55. Lavallard VJ, Gual P (2014) Autophagy and non-alcoholic fatty liver disease. Biomed Res Int 2014: 120179.

56. Yang L, Li P, Fu S, Calay ES, Hotamisligil GS (2010) Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. Cell Metab 11(6): 467-478.

57. Meijer AJ (2008) Amino acid regulation of autophagosome formation. Methods Mol Biol 445: 89-109.

58. Inami Y, Yamashina S, Izumi K, Ueno T, Tanida I, et al. (2011) Hepatic steatosis inhibits autophagic proteolysis via impairment of autophagosomal acidification and cathepsin expression. Biochem Biophys Res Commun 412(4): 618-625.

59. Fukuo Y, Yamashina S, Sonoue H, Arakawa A, Nakadera E, et al. (2014) Abnormality of autophagic function and cathepsin expression in the liver from patients with non-alcoholic fatty liver disease. Hepatol Res 44(9): 1026-1036.

60. Hooper AJ, Adams LA, Burnett JR (2011) Genetic determinants of hepatic steatosis in man. J Lipid Res 52(4): 593-617.

61. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, et al. (2005) The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 129(1): 113-121.

62. Fan JG (2013) Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 28(S1): 11-17.

63. Flegal KM, Carroll MD, Ogden CL, Curtin LR (2010) Prevalence and trends in obesity among US adults, 1999-2008. JAMA 303(3): 235-241.

64. Rinella ME, Sanyal AJ (2015) NAFLD in 2014: genetics, diagnostics and therapeutic advances in NAFLD. Nat Rev Gastroenterol Hepatol 12(2): 65-66.

65. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, et al. (2008) Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 40(12): 1461-1465.

66. Speliotes EK, Yerges-Armstrong LM, Wu J, Hernaez R, Kim LJ, et al. (2011) Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits. PLoS Genet 7(3): e1001324.

67. Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, et al. (2014) Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 46(4): 352-356.

68. Kumari M, Schoiswohl G, Chitraju C, Paar M, Cornaciu I, et al. (2012) Adiponutrin functions as a nutritionally regulated lysophosphatidic acid acyltransferase. Cell Metab 15(5): 691-702.

69. Basantani MK, Sitnick MT, Cai L, Brenner DS, Gardner NP, et al. (2011) Pnpla3/Adiponutrin deficiency in mice does not contribute to fatty liver disease or metabolic syndrome. J Lipid Res 52(2): 318-329.

70. Smagris E, BasuRay S, Li J, Huang Y, Lai KM, et al. (2015) Pnpla3I148M knock in mice accumulate PNPLA3 on lipid droplets and develop hepatic steatosis. Hepatology 61(1): 108-118.

71. Pirazzi C, Adiels M, Burza MA, Mancina RM, Levin M, et al. (2012) Patatin-like phospholipase domain containing 3 (PNPLA3) I148M (rs738409) affects hepatic VLDL secretion in humans and in vitro. J Hepatol 57(6): 1276-1282.

72. Petersen KF, Dufour S, Hariri A, Nelson-Williams C, Foo JN, et al. (2010) Apolipoprotein C3 gene variants in nonalcoholic fatty liver disease. N Engl J Med 362(12): 1082-1089.

73. Kozlitina J, Boerwinkle E, Cohen JC, Hobbs HH (2011) Dissociation between APOC3 variants, hepatic triglyceride content and insulin resistance. Hepatology 53(2): 467-474.