Review Article

Dyslipidaemia in Liver Diseases

(chronic liver diseases / lipid metabolism / dyslipidaemia / liver cirrhosis / cholestasis / lipoprotein X)

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Abstract. The liver is the central organ in lipid metabolism and plays a key role in a variety of biochemical processes. It is involved in lipoprotein synthesis, fatty acid beta oxidation, ketone body production, cholesterol synthesis, bile production, and storage and mobilization of lipids. Metabolic diseases such as obesity, type 2 diabetes mellitus and certain dyslipidaemias can lead to chronic liver conditions, especially non-alcoholic fatty liver disease. Conversely, chronic liver diseases such as liver cirrhosis and chronic cholestasis can induce dyslipidaemias. This review provides a comprehensive biochemical and clinical overview of the intricate relationship between the lipid-lipoprotein metabolism and chronic liver diseases, including non-alcoholic fatty liver disease, cholestasis, alcohol-related liver disease, viral hepatitis and cirrhosis, all of which have been selected due to their importance in current clinical practice. These conditions not only affect liver function but also have widespread metabolic implications critical for patient management and therapeutic strategies. In addition to discussing the clinical manifestations and pathophysiology of liver diseases, this review delves into the genetic and non-genetic factors that influence their development and progression. By bridging clinical observations with biochemical mechanisms, this review aims to improve the understanding of how lipid metabolism disorders contribute to chronic liver diseases and to identify potential targets for therapeutic intervention.

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Abbreviations: ADL – atherogenic dyslipidaemia, APO – apolipoprotein, ARLD – alcohol-related liver disease, BA – bile acid, DCA – deoxycholic acid, FFA – free fatty acid, HCV – hepatitis C virus, HDL – high-density lipoprotein, HDL-C – high-density lipoprotein cholesterol, HTG – hypertriglyceridaemia, IDL – intermediate-density lipoprotein, LCAT – lecithin-cholesterol acyltransferase, LDL – low-density lipoprotein, LDL-C – low-density lipoprotein cholesterol, LPL – lipoprotein lipase, LpX – lipoprotein X, MetS – metabolic syndrome, MTTP – microsomal triglyceride transfer protein, NAFLD – non-alcoholic fatty liver disease, NASH – non-alcoholic steatohepatitis, NO – nitric oxide, NPC1L1 – Niemann-Pick C1-like 1, OMIM – Online Mendelian Inheritance in Man, PSC – primary sclerosing cholangitis, sdLDL – small dense low-density lipoprotein, T2DM – type 2 diabetes mellitus, TAG – triacylglycerol, UDCA – ursodeoxycholic acid, VLDL – very-low-density lipoprotein.

Introduction

The liver plays a key role in the synthesis, storage, secretion and catabolism of lipoproteins, which involve mechanisms such as free fatty acid (FFA) metabolism, synthesis of complex lipids and cholesterol homeostasis. As the central organ of lipid metabolism, the liver contributes to the formation and storage of lipids. It converts excess carbohydrates to FFAs, which are subsequently esterified to form triglycerides (TAGs) and other complex lipids through *de novo* lipogenesis. In addition to serving as a steroid hormone precursor, the liver is the primary site for the synthesis of cholesterol, which is crucial for cell membrane structure and bile acid production (Arvind et al., 2019).

The liver synthesizes the majority of apolipoproteins, certain lipoprotein-transforming enzymes and lipid transfer proteins. It also plays a crucial role in the metabolism of lipoproteins (Roy-Chowdhury and Roy-Chowdhury, 2006; Pownal et al., 2015). The liver packages triglycerides and cholesterol molecules into very-low-density lipoproteins (VLDLs), which transport lipids – primarily endogenous triglycerides – to peripheral tissues. VLDLs are then converted into low-density lipoproteins (LDLs), which deliver cholesterol to peripheral cells. In addition, the liver is equipped with specific LDL receptors (LDLRs) and LDL receptor-related protein (LRP), which are responsible for the uptake of LDL particles, intermediate-density lipoproteins (IDLs) and chylomicron remnants (Pownal et al., 2015).

The liver also has a function in cholesterol metabolism and is the only organ capable of cholesterol excretion, accounting for two-thirds of overall cholesterol synthesis.

Low-density lipoprotein cholesterol (LDL-C) serves as the primary source of cholesterol for the synthesis of bile acids, while cholesterol transported by high-density lipoprotein cholesterol (HDL-C) is the main contributor to bile cholesterol levels (Dikkers and Tietge, 2010). In the liver, cholesterol is converted into bile acids, which make up a substantial proportion of bile. The liver secretes bile into the bile ducts, storing it in the gallbladder for release into the small intestine, where it emulsifies fats, aiding their digestion and absorption (Russell and Setchell, 1992). The liver also synthesizes and secretes apolipoproteins essential for HDL formation. These apolipoproteins play a role in the reverse transport of cholesterol from peripheral tissues back to the liver for excretion (Dikkers and Tietge, 2010).

FFAs in the liver are either re-esterified to form TAGs and other esters, or oxidized in the mitochondria or peroxisomes. An imbalance in FFA flux to the liver, oxidation for hepatic intermediary metabolism or ketone body formation, or export as VLDLs leads to hepatic steatosis, increased VLDL secretion and elevated plasma TAG concentrations (Saponaro et al., 2015).

Responses to hormonal signals, such as insulin and glucagon, play a critical role in regulating lipid metabolism in the liver. Insulin promotes lipogenesis, while glucagon stimulates lipolysis and FFA oxidation. Conditions associated with increased TAG and VLDL synthesis as well as VLDL secretion are closely linked to insulin resistance, defined as the reduced ability of cells to respond to the action of insulin. Insulin resistance is a hallmark of several metabolic diseases, including obesity, type 2 diabetes mellitus, metabolic syndrome and dyslipidaemia associated with hypertriglyceridaemia (HTG) (Žák et al., 2008; Packard et al., 2020).

In contrast, alcohol abuse is associated with alcoholic fatty liver or steatosis (Osna et al., 2017). On the one hand, changes in bile composition – cholesterol, phospholipids and bile acids – are pathogenic factors in the development of cholesterol cholelithiasis, also known as cholesterol gallstones. Cholestasis, on the other hand, is associated with the presence of atypical lipoprotein X (LpX) in the plasma. A schematic representation of the lipid metabolism in the liver is shown in Fig. 1.

It is evident that chronic liver diseases associated with hepatic tissue remodelling and impaired liver function result in significant changes to the lipid metabolism (Arvind et al., 2019; Perez-Matos et al., 2019). This review highlights various changes in the lipid metabolism associated with common liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcohol-related liver disease (ARLD), cholestasis, viral hepatitis and liver cirrhosis.

Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis

NAFLD, also known as metabolic dysfunction-associated steatotic liver disease (MASLD), is currently the most common chronic liver disease in both developed and developing countries, affecting 20–30 % of the adult population. Non-alcoholic steatohepatitis (NASH), or metabolic dysfunction-associated steatohepatitis (MASH), is a progressive form of NAFLD that can advance through liver fibrosis to liver cirrhosis and hepatocellular carcinoma, which may also directly arise from NAFLD (Chrysavgis et al., 2022). NAFLD is characterized by excessive hepatic fat accumulation and is closely associated with insulin resistance. It is histologically diagnosed by the presence of steatosis in more than 5 % of hepatocytes. Quantitative fat-water magnetic resonance imaging defines NAFLD as an increase in the fat volume fraction exceeding 5.6 % (Han et al., 2023). Several metabolic comorbidities, including obesity, type 2 diabetes mellitus, dyslipidaemia, arterial hypertension and metabolic syndrome, are risk factors for NAFLD. The common mechanism underlying these conditions is insulin resistance.

Insulin resistance in adipose tissue leads to impaired glucose transport, which is necessary to produce glycerol 3-phosphate, a molecule required to esterify FFAs to TAGs. Since adipose tissue lacks glycerol kinase, glycerol 3-phosphate can only be produced by glucose oxidation during glycolysis. As a result, insulin resistance in adipose tissue increases basal lipolytic activity, accompanied by a release of FFAs into the bloodstream. Note that not all insulin functions are identically impaired in insulin resistance. Some insulin-signalling pathways in hyperinsulinaemia remain highly responsive to insulin, a phenomenon known as selective insulin resistance (Wu et al., 2012). In hepatic insulin resistance, for example, insulin fails to suppress hepatic glucose production, resulting in hyperglycaemia. At the same time, insulin stimulates lipogenesis, leading to dyslipidaemia and hepatic steatosis. In NAFLD, selective hepatic insulin resistance stimulates *de novo* lipogenesis without reducing VLDL production (Petersen and Shulman, 2018; Lee at al. 2022)

According to the current "multiple-hit" theory, NAFLD develops as a result of various factors. Hepatic steatosis, or ectopic accumulation of fat in the liver, is driven by an excess influx of FFAs, considered the first hit. This is followed by subsequent hits, including inflammation, fibrosis and other pathological changes caused by oxidative stress, endoplasmic reticulum stress, lipoperoxidation and other insults (Nassir, 2022). Hepatic steatosis in NAFLD is triggered by excessive TAG synthesis in hepatocytes. Around 60 % of the substrates for TAG synthesis originate from FFAs released by white adipose tissue, 25 % from *de novo* lipogenesis and 15 % from the consumption of a high-fat diet, a high-fructose diet, or both. During the initial stages of NAFLD, both VLDL secretion and beta oxidation of FFAs increase to com-

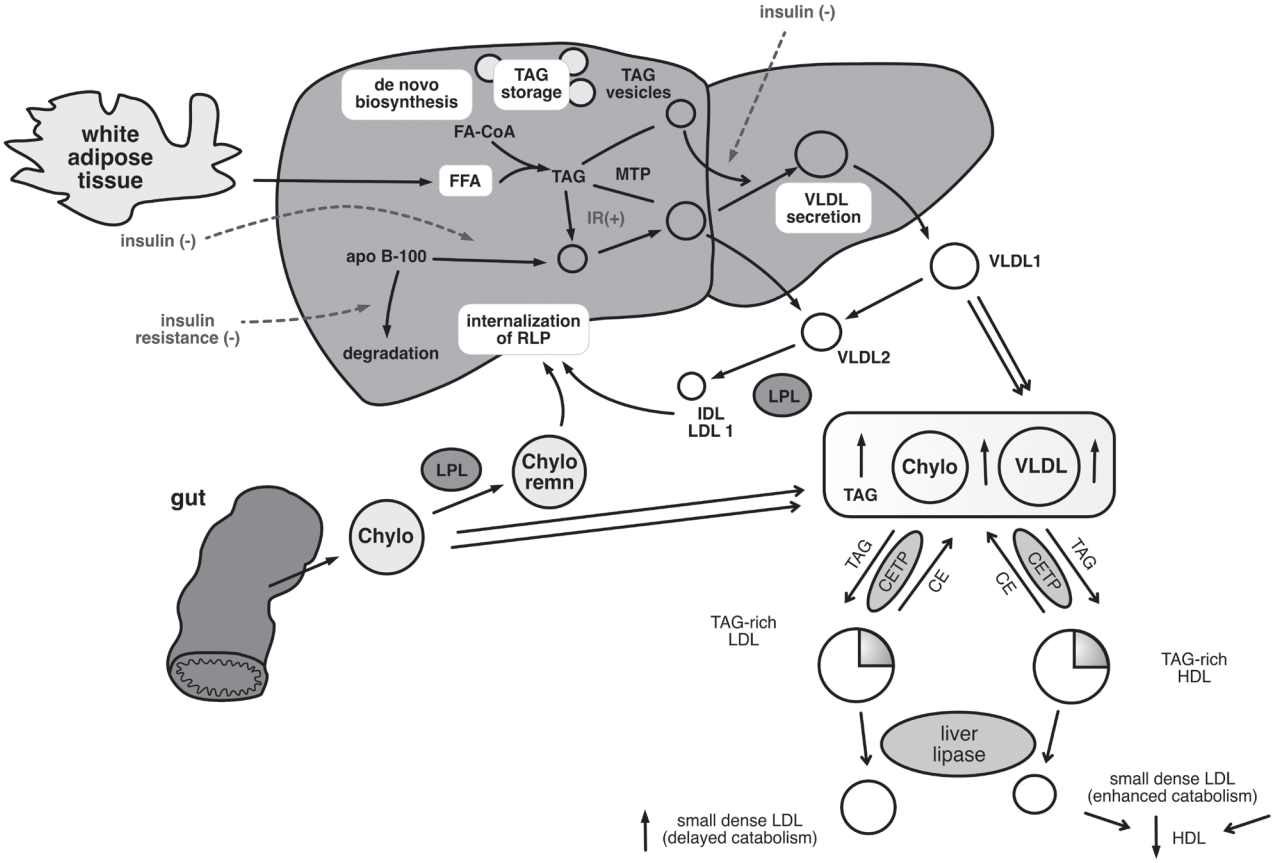

Fig. 1. Schematic representation of hepatic lipid metabolism, highlighting the central role of the liver in the synthesis, storage and secretion of triglycerides (TAGs) and very-low-density lipoproteins (VLDLs). Free fatty acids (FFAs) derived from white adipose tissue are converted to TAGs in the liver before being stored or secreted as VLDLs. Insulin resistance disrupts this pathway by increasing TAG and VLDL secretion, contributing to dyslipidaemia. While chylomicrons (CMs, in Fig. 1 as Chylo) from the gut interact with lipoproteins crucial for lipid transport and metabolism, liver lipase plays a key role in modifying lipoproteins such as LDL and HDL (Hirano, 2018; Heeren, 2021).
Abbreviations: CE – cholin esterase, CETP – cholesterol ester transfer protein, IDL – intermediate-density lipoproteins, IR – insulin resistance, LPL – lipoprotein lipase, MTP – microsomal triglyceride transfer protein, RLP – remnant lipoprotein cholesterol.

pensate for the increased influx of FFAs into the liver. However, as the disease advances to NASH, VLDL secretion and FFA oxidation both decrease. Excessive synthesis and deposition of FFAs in turn increase ceramide synthesis in cells and tissues. Some ceramides, such as Cer 40 : 1 and Cer 42 : 1, are understood to be associated with insulin resistance and impaired insulin action (Zhu et al., 2023).

Although NAFLD and NASH are predictors of liver cirrhosis, the leading cause of death in persons with NAFLD is atherosclerotic cardiovascular disease resulting from atherogenic dyslipidaemia (ADL) (Kasper et al., 2021). ADL is characterized by elevated fasting and postprandial hypertriglyceridaemia, decreased plasma HDL-C concentrations and an increase in the pattern-B subclass of LDL, predominantly small dense LDL (sdLDL) particles. HTG constitutes the primary event, while the reduction in HDL and the formation of sdLDL are secondary consequences of HTG. Current criteria define HTG as a fasting plasma TAG concentration greater than or equal to 1.7 mmol/l. The cut-off values for HDL-C are 1.3 mmol/l for women and 1.03 mmol/l for men. The LDL B phenotype is characterized by a predominance of class III and IV LDL sub-fractions with a particle size greater than 25.5 nm and a density of between 1.038 and 1.065 g/ml.

ADL is the primary risk factor for atherosclerotic cardiovascular disease in individuals with abdominal obesity, metabolic syndrome and type 2 diabetes mellitus (Hoogeveen et al., 2014; Taskinen and Borén, 2015). In patients with coronary artery disease, ADL symptoms are present in 50–70 % of cases. Epidemiological studies have shown that individuals with ADL are three to four times more likely to experience cardiovascular events (Targher et al., 2010; Corey and Chalasani, 2014; Lim et al., 2019). The development of NAFLD and other liver diseases is influenced by germline variants in several genes encoding proteins involved in the regulation of

Table 1. Genetic factors affecting the development of NAFLD

Causal gene (*OMIM)	Associated disease (#OMIM) / inheritance	Mechanism of action
Patatin-like phospholipase domain-containing protein 3 – *PNPLA3* (*609567)	Fatty liver disease (#613282) / polygenic	Enzyme regulating production and breakdown of fats in adipocytes and hepatocytes
Transmembrane 6 superfamily member 2 – *TM6SF2* (*606563)	Fatty liver disease, (no OMIM entry) / AD	Regulation of normal VLDL secretion, VLDL production lowered by certain variants
MER proto-oncogene, tyrosine kinase – *MERTK* (*604705)	Retinitis pigmentosa 38; RP38 (#613862) / AR	Liver fibrosis progression
Glucokinase regulatory protein – *GCKR* (*600842)	Fasting plasma glucose level quantitative trait locus 5; FGQTL5 (#613463) / AD	Inhibition of glucokinase and disruption of normal glucose homeostasis
17β-Hydroxysteroid dehydrogenase XIII – *HSD17B13* (*612127)	Fatty liver disease (#620116) / AD	Protective factor for all categories of chronic liver diseases, including alcohol-related liver disease, non-alcoholic liver disease, alcoholic cirrhosis and non-alcoholic cirrhosis

Primary genes involved in the development of NAFLD and other associated diseases. Each gene is assigned its respective causal disease and mechanism of action. Genes and diseases are mapped to their corresponding entries in the OMIM database (www.OMIM.org). Abbreviations: AD – autosomal dominant, AR – autosomal recessive, OMIM – Online Mendelian Inheritance in Man.

lipid metabolism. The main genetic factors responsible for increasing the risk of NAFLD, exacerbating the progression of liver injury (whether NAFLD or alcoholic steatosis) and contributing to lipid metabolism dysregulation are summarized in Table 1. High cardiovascular risk is associated not only with ADL but also with diabetic and other metabolic dyslipidaemias. Certain gene variants encoding enzymes that regulate the lipid metabolism significantly elevate the morbidity and mortality risk (Fig. 2 and Table 2). TG concentrations are affected by a number of common gene variants (polymorphisms) with low effects on TG concentrations and/or heterozygous mutations of rare genes with large effects on TG concentrations. Here, mutations in genes encoding lipoprotein lipase (*LPL*), apoC2 (*APOC2*), apoA5 (*APOA5*) and others are implicated. In 95 % of cases, *LPL* mutations are involved; *APOC2* mutations were detected in 2.5 % of cases, *APOA5* in 1.5 % of affected patients. Overall, mutations or polymorphisms were detected in 40–60 cases of polygenic HTG (Lewis et al., 2015; Dron et al., 2020).

ADL is also caused by non-genetic factors, most commonly associated with unhealthy lifestyle behaviours. The key contributors include obesity, metabolic syndrome, physical inactivity, smoking, excessive alcohol consumption and diets high in carbohydrates (especially fructose and sucrose) or foods with a glycaemic index above 60. Additionally, diseases such as Cushing's syndrome, human immunodeficiency virus infection and systemic lupus erythematosus further increase the risk of ADL. In rare cases, chronic use of certain medications can also trigger ADL. These include hormonal contraceptives (especially in the presence of external factors such as obesity or genetic predispositions), tamoxifen, corticosteroids, beta blockers, retinoids, protease inhibitors, bile acid sequestrants, sirolimus, L-asparaginase and antipsychotics (Herink and Ito, 2018; Berberich and Hegele, 2022).

Cholestasis

Chronic cholestasis occurs in primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC). It is characterized by hypercholesterolaemia featuring a distinct lipoprotein composition due to the retention of cholesterol, phospholipids and bile acids, which are physiologically secreted into the bile (Roy-Chowdhury and Roy-Chowdhury, 2006). A hallmark of chronic cholestasis is the presence of LpX, a unique lipoprotein with a lamellar structure and a particle diameter of 30–70 nm (Crook, 2013; Brewer, 2015). LpX significantly differs from other lipoproteins in both composition and structure. It is mainly composed of phospholipids (66 % w/w), non-esterified cholesterol (22 % w/w), and albumin (6 % w/w), which constitutes the particle core. The apolipoproteins ApoC, ApoE and ApoA1 form the surface of the protein. Although its origin is not precisely understood, LpX is thought to form upon the interaction of the plasma with bile-containing bilamellar vesicles of cholesterol and phospholipids through physicochemical and non-enzymatic reactions, as documented by the incubation of bile with albumin *in vitro* (Manzato et al., 1976).

LpX in the plasma is associated with three pathological conditions: intra- and extrahepatic cholestasis, caused by bile reflux; primary or secondary deficiency of lecithin-cholesterol acyltransferase (LCAT); and administration of intravenous fat emulsions. LpX has been documented in PBC, PSC, viral hepatitis with cholestatic features, drug-induced cholestasis, Wegener's granulomatosis, graft-versus-host disease (GVHD) with liver involvement, intrahepatic cholestasis of pregnancy

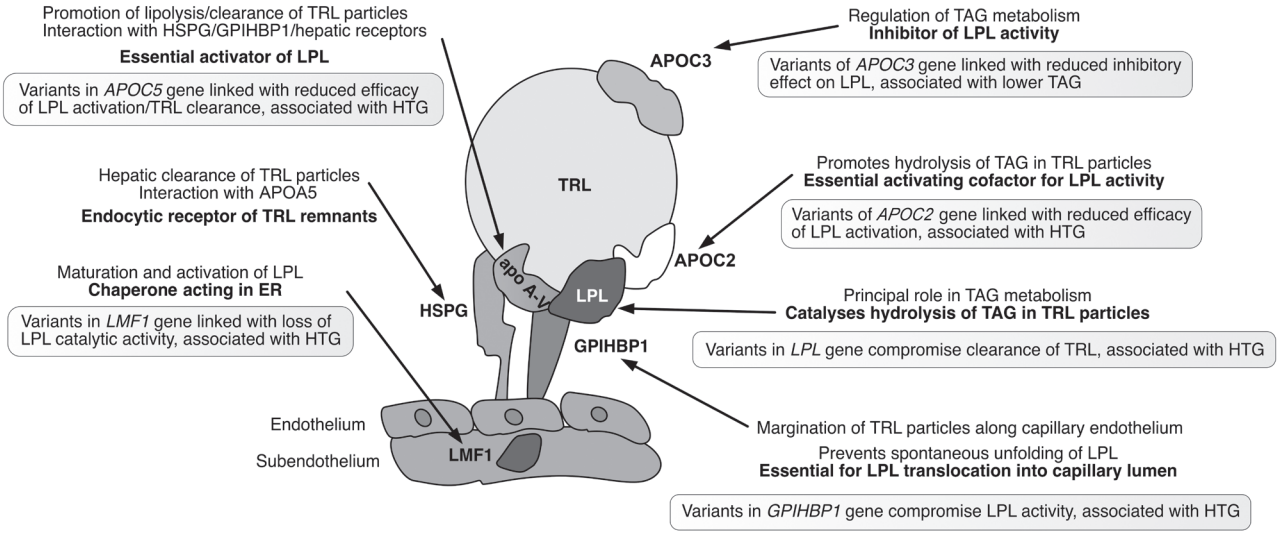

Fig. 2. Scheme of anchoring of lipoprotein lipase on endothelial cells and factors influencing its activity, illustrating the regulation of triglyceride-rich lipoprotein (TRL) metabolism, focusing on the role of lipoprotein lipase (LPL) and its interactions with various proteins. Key elements include APOC2, which activates LPL to hydrolyse triglycerides in TRL particles, and APOC3, which inhibits LPL activity. GPIHBP1 – glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1 – is essential for LPL translocation to the capillary lumen, and LMF1 – lipase maturation factor 1 – functions as a chaperone for LPL maturation. Variants in genes such as *APOC2*, *APOC3*, *LPL* and *LMF1* can impair these processes, leading to hypertriglyceridaemia (Alves et al., 2024).

Table 2. Monogenic germline variants in genes implicated in the development of various types of dyslipidaemia

Causal gene (*OMIM)	Associated disease (#OMIM) / inheritance	Mechanism of action
	Dyslipidaemia: Hypertriglyceridaemia	
Lipoprotein lipase – *LPL* (*609708)	Hyperlipoproteinaemia Type I (# 238600) / AR	Reduced activity of LPL and TAG clearance
Apolipoprotein C2 – *APOC2* (*608083)	Apolipoprotein C2 deficiency (#207750) / AR	Defective activation of LPL leading to impaired lipolysis
Apolipoprotein A5 – *APOA5* (*606368)	Hypertriglyceridaemia 1 (# 145750) / AD Hyperlipoproteinaemia type V (#144650) / AD	Reduced APOA5 expression in association with decreased LPL activity and TAG clearance
Lipase maturation factor 1 – *LMF1* (*611761)	Combined lipase deficiency (#246650) / AR	Impaired LPL maturation accompanied by decreased LPL activity
Glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 – *GPIHBP1* (*612757)	Hyperlipoproteinaemia type ID (#615947) / AR	Impaired lipolytic processing, subsequent elevation of chylomicrons
Glycerol-3-phosphate dehydrogenase 1 – *GPD1* (*138420)	Transient infantile hypertriglyceridaemia (#614480) / AR	Altered synthesis and secretion of chylomicrons
	Dyslipidaemia: Reduced HDL cholesterol	
ATP-binding cassette subfamily A member 1 – *ABCA1* (*600046)	Tangier disease (#205400): AR Hypoalphalipoproteinaemia (#604091) / AD	Reduced efflux of cholesterol from cells, decreased production of HDL particles and impaired reverse cholesterol transport
Lecithin-cholesterol acyltransferase – *LCAT* (*606967)	Fish-eye disease (# 136120) / AR LCAT deficiency (#245900) / AR	Reduced HDL cholesterol and impaired reverse cholesterol transport
Apolipoprotein A1 – *APOA1* (*107680)	Primary hypoalphalipoproteinaemia 2 (#618463) / AR	Disrupted synthesis or function of APOA1 and HDL particles

Gene polymorphisms involved in the development of dyslipidaemias associated with high cardiovascular risk. Each gene is assigned its respective causal disease and mechanism of action. Genes and diseases are mapped to their corresponding entries in the OMIM database (www.OMIM.org).
Abbreviations: AD – autosomal dominant, AR – autosomal recessive, OMIM – Online Mendelian Inheritance in Man.

and several other rare conditions (Phatlhane and Zemlin, 2015; Nemes et al., 2016; Ha et al., 2017). In LCAT deficiency, LpX forms secondary to the plasmatic accumulation of non-esterified cholesterol and phospholipids. In conditions associated with a loss of LCAT activity, such as advanced liver cirrhosis or Zieve's syndrome, LpX forms upon the accumulation of lipoprotein membranes composed of non-esterified cholesterol and phospholipids, which are released from TAG-rich lipoproteins. This process occurs when the reduced lipoprotein volume prevents adequate TAG hydrolysis. Infusions of fat emulsions can also induce the formation of LpX by exceeding the clearance of phospholipids such as phospholipase, leading to their retention along with the accumulation of non-esterified cholesterol (Brewer, 2015; Perez-Matos et al., 2019).

Laboratory evidence of LpX often reveals elevated plasma total cholesterol, ranging from the upper limit of normal to concentrations as high as 40 mmol/l. From a practical point of view, lipoprotein electrophoresis and the ratio of plasma total cholesterol to apolipoprotein B100 (ApoB100) can be useful for detecting LpX (Fig. 3). In the absence of LpX, the ratio of total cholesterol to ApoB100 (w/w) is typically 2–3 : 1 under both physiological and dyslipidaemic conditions. However, in cases of hypercholesterolaemia caused by excess LpX, the ratio is 7–10 : 1. In patients with a more advanced form of PBC, TAG concentrations are elevated. Cholestasis does not increase cardiovascular risk, likely due to the assumed anti-atherogenic properties of LpX. As PSC progresses to liver cirrhosis, there is a terminal decrease in the concentrations of all lipoprotein classes, including VLDL, LDL and HDL (Hao et al., 2017).

Due to the overall lack of clinical evidence, there are no formal recommendations for the treatment of hypercholesterolaemia associated with cholestasis. In PBC, ursodeoxycholic acid (UDCA) slows disease progression, prolongs survival (Lindor et al., 2009; Reshetnyak, 2012) and reduces plasma LDL-C concentrations with chronic treatment. In patients with PBC, statin therapy is generally considered safe and effective for lowering LDL-C. However, UDCA is currently not recommended for the treatment of PSC (Reshetnyak, 2012; Lindor et al., 2015). As mentioned previously, LpX also plays a role in familial LCAT deficiency (Brewer, 2015).

Alcohol-Related Liver Disease

ARLD is primarily characterized by steatosis – abnormal retention of fat in the liver – which occurs in over 90 % of heavy drinkers. However, only a certain subset of individuals progress to more severe conditions such as alcoholic hepatitis, cirrhosis and hepatocellular carcinoma. Risk factors include female sex, obesity, poor diet and smoking (O'Shea et al., 2010; Perumpail et al., 2017; Scott and Anstee, 2018).

Another hallmark of ARLD is HTG, caused by increased FFA synthesis and impaired beta oxidation due to alcohol metabolism. Alcohol oxidation increases NADH levels, which impairs mitochondrial FFA oxidation. This inhibition extends to peroxisome proliferator-activated receptor alpha (PPARα), a ligand-activated transcription factor that regulates FFA breakdown, diverting FFAs toward TAG synthesis rather than energy production (Roy-Chowdhury and Roy-Chowdhury, 2006; Gao and Bataller, 2011).

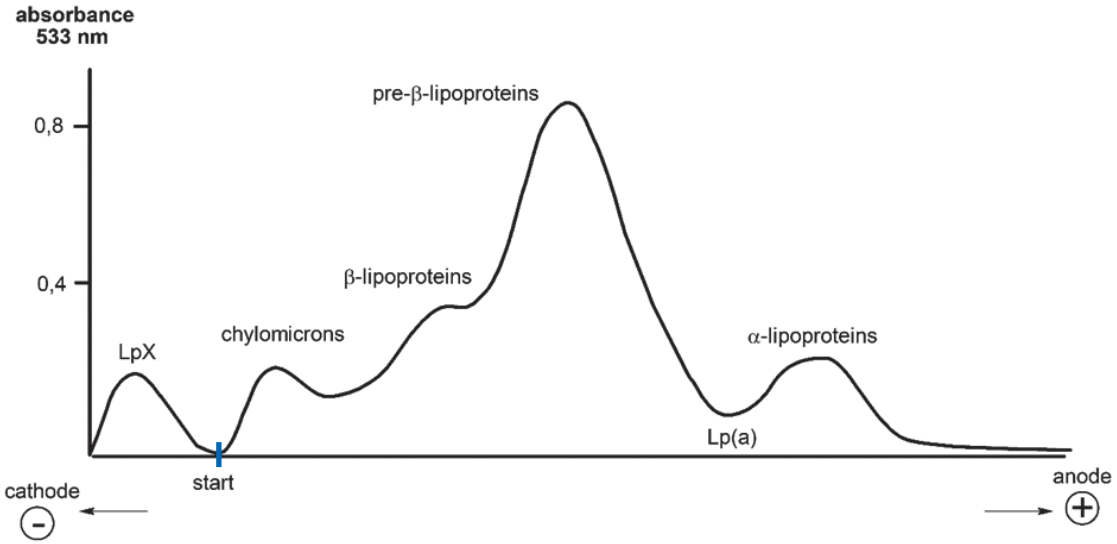

Fig. 3. Lipid electrophoresis densitogram. LpX typically migrates towards the cathode, which is opposite to the direction of most other physiologically present lipoproteins that move toward the anode (chylomicrons residing close to the application start, β-lipoproteins – mostly LDL, pre-β-lipoproteins formed by VLDL and fastest migrating α-lipoproteins corresponding to HDL). This is due to the high content of free cholesterol and phospholipids in LpX, giving it a unique charge-to-mass ratio (Reshetnyak, 2012; Crook, 2013; Suzuki et al., 2017).

Alcohol alters the lipid and lipoprotein metabolism in several ways. It increases *de novo* lipogenesis by up-regulating sterol regulatory element-binding protein 1c (SREBP1c), a transcription factor involved in fat production. At the same time, alcohol increases VLDL secretion, which transports TAG from the liver. However, impaired LPL activity reduces the clearance of these lipids, contributing to HTG. Alcohol also stimulates FFA uptake in the liver via the CD36 transporter, exacerbating fat accumulation (You and Arteel, 2019; Jeon and Carr, 2020; Hyun et al., 2021).

The cholesterol metabolism is also disrupted. Moderate alcohol consumption can increase HDL-C, particularly the HDL3 sub-fraction, which enhances reverse cholesterol transport, the process of moving cholesterol from tissues to the liver for elimination. However, in advanced ARLD, total cholesterol, HDL-C and LDL-C levels all decline, reflecting liver damage (Brinton, 2012). In addition to lipid imbalances, alcohol contributes to liver injury by promoting inflammation and fibrosis. Alcohol induces oxidative stress, generating free radicals that damage liver cells, and activates hepatic stellate cells, leading to collagen deposition and scarring (fibrosis) (Osna et al., 2017). Genetic factors, such as polymorphisms in the apolipoprotein C3 gene (*APOC3*), can further exacerbate the effects of alcohol by inhibiting LPL activity, worsening HTG (Van de Wiel et al., 2012).

Although moderate alcohol consumption has been linked to increased HDL-C and anti-inflammatory properties, no amount of alcohol is considered safe for overall health, especially given its harmful effects on the liver (WHO, 2023). In summary, ARLD leads to profound disruptions in the lipid metabolism, including increased FFA synthesis, impaired oxidation and altered lipoprotein processing, which promote fat accumulation in the liver. These metabolic disturbances, coupled with inflammation and fibrosis, drive the progression of ARLD from steatosis to cirrhosis and liver failure.

Viral Hepatitis B and C

The pathophysiological mechanisms underlying dyslipidaemia in patients with hepatitis B virus (HBV) infection are not fully understood, but hepatic insufficiency has been proposed as a potential cause. HBV can influence the expression of genes involved in the lipoprotein metabolism. For instance, HBV attenuates the expression of *APOA1*, resulting in a decrease in HDL-C levels, and apolipoprotein A5 (*APOA5*), which may increase TAG concentrations by slowing the lipolysis of TAG in chylomicrons and VLDL (Su et al. 2004; Jabeen et al., 2020). Altered hepatic VLDL secretion is also associated with the HBV X antigen (HBV X protein), which alters the structure of the ApoB-bound glycoprotein and down-regulates microsomal triglyceride transfer protein (MTTP). These changes result in TAG accumulation in the liver and reduced VLDL secretion (Su et al. 2004; Speliotes et al. 2018; Jabeen et al., 2020). Additionally, the slower conversion of IDL to LDL due to the reduced activity of hepatic lipase, hepatic Niemann-Pick C1-like 1 (NPC1L1), and scavenger receptor class B type 1 (SRB1) can also contribute to a decrease in LDL-C concentrations (Speliotes et al., 2018).

Hepatitis C virus (HCV) infection is associated with reductions in total cholesterol, LDL-C, HDL-C and APOB100 concentrations. HCV inhibits MTTP, which is required for the assembly of chylomicrons in the intestine and VLDL in the liver (André et al., 2005). This in turn leads to a reduction in the secretion of both lipoprotein particles. Patients with HCV infection often exhibit hypocholesterolaemia and hypotriglyceridaemia, where TAG concentrations significantly correlate with the duration of HCV infection and total cholesterol levels. Laboratory findings of HCV infection can manifest as mixed hypobetalipoproteinaemia. In the plasma, HCV is transported in lipoprotein-containing complexes to form HCV lipoviral particles (HCV-LVP). These particles enter hepatocytes via specific receptors, including LDLR, SRB1 and NPC1L1 (Dabbagh, 2020). HCV then exploits the host lipoprotein metabolism at multiple stages of its life cycle, including hepatocyte entry, virus synthesis and replication, and secretion of viral particles from the liver into the bloodstream. Ezetimibe, an NPC1L1 inhibitor of cholesterol absorption from the small intestine, has been advanced as a potential therapeutic strategy. (Aizawa et al., 2015; Almani et al., 2016). Although HCV is associated with reductions in LDL and non-HDL-C, it paradoxically increases cardiovascular risk. Therefore, in HCV-infected patients, the lipid levels do not accurately reflect the risk of cardiovascular disease (Yang et al., 2015).

Liver Cirrhosis

Liver cirrhosis is the final stage of chronic liver disease, encompassing a wide spectrum of clinical parameters, ranging from well-compensated liver function to advanced decompensated liver disease with portal hypertension and attendant complications. Changes in the lipid metabolism associated with cirrhosis reflect the degree of liver dysfunction. A study by Cicognani et al. (1997) found that variations in the plasma concentrations of total cholesterol, HDL, LDL and VLDL correlated with an increase in prothrombin time and a decrease in albumin, reflecting the decreased proteosynthetic capacity of hepatocytes. On the other hand, total cholesterol levels in non-cholestatic liver disease have proved to be a reliable marker of liver function, with concentrations decreasing in proportion with worsening liver dysfunction (Boemeke et al., 2015; Yang et al., 2015). Liver cirrhosis is associated with reduced plasma concentrations across all lipoproteins, with total cholesterol levels dropping by 20–30 %, HDL by 8–46 %, LDL by 18–41 % and TAG by 3–56 % (Privitera et al., 2018). The reduction in plasma total cholesterol, which affects all lipoprotein classes, is characterized by a decrease in cholesterol ester fractions (Yang et al., 2015; Privitera et al., 2018).

In liver cirrhosis, LDLs are enriched with TAG and exhibit lower cholesterol ester content, while HDL particles show increased concentrations of TAG, non-esterified cholesterol and phospholipids. These changes result from the reduced activity of enzymes involved in the lipoprotein metabolism, especially LCAT, hepatic lipase and phospholipid transfer protein (Loria et al., 2014).

Conclusion

Liver diseases and lipoprotein metabolism are closely related. Liver dysfunction affects the lipid metabolism and alters the concentrations of circulating lipoproteins. Conversely, inherited or acquired pathological conditions that alter the lipid metabolism can lower the threshold for developing chronic liver diseases such as steatosis, ARLD, and especially NAFLD, the most common liver disease in developed countries. NAFLD is characterized by an atherogenic lipoprotein phenotype consisting of HTG, reduced HDL-C levels and increased concentrations of sdLDL. Hypercholesterolaemia and the presence of LpX are characteristic findings in cholestasis, but these symptoms do not increase the cardiovascular risk.

ARLD is characterized by steatosis and elevated concentrations of TAG, VLDL and HDL-C. Similarly, viral hepatitis, including HCV infection, is associated with pathophysiological changes in the lipoprotein metabolism. The final stage of liver disease, hepatic cirrhosis, is associated with hepatocyte dysfunction and reduced concentrations of all lipoprotein classes.

Looking ahead, future research should focus on integrating clinical and biochemical studies to improve our understanding of the relationship between the lipid metabolism and liver diseases. This approach should pave the way for development of innovative diagnostic tools and targeted therapies, ultimately improving the outcomes for patients with liver diseases.

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