Hypercholesterolemia of Cholestasis

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Abstract: Cholesterol is a lipid of widespread physiologic and pathologic importance, whose homeostasis is tightly regulated through multiple mechanisms, including transport via low-density lipoprotein. Elevated serum low-density lipoprotein strongly correlates with the development of atherosclerotic cardiovascular disease. Cholestatic liver diseases, such as primary biliary cholangitis (PBC), are associated with impaired cholesterol homeostasis. The pathophysiology of hypercholesterolemia of PBC involves defective hepatocyte cholesterol clearance, downregulation of bile synthesis, and increased cholesterogenesis. Lipoprotein X is a highly specific biomarker for cholestasis and, in rare cases, contributes to serum total cholesterol levels >1000 mg/dL. The extent of hypercholesterolemia in PBC is associated with worse liver-related outcomes; nevertheless, patients with PBC do not have increased risk for atherosclerotic cardiovascular disease. Cardiovascular risk stratification of patients with PBC is most accurately achieved by direct measurement of apolipoprotein B, the protein component of pro-atherosclerotic lipoproteins involved in cholesterol transport. First and second line therapies for the treatment of hypercholesterolemia in cholestatic liver disease are statins and proprotein convertase subtilisin/kexin type 9 inhibitors, respectively. Apolipoprotein B level should be rechecked periodically to measure therapeutic response.

Key Words: cholestatic liver disease, hypercholesterolemia, atherosclerotic cardiovascular disease, lipoprotein X, primary biliary cholangitis

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Cholesterol is a fundamental lipid molecule with essential structural and metabolic functions in human physiology. It serves as a precursor for steroid hormones, bile acids, and vitamin D, and plays a critical role in maintaining cell membrane integrity.[1] However, disturbances in cholesterol homeostasis are central to the pathogenesis of several diseases, most notably atherosclerotic cardiovascular disease (ASCVD). Elevated circulating levels of low-density lipoprotein (LDL) cholesterol are strongly implicated in the progression of ASCVD, prompting extensive study into the mechanisms governing cholesterol synthesis, transport, and clearance.[2]

While cholesterol metabolism has been traditionally studied in the context of cardiovascular risk, increasing attention has been paid to its dysregulation in chronic liver diseases. Cholestatic liver disorders, particularly primary biliary cholangitis (PBC), represent a unique model in which impaired bile flow and hepatobiliary dysfunction lead to paradoxical patterns of hypercholesterolemia. In these conditions, extremely elevated serum cholesterol levels may be observed without a commensurate increase in ASCVD events, challenging conventional paradigms of lipid-associated cardiovascular risk.[3]

This review explores the physiologic and pathologic dimensions of cholesterol metabolism, with an emphasis on the molecular and clinical consequences of its dysregulation in cholestatic liver disease. Fundamental aspects of cholesterol biosynthesis, transport, and catabolism are first outlined, followed by an examination of lipid abnormalities characteristic of PBC. Special attention is given to the role of lipoprotein X (LpX), apolipoprotein B, and current therapeutic strategies aimed at mitigating hypercholesterolemia in the context of impaired bile acid metabolism.

CHOLESTEROL METABOLISM

Physiologic Role of Cholesterol

Cholesterol, a lipid of widespread physiologic and pathologic importance, is derived from a steroid backbone. A steroid is an organic compound composed of 4 fused rings (A–D) with a distinct molecular architecture. The addition of a hydroxyl group to the C-3 position of the A-ring transforms the steroid into a sterol. The principal sterol synthesized by all mammalian cells is cholesterol, defined by a flexible hydrocarbon tail extending off of the sterol's D-ring. Despite the hydroxyl group, cholesterol ($C_{27}H_{46}O$) is largely hydrophobic given the extent of the molecule's carbon-hydrogen composition.[1]

On the cellular membrane, cholesterol coalesces with sphingolipids and glycosylphosphatidylinositol-anchored proteins to form microdomains, which regulate signal transduction, host-pathogen interaction, and membrane trafficking.[4] Steroidogenesis involves the importation of cholesterol into the mitochondria of endocrine cells and the multistep oxidation of cholesterol into pregnenolone. Important pregnenolone derivatives include mineralocorticoids, glucocorticoids, and gonadocorticoids.[5] Cholesterol also gives rise to oxysterols, oxidized derivatives of cholesterol, which are further metabolized into bile acids. Bile acids promote lipid absorption, acting as emulsifiers in the gastrointestinal tract. Excretion of bile acids is the primary pathway of cholesterol catabolism.[6,7] Elevated serum cholesterol is strongly associated with the development of ASCVD. Thus, the details of cholesterol metabolism and bile acid excretion are of great importance for the prevention of ASCVD.

Lipoproteins and Apolipoproteins

Cholesterol transport through the aqueous blood plasma requires association with lipoproteins. Lipoproteins contain a central hydrophobic core, which consists of cholesterol esters and triglycerides. The surrounding hydrophilic membrane is composed of phospholipids, free cholesterol, and proteins known as apolipoproteins. Five classes of lipoproteins are defined by their distinct size, lipid composition, and apolipoproteins: chylomicrons (CM), very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL).[8] The major functions of apolipoproteins include maintaining lipoprotein structure, modulating enzymes involved in lipoprotein metabolism, guiding lipoprotein formation, and acting as ligands for lipoprotein receptors.[9] In the clinical setting, apolipoproteins (ApoA, ApoB, etc.)

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serve as identification markers to measure the abundance of various lipoproteins in systemic circulation.

The Endogenous and Exogenous Pathway of Cholesterol Metabolism

Cholesterol is synthesized in the cytoplasm of most human cells via enzymes in the cytoplasm and smooth endoplasmic reticulum; however, more than 70% of daily cholesterol synthesis occurs in hepatocytes.[10] Synthesis begins with the condensation of 3 AcetylCoA molecules to form 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA). The rate-limiting step in cholesterol synthesis involves the reduction of HMG-CoA to mevalonate by HMG-CoA reductase. Mevalonate is subsequently converted to squalene, followed by lanosterol. Finally, the multistep Bloch pathway or Kandutsch–Russell pathway results in the conversion of lanosterol into cholesterol.[8]

The exogenous pathway of cholesterol metabolism involves the uptake of cholesterol from dietary or biliary sources (Fig. 1). In the duodenum and proximal jejunum, lipids, fat-soluble vitamins, and cholesterol are solubilized by bile salts into micelles, which are absorbed by enterocytes. After absorption, cholesterol is esterified and combined with other lipids into CM, the lipoprotein of lowest density defined by the presence of ApoB-48. CMs are secreted into mesenteric lymph, released into plasma, and reduced to CM remnants. CM remnants are rapidly removed from circulation by hepatocytes.[12]

Cholesterol Transport

Hepatic cholesterol is delivered to peripheral tissues via LDLs. In the liver, ApoB-100 combines with free cholesterol to form VLDL. Triglycerides in VLDL are metabolized by the enzymes hepatic lipase and lipoprotein lipase, producing IDLs, followed by LDLs, which are transported in the bloodstream. During this process of lipoprotein metabolism, atherogenic lipoproteins VLDL, IDL, and LDL maintain their ApoB-100 component. Tissues such as the liver and vascular endothelium extract LDL via receptor-mediated transcytosis.[13] The principle receptor for LDL on peripheral tissues is the LDL receptor, whereas endothelial cells primarily utilize scavenger receptor class B type 1 and activin receptor-like kinase 1.[14]

The term reverse cholesterol transport (RCT) describes the transport of peripheral cholesterol back to the liver for excretion into bile. ApoA-1, which constitutes 70% of HDL's protein content, is produced by the liver and intestine and interacts with receptors of hepatocytes, enterocytes, and macrophages. In macrophages, cholesterol and phospholipids combine with ApoA-1 to produce nascent

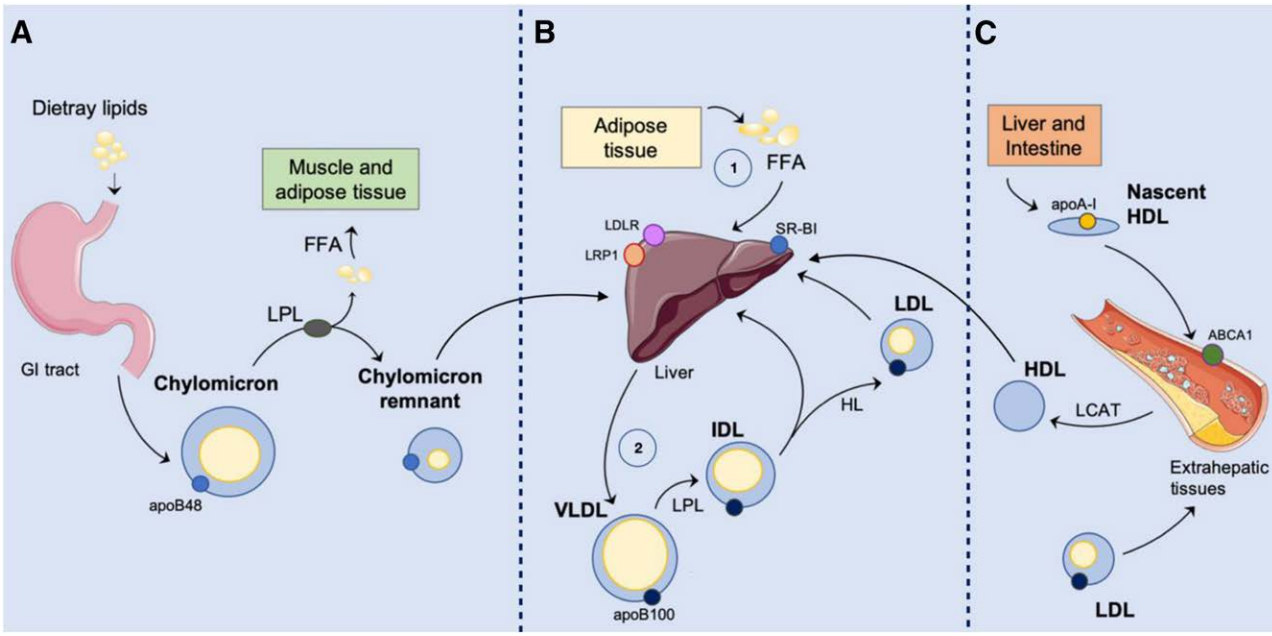

FIGURE 1. The 3 principal pathways of cholesterol metabolism. A, Exogenous lipoprotein pathway: digested lipids are converted to chylomicron particles, which are secreted into lymphatic vessels and released into circulation. In the capillary beds of adipose tissue and muscles, LPL releases FFA from the chylomicron core. FFA is metabolized by muscle or stored in adipose tissue. The cholesterol-rich chylomicron remnant is endocytosed by hepatocytes via LDLR and LRP1. B Endogenous lipoprotein metabolism: (1) Under fasting conditions, FFA are released from adipocytes and delivered to the liver. (2) After being released into circulation from the liver, VLDL is hydrolyzed by LPL and converted to IDL. HL converts IDL to LDL, in which the triglyceride core is largely depleted. C, reverse cholesterol transport: Nascent HDL is synthesized by the intestine and liver. Cholesterol efflux regulatory protein ABCA1 removes cholesterol from extrahepatic tissue, which subsequently combines with nascent HDL. ApoA-I activates LCAT, which catalyzes the esterification of said cholesterol and contributes to HDL maturation. Cholesterol esters in HDL are taken up by hepatocytes via SR-BI. The cholesterol component of circulating LDL is oxidized and contributes to the formation of atherosclerosis. ABCA1, ATP-binding cassette subfamily A1; ApoA-I, Apolipoprotein A-I; FFA, free fatty acids; HDL, high-density lipoprotein; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, LDL receptor; LPL, lipoprotein lipase; LRP1, LDLR-related protein 1; SR-BI, scavenger receptor BI; VLDL, very low-density lipoprotein. Adapted from Advanced Drug Delivery Reviews, 159, Stemmer et al, Insights into incretin-based therapies for treatment of diabetic dyslipidemia, 34-53, Copyright 2020, with permission from Elsevier.[11]

HDL. These small HDL particles sequester cholesterol and lipids effluxed from cells, forming mature HDL. Direct cholesterol delivery to the liver occurs when HDL binds to the hepatic surface receptor scavenger receptor class B type 1. In contrast, the indirect pathway involves transferring cholesterol to LDL, a process catalyzed by cholesteryl ester transfer protein. Following the transfer of cholesterol to LDL, HDL can continue sequestering cholesterol and lipids and repeat the RCT pathway.[15]

The final step in RCT is biliary cholesterol secretion in the form of free cholesterol or bile acids. Cholesterol uptake from plasma occurs on the basolateral membrane of hepatocytes. As demonstrated by Schwartz et al,[16] cholesterol derived from HDL appears to be preferentially secreted into bile; however, cholesterol from endogenous synthesis and LDL is secreted into bile as well. The intracellular compartment is the site of bile acid synthesis from cholesterol. The canalicular membrane houses numerous transporters involved in bile secretion. Both biliary phospholipid secretion and bile acid secretion appear to be the principal drivers for the secretion of cholesterol.[17] After secretion, bile is concentrated and stored in the gallbladder until dietary fat and protein stimulate cholecystokinin release, causing gallbladder contraction. In the intestine, bile acids act as detergents, emulsifying fats and contributing in their digestion and absorption. After participating in digestion, about 95% of bile acids are absorbed in the distal ileum, with the remainder excreted in feces.[18] The ratio of recycled to excreted cholesterol is tightly regulated in response to expansion or reduction of the body's total cholesterol (TC) pool.

ATHEROSCLEROSIS

Pathophysiology of Atherosclerosis

Atherosclerosis involves the accumulation of lipids, fibrous plaque, and calcification within arteries, leading to luminal narrowing and cardiovascular complications. Chronic stress on the endothelium due to arterial hypertension and turbulence results in endothelial cell dysfunction. Inflammatory cells, including monocytes and lymphocytes, invade the endothelium through the disrupted endothelial barrier. The damaged vessel wall serves as an adhesion point for platelets, which subsequently release proinflammatory cytokines and platelet-derived growth factor. Platelet-derived growth factor stimulates smooth muscle cell (SMC) proliferation in the tunica intima, resulting in the differentiation of fibroblasts into myofibroblasts. Macrophages and SMCs ingest cholesterol from oxidized LDL and transform into foam cells. Foam cells accumulate to form early atherosclerotic lesions called fatty streaks. Foam cells and SMCs produce collagen, leading to the development of a fibrous plaque, or atheroma. Macrophages in the atheroma secrete matrix metalloproteinases, which weaken the plaque's fibrous cap. Eventually, plaque rupture can ensue, resulting in exposed thrombogenic collagen and thrombus formation with vascular occlusion.[12]

Correlation Between Low-Density Lipoprotein and Atherosclerotic Cardiovascular Disease

Numerous clinical and genetic studies have unequivocally established LDL as a causal factor for ASCVD. Familial hypercholesterolemia is an autosomal dominant disease that typically results in a loss-of-function mutation to the LDL receptor gene, and leads to markedly increased concentration of circulating LDL. Studies comparing siblings who inherited familial hypercholesterolemia to those who did not demonstrate a dose-dependent increase in lifetime risk for ASCVD.[19] Multiple prospective observational epidemiologic studies involving participants without vascular disease at baseline recorded risk factors for the development of cardiovascular disease. Meta-analysis of these studies, involving hundreds of thousands of individuals, demonstrate a consistent log-linear association between the absolute magnitude of exposure to plasma LDL levels and the risk of ASCVD.[20,21] HMG-CoA reductase inhibitors, commonly referred to as statins, are among the most effective agents for reducing serum LDL.[22] In a meta-analysis of involving 170,000 individuals across 26 statin trials, treatment with a statin was associated with a 22% log-linear reduction in the risk of major cardiovascular events per millimole per liter reduction in LDL.[23] Thus, LDL has emerged not only as a biomarker of increased ASCVD risk, but a causal factor in the pathophysiology of ASCVD.[13]

Given the relationship between hypercholesterolemia and CVD, lipid-lowering therapy has emerged as an integral part of ASCVD primary and secondary prevention. The 2018 American Heart Association Guideline on the Management of Blood Cholesterol designates 3 populations at high-risk for ASCVD: individuals with severe hypercholesterolemia (LDL-C ≥ 190 mg/dL), adults with diabetes, and adults 40–75 years of age. The former 2 populations are candidates for immediate treatment with statins. In other adults 40–74 years of age, the decision to start statin therapy depends on the patient's risk of developing ASCVD over the next 10 years. Risk is calculated according to the patient's age, sex, race, TC, HDL cholesterol, systolic blood pressure, blood pressure-lowering medication use, diabetes status, and smoking status. In patients with evidence of clinical ASCVD 75 years of age or younger, high-intensity statins should be initiated.[24]

HYPERCHOLESTEROLEMIA OF CHOLESTASIS

Cholestatic Liver Diseases

Cholestasis is defined as the stagnation or marked reduction of bile flow.[25] Cholestasis may be caused by impaired hepatocyte bile production or obstruction of bile flow at any point from the basolateral hepatocyte membrane to the ampulla of Vater in the duodenum. Some etiologies of intrahepatic cholestasis include hepatocellular impairment (eg, hepatitis, intrahepatic biliary atresia), canalicular membrane changes (eg, medications, cholestasis of pregnancy), genetic defects in bile transporters [eg, benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis (PFIC)], canalicular or ductal luminal obstruction (eg, hereditary protoporphyria, cystic fibrosis), and ductopenia [eg, primary sclerosing cholangitis (PSC), PBC]. Causes of extrahepatic cholestasis include choledocholithiasis, PSC, and Mirizzi syndrome.[26]

The pathophysiology of cholestasis is specific to the underlying etiology. PFIC is a group of heterogeneous autosomal recessive liver disorders of childhood that result in defects to hepatocyte canalicular membrane transport proteins. In PFIC1 and PFIC2, impaired bile salt secretion results in hepatocyte bile salt overload and severe hepatocellular damage. PFIC3 is characterized by impaired biliary phospholipid secretion. The potent detergent effects of bile acids, in the absence of phospholipids, result in chemical damage to the bile canaliculi and biliary epithelium, leading to cholangitis and outflow obstruction.[2]

Cystic fibrosis-associated liver disease (CFLD) has emerged as the third most common cause of death in patients with cystic fibrosis, following lung disease and lung transplant complications. One study retrospectively analyzed 3328 CF patients in France and estimated the prevalence of CFLD to be 32.2% by age 25.[27] Cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride and bicarbonate epithelial membrane transporter and regulates the viscosity and acidity of mucus secreted various tissues, including the lungs, pancreas, and liver. CFLD is caused by mutations to CFTR anchored to the apical membrane of cholangiocytes, the epithelial cells that line the bile duct. An abnormal CFTR leads to impaired bile secretion and accumulation of thick, viscous bile with

reduced alkalinity. Alterations in bile flow, consistency, and chemical composition result in periductal inflammation, periportal fibrosis, and cholestasis.[28]

Primary Biliary Cholangitis and Hypercholesterolemia

PBC is a chronic, female-predominant cholestatic disease with a female-to-male ratio of 4–6:1.[29] The hallmark serologic marker of the disease is antimitochondrial antibody, which is positive in about 84% of patients.[30] PBC is characterized by autoimmune-mediated progressive destruction of intrahepatic bile ducts and defective bile duct regeneration, resulting in chronic cholestasis. Secondary hepatocyte damage ensues due to increased concentration of toxins, which are normally excreted in bile. Periportal fibrotic changes lead to liver cirrhosis and ultimately liver failure.[31]

The pathophysiology of hyperlipidemia in PBC is complex. Campesterol and sitosterol, cholesterol-like compounds found in plants, are elevated in patients with PBC. These sterols are absorbed by enterocyte transporters and selectively effluxed back into the intestinal lumen by ATP-binding cassette transporters G5 and G8 (ABCG5/ABCG8). ABCG5/ABCG8 are also located at the canalicular membrane of hepatocytes, where they facilitate the efflux of cholesterol and plant sterols into bile. Elevated campesterol and sitosterol levels have been observed in patients with PBC. Baila-Rueda et al[32] propose that defective canalicular membrane ABCG5/ABCG8-mediated cholesterol clearance contributes to hypercholesterolemia.

With bile duct destruction, intrahepatic and serum bile acid levels rise. This triggers a negative feedback mechanism that suppresses the expression of 7α-hydroxylase (CYP7A1), the rate-limiting step in the classic pathway of bile acid synthesis. Feedback inhibition of CYP7A1 is partially mediated by the farnesoid X receptor (FXR), a ligand-activated transcription factor responsible for downregulating hepatic bile acid production.[33] In 2016, the FDA approved obeticholic acid (OCA), a FXR agonist, for the treatment of PBC. The drug activates FXR, which suppresses de novo bile acid synthesis, blunting the harmful effects of bile acids on hepatic tissue.[34] A 2021 study enrolled 196 patients with metabolic dysfunction-associated steatohepatitis and compared the lipid profiles of 99 patients on OCA therapy to 97 controls. After 12 weeks of therapy, LDL-C concentration was higher in the OCA group compared to placebo (64.3 vs 51.3 mg/dL; $P < 0.0001$).[35] Unfortunately, since its approval, OCA has been associated with cases of serious liver injury, which limits its use in clinical practice.[36] Nevertheless, the study above demonstrates an inverse relationship between bile acid synthesis and serum cholesterol concentration.

In addition to defective cholesterol efflux via ABCG5/ABCG8 and decreased cholesterol clearance via the bile acid synthesis pathway, enhanced cholesterogenesis is another etiology of hypercholesterolemia in PBC. Despite elevated serum cholesterol, PBC is associated with increased activity of HMG-CoA reductase, the rate-limiting step in cholesterol synthesis.[37] LpX is formed when bile lipoprotein regurgitates into serum and combines with triglycerides, apo-C, and esterified cholesterol.[38] In the setting of progressive ductopenia, hypercholesterolemia is largely due to an increased level of LpX.[39] Walli et al incubated rat liver cells, human lymphocyte suspensions, or fibroblast cultures with LpX. They observed that uptake of LpX into lymphocytes was associated with diminished HMG-CoA reductase activity. In contrast, perfused livers did not absorb LpX, and HMG-CoA reductase activity was not diminished.[37] Whereas atherogenic lipoproteins VLDL and LDL contain ApoB, LpX does not contain ApoB, cannot be cleared by liver LDL receptors, and does not trigger negative feedback on cholesterol production.[40] Thus, PBC is characterized by elevated serum TC with a paradoxical increase in endogenous cholesterol synthesis.

Experimental evidence indicates that the accumulation of cholesterol in lymphocytes causes immune dysregulation and exacerbates autoimmune disease.[41] A moderate increase in plasma cholesterol can disrupt human T cell homeostasis.[42] A recent retrospective study stratified 531 PBC patients without prior liver-related complications into those with TC <200 mg/dL group (n = 326) versus TC ≥200 mg/dL group (n = 205). Additional baseline characteristics of the respective groups were as follows: total bilirubin (14.4 μmol/L vs 24.0 μmol/L; $P < 0.001$), and alkaline phosphatase [1.66 × upper limit of normal (ULN) vs 3.33 × ULN; $P < 0.001$], aspartate aminotransferase (1.35 × ULN vs 1.93 × ULN; $P < 0.001$). The authors' major conclusion was that TC levels were an independent parameter that can be used to stratify PBC patients as high- or low-risk of poor liver-related outcomes.[43] However, it remains to be determined whether elevated TC exacerbates PBC progression or is a manifestation of more severe disease.

Prevalence of Hypercholesterolemia in Cholestatic Liver Diseases

As discussed above, there is a strong association between PBC and hypercholesterolemia. Of the 16,327 Americans aged 20 years and older enrolled in the National Health and Nutrition Examination Survey between 2013 and 2018, 11.3% of participants were found to have hypercholesterolemia (ie, TC ≥ 200 mg/dL).[44] A study of 400 patients with PBC found the occurrence of hypercholesterolemia to be about 76%.[3] Others have reported the prevalence of hypercholesterolemia in PBC to be as high as 95%.[45,46]

Another cholestatic liver disease characterized by hypercholesterolemia is intrahepatic cholestasis of pregnancy (ICP). In ICP, hormonal and genetic factors impair the function of hepatocellular bile salt transporters, particularly the bile salt export pump, leading to decreased bile acid secretion and subsequent intrahepatic cholestasis. This disruption results in the accumulation of bile acids and cholesterol-rich bile constituents within hepatocytes and systemic circulation. The impaired canalicular secretion and associated hepatocellular membrane dysfunction facilitate the reflux of biliary lipids into the bloodstream, promoting the formation and systemic accumulation of LpX.[47] Elevated estrogen and progesterone levels during pregnancy further exacerbate transporter downregulation and cholestasis, amplifying disturbances in cholesterol metabolism characteristic of the condition.[48] A meta-analysis combining data from 11 studies across 5 countries compared the lipid profiles of 427 patients with ICP to 359 healthy pregnant controls. Women with ICP were found to have significantly higher plasma TC than their healthy counterparts, with a weighted mean difference of 18.0 mg/dL.[49]

Despite the association between PBC, ICP, and elevated TC, hypercholesterolemia is not a feature of all cholestatic liver diseases. In PFIC, autosomal recessive mutations disrupt key canalicular transport proteins, leading to impaired secretion of bile salts, phospholipids, and cholesterol from hepatocytes into bile. As a result, the essential components that would normally enter bile and potentially reflux into circulation in the setting of cholestasis are largely absent.[50] This prevents the formation of LpX. Additionally, fat malabsorption and poor nutritional status in affected children may further contribute to lower serum cholesterol levels.[51]

In CFLD, the hepatocyte canalicular membrane remains largely intact, thereby preserving the polarized secretion of bile constituents and preventing pathological reflux of biliary lipids into the systemic circulation. The cholestatic obstruction occurs primarily at the level of the intrahepatic bile ducts due to inspissated bile resulting from CFTR dysfunction in cholangiocytes, rather than hepatocellular injury.[52] Consequently, although bile flow is impaired, the structural and functional integrity of hepatocyte canalicular transporters is maintained, which precludes significant leakage of cholesterol-rich

bile components into the bloodstream.[53] This mechanism accounts for the absence of hypercholesterolemia in CFLD, distinguishing it from PBC, which is characterized by the formation of LpX.

Syndromes of Extreme Hypercholesterolemia

Numerous case reports describe syndromes of extreme hypercholesterolemia with TC levels far > 240 mg/dL, the mean baseline TC in PBC according to a retrospective study that analyzed the serum lipid profile of 400 PBC patients.[3] Huygen et al report 2 cases of marked hypercholesterolemia attributed to drug-induced liver injury. An 82-year-old woman with a diagnosis of nonsmall-cell lung carcinoma was treated with pembrolizumab. Her TC peaked at 406 mg/dL, but improved with discontinuation of the offending agent and corticosteroids. The second case involved a 79-year-old man treated with amoxicillin/clavulanic acid for a respiratory tract infection and erysipelas who was found to have cholestasis and a TC of 654 mg/dL attributed to the antibiotic.[54] Papakonstantinou et al report a 39-year-old male who underwent biliary stent placement for acute pancreatitis 2 years prior was found to have common bile duct dilation (15 mm) secondary to 2 gallstones and a TC of 958 mg/dL. Following ERCP with gallstone removal and new stenting, his cholesterol level gradually decreased over 3 months.[55] Phatlhane et al report a 46-year-old female with a history of abdominal tuberculosis (TB) who completed her antituberculosis therapy. She was subsequently found to have a TC of 1249 mg/dL. Liver biopsy revealed granulomatous hepatitis, focal necrotizing granulomas, and portal tract fibrosis. The patient was treated with a second TB regimen, and her liver function tests significantly improved.[56]

LpX is a biomarker that is strongly associated with cholestasis. There is a high concordance between the presence of LpX and histology-proven cholestasis.[57,58] The authors above suspected LpX as the underlying cause of hypercholesterolemia, and in some cases, conducted further testing to prove their hypothesis. Huygen et al observed a discordance between laboratory-reported LDL and serum ApoB, the latter being a component of LDL but absent from LpX.[54] Phatlhane et al used gradient gel electrophoresis to prove the presence of LpX in the patient with TB-mediated cholestasis.[56] The first line treatment of LpX-mediate hypercholesterolemia involves correcting the underlying cause of cholestasis.[59] The cases above demonstrate resolution of each patients' abnormal liver function tests and lipid panel once the underlying cause was addressed.

Rapid correction of the underlying cause of extreme cholestasis is not always feasible and warrants a more aggressive treatment approach. Complications of chronic, marked serum LpX exposure include the development of retinal cholesterol, thromboembolism, xanthoma, and hyperviscosity syndrome.[56] Xiao et al report a case of a patient with advanced PSC awaiting liver transplant without viable means to alleviate biliary obstruction. She presented with periorbital xanthelasmata and palmar xanthomata in the setting of TC of 832 mg/dL. Given the patient's severe liver dysfunction, there were safety concerns about using cholesterol-lowering medications. Instead, the authors opted to perform plasma exchange weekly initially and then biweekly after an effective reduction in TC. The patient's TC was maintained ≤500 mg/dL for 5 months as the patient awaited liver transplantation and avoided any major complications of extreme hypercholesterolemia.[60]

MANAGEMENT OF HYPERLIPIDEMIA IN CHOLESTATIC LIVER DISEASE

Hypercholesterolemia is not Associated With Cardiovascular Disease in Primary Biliary Cholangitis

Among cholestatic liver diseases, PBC has the most robust literature regarding the long-term cardiovascular implications of chronic, isolated cholestasis. A systemic epidemiologic review of PBC found the incidence and prevalence of PBC per 100,000 inhabitants per year to be 0.33 to 5.8 and 1.91 to 40.2, respectively.[61] Despite the association between elevated TC and liver disease, elevated risk for CVD based on hypercholesterolemia alone has not been borne out in patients with PBC. In a study of 930 patients with PBC, the risk of transient ischemic attack, stroke, or myocardial infarction was not increased compared to age- and sex-matched controls.[62]

The conventional lipid panel measures serum cholesterol lipoproteins according to their density. LpX has a similar density to that of LDL, making the antiatherogenic vesicle indistinguishable from that of the pro-atherogenic lipoprotein. Despite their similar density, the diameter of LDL is 18–25 nm, while LpX is 3 times larger at 50–70 nm, similar to the size of VLDL.[63,64] Endothelial uptake of VLDL is limited given the particle's size. Some authors postulate that the size of LpX may also prevent its uptake into the vascular endothelium.[65] Another unique feature of LpX is the particle's intrinsic antioxidant properties. Chang et al collected LDL from healthy patients (control LDL) and LDL from patients with PBC (PBC-LDL). After prolonged incubation with the oxidizing agent copper sulfate, the oxidation index of control LDL was increased, whereas the oxidation index of PBC-LDL was unchanged. When PBC-LDL or LpX were combined with control LDL, they prevented oxidation of the latter in a dose-dependent manner. The authors concluded that LpX reducedes LDL atherogenicity by preventing LDL oxidation, the key step in atherogenesis that leads to foam cell formation.[39]

Atherosclerotic Cardiovascular Disease Risk Stratification of Cholestatic Liver Disease Patients

Wah-Suarez et al[66] provide a framework for the management of hypercholesterolemia in PBC. To mitigate the overlap between LDL and LpX, they propose ApoB measurement as a surrogate for LDL. ApoB is not present in LpX and has a well-established linear relationship with the level of circulating LDL.[67] Furthermore, there is mounting evidence to suggest that ApoB is a superior lipid parameter for ASCVD risk stratification of the general population compared to LDL cholesterol. Whereas ApoB measurement reflects the total serum atherogenic particle pool, LDL measurement excludes atherogenic particles such as CM remnants, VLDL, and lipoprotein(a).[68] As ApoB assays become more widely available, this will ease the process of ASCVD risk stratification of patients with cholestatic liver disease.

The 2021 Canadian Cardiovascular Society Guidelines recommend that, for patients with serum triglyceride levels >133 mg/dL, non-HDL cholesterol or ApoB be used instead of LDL as the preferred parameter for lipid screening.[2] Given this stance, their ASCVD guidelines offer treatment recommendations according to ApoB level (in addition to the level of LDL and non-HDL cholesterol). This provides a useful framework for risk stratifying PBC patients in whom ApoB measurement is preferred over LDL for assessing ASCVD risk (Fig. 2). Based on the Canadian Cardiovascular Society guidelines, treatment of hypercholesterolemia should be started in PBC patients with preexisting CVD, diabetes, or CVD risk factors (eg, hypertension, tobacco use) and an ApoB level >90 mg/dL. Patients with CVD risk factors who have an ApoB level <90 mg/dL should have their ApoB level rechecked annually. In patients without CVD risk factors, an ApoB level <120 mg/dL warrants rechecking ApoB level every 5 years, whereas patients with an ApoB-100 level >120 should initiate treatment.[2]

Management of Hyperlipidemia in Cholestatic Liver Disease

Patients who meet the above criteria for treatment initiation may be started on a moderate intensity statin (eg, atorvastatin

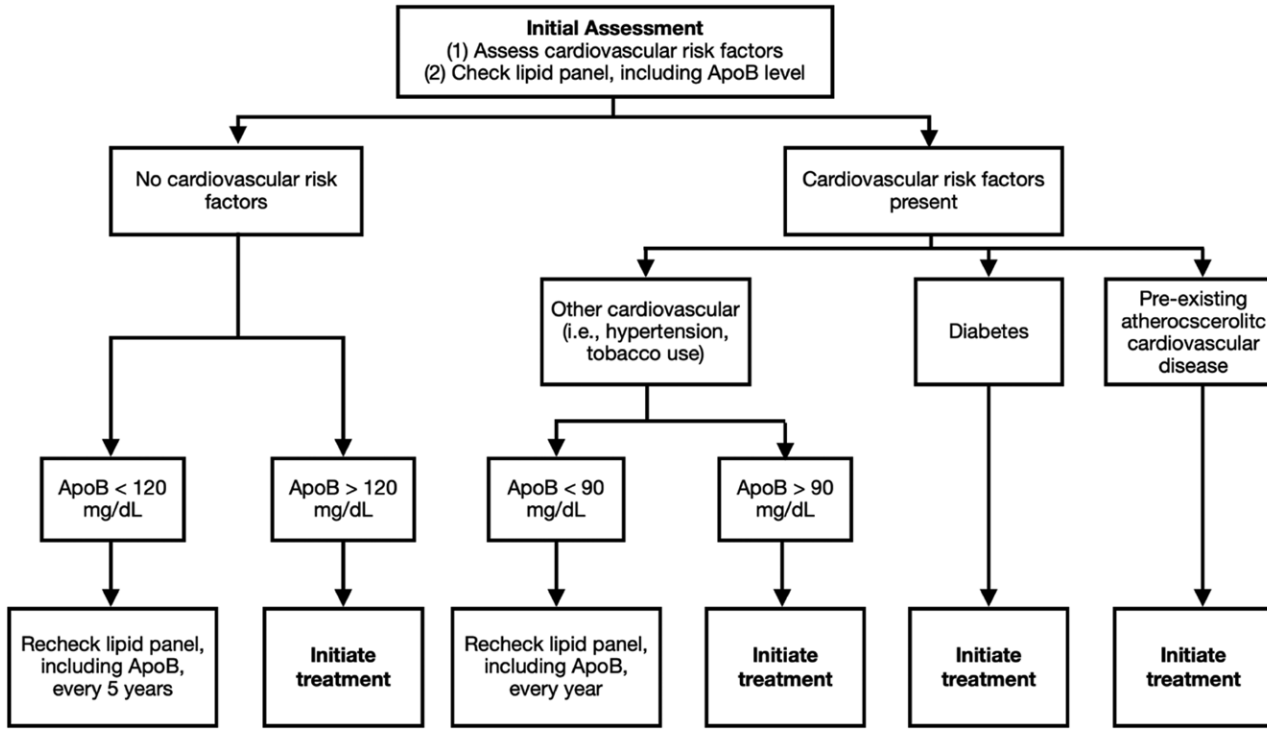

FIGURE 2. Algorithm for the evaluation of hypercholesterolemia in PBC. Treatment should be initiated in patients without cardiovascular risk factors but ApoB > 120 mg/dL, hypertension or tobacco use and ApoB > 90 mg/dL, diabetes, or preexisting atherosclerotic cardiovascular disease. ApoB, apolipoprotein B; PBC, primary biliary cholangitis. Wah-Suarez et al.[66]

10–20 mg daily or simvastatin 20–40 mg daily). After 3 months of statin therapy, an ApoB level should be remeasured and is expected to decrease by 30–50%. In compliant patients who do not achieve the expected response, the statin should be up-titrated as tolerated. Patients who cannot tolerate the moderate- or high-intensity statin, or fail to adequately respond, should be started on a proprotein convertase subtilisin kexin 9 (PCSK9) inhibitor as second-line therapy (Fig. 3).[66]

Evidence from multiple large randomized control trials demonstrates that statins reduce the risk of major cardiovascular events by about 25% per mmol/L reduction in LDL for every year that therapy is continued after the first year of initiation.[69] In the PBC population, statins have been shown to lower serum LDL without causing elevations in alanine aminotransferase (ALT).[70,71]

There is absolutely no contraindication between ALT elevation or chronic liver disease, and statin use. Statin-induced hepatotoxicity has been described as a "myth."[72] Multiple large randomized control trials have shown no significant difference in the frequency of ALT elevation greater than 3 times the ULN between the statin versus placebo group.[73–75] Furthermore, in patients with chronic liver disease, statins are associated with a lower risk of hepatic decompensation and mortality.[76] Recent literature supports the use of statins for select liver diseases, regardless of the patient's cardiovascular profile. Statin use is associated with reduced risk of fibrosis progression in patients with advanced chronic hepatitis C,[77] and decreased hepatic venous pressure gradient in patients with portal hypertension and cirrhosis.[78] According to the 2014 guidelines published by the National Lipid Association's Statin Safety Task Force, baseline liver enzymes should be obtained prior to initiating statin therapy, but postinitiation liver enzyme monitoring in not warranted.[79]

PCSK9 inhibitors have been proposed as second-line therapy for hyperlipidemia in chronic cholestasis. PCSK9 is produced by hepatocytes, secreted into plasma, and tags LDL receptors for lysosomal degradation. Increased activation of PCSK9 prevents clearance of cholesterol by the nonatherogenic pathway (ie, hepatic endocytosis), increases plasma LDL, and causes more LDL cholesterol to be removed by the pro-atherogenic scavenger pathway. PCSK9 inhibitors increase hepatic cholesterol uptake by preserving LDL receptor activity. As of 2024, alirocumab and evolocumab are 2 humanized antibodies approved by the FDA to inhibit or reduce PCSK9 activity.[80] A meta-analysis of 25 randomized control trials found that alirocumab and evolocumab reduced LDL cholesterol levels by over 50% and were not associated with an elevation in liver enzymes.[81] A parallel-group study found that evolocumab was well-tolerated in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). As of this writing, no studies have evaluated the safety and efficacy of PCSK9 inhibitors in the PBC population; however, based on the above data, it is reasonable to start a PCSK9 inhibitor in a PBC patient so long as their hepatic impairment is less than severe.

Ursodeoxycholic acid (UDCA) is an FDA-approved therapy for PBC and has been shown to significantly delay the progression to cirrhosis in patients with early-stage disease.[82] As a hydrophilic bile acid, UDCA promotes choleresis, displaces cytotoxic bile acids, and exerts anti-inflammatory and immunomodulatory effects within the intrahepatic biliary system. It also reduces cholesterol saturation in bile, thereby facilitating the dissolution of cholesterol gallstones.[83] The use of UDCA in PSC is controversial, with randomized control trials showing some improvement in liver enzymes, but no significant improvement clinically significant endpoints, such as development of cirrhosis, liver transplantation, or death.[84] In patients with PBC, UDCA has been shown to lower TC, LDL, and VLDL.[85] In the absence of contraindications, all patients with PBC should be treated with UDCA.

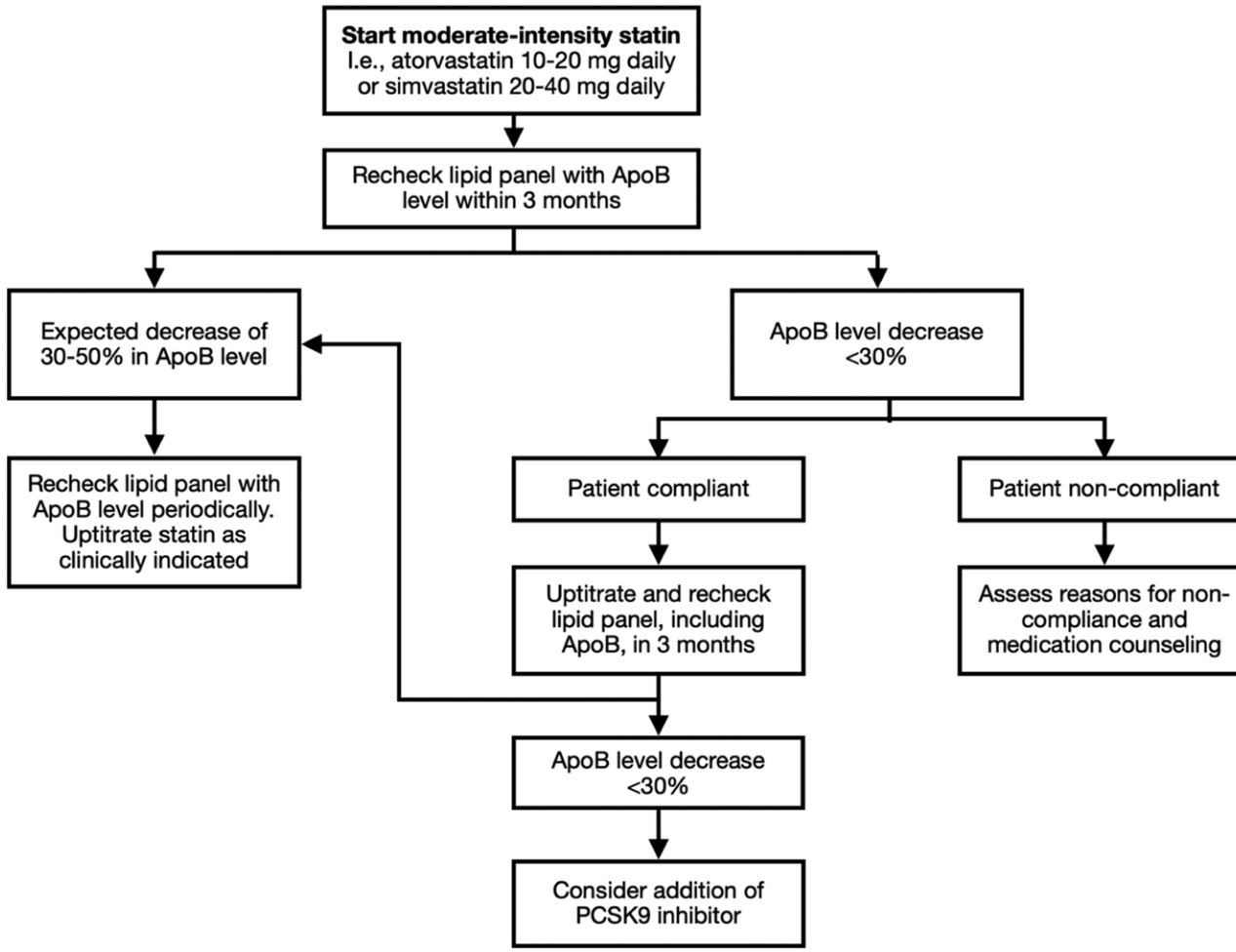

FIGURE 3. Algorithm for the treatment of hypercholesterolemia in PBC. Moderate-intensity statin is recommended as first-line treatment. In patients with persistent ApoB elevation despite increasing the statin dose, a PCSK9 inhibitor is recommended for second-line therapy. ApoB, apolipoprotein B; PBC, primary biliary cholangitis; PCSK9, proprotein convertase subtilisin/kexin type 9. Wah-Suarez et al.[66]

CONCLUSIONS

In conclusion, hypercholesterolemia in cholestatic liver disease is a common yet paradoxical finding in cardiovascular risk assessment. Although cholestatic liver disease is associated with hypercholesterolemia, these patients do not have an increased risk for ASCVD. This is likely due to the cardioprotective effects of LpX seen in these patients. Clinicians should be aware that ApoB measurement, rather than conventional LDL measurements, is a more accurate way of determining ASCVD risk stratification in patients with cholestatic liver disease. Treatment strategies for hypercholesterolemia in cholestatic liver disease primarily involve statins as first-line therapy, with PCSK9 inhibitors serving as a second-line option.[66] Additionally, regular monitoring of ApoB is crucial to evaluate therapeutic efficacy. This review highlights the complexities of cholesterol metabolism in cholestasis, as well as the need for tailored approaches in managing hypercholesterolemia in patients with cholestatic liver disease.

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