

LIPID AND LIPOPROTEIN METABOLISM IN LIVER DISEASE

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ABSTRACT

The liver plays a central role in lipid metabolism, serving as the center for lipoprotein uptake, formation, and export to the circulation. Alterations in hepatic lipid metabolism can contribute to the development of chronic liver disease, such as nonalcoholic fatty liver disease (NAFLD) and add to the progression of other chronic liver disease, as occurs in hepatitis C. Moreover, chronic liver disease can impact hepatic lipid metabolism leading to alterations in circulating lipid levels contributing to dyslipidemia. This chapter discusses the interplay between lipid metabolism and chronic liver diseases focusing on NAFLD, alcoholic liver disease, hepatitis C, hepatitis B, cholestatic liver disease, and cirrhosis.

NONALCOHOLIC FATTY LIVER DISEASE

Case Presentation

A 60-year-old woman with a past medical history significant for hypertension, dyslipidemia and diabetes mellitus presents for management of newly diagnosed nonalcoholic steatohepatitis (NASH). She has a strong family history of coronary artery disease and a personal history of dyslipidemia characterized by a serum triglyceride level of 220 mg/dl, low-density lipoprotein (LDL) cholesterol of 180 mg/dl, high-density lipoprotein (HDL) cholesterol of 50 mg/dl and total cholesterol of 274 mg/dl. Based on these values, her primary physician has recommended she start a lipid lowering medication. However, with her history of liver

disease she is uncertain whether she can safely take lipid-lowering medications.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States, affecting up to a third of adults (1,2). NASH is the progressive form of NAFLD and can lead to cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. In addition to significant morbidity and mortality from end-stage liver disease, NAFLD confers an increased risk of cardiovascular disease (CVD) (3). CVD is the leading cause of mortality among individuals with NAFLD (4). The dyslipidemia of NAFLD may be one of several important and modifiable CVD risk factors.

Changes in Lipoprotein Metabolism and Clinical Manifestations

DEVELOPMENT OF STEATOSIS

NAFLD is characterized in part by steatosis, excess lipid deposition as lipid droplets within hepatocytes. These lipid droplets consist largely of triglycerides and are the result of an imbalance of hepatic lipid handling. Steatosis can occur when one or more of the following conditions is present; 1) excess delivery of free fatty acids (FFA) to the liver from adipose tissue, 2) increased de novo lipogenesis (DNL) within the liver, 3) decreased oxidation of fatty acids within

hepatocytes and 4) impaired export of triglycerides from the liver in the form of very-low density lipoproteins (VLDL).

Excess FFA Delivery to the Liver

When excess adiposity and insulin resistance are present, FFA release from adipocytes is increased (5). Upon release FFA are then delivered via the circulation to the liver and may overwhelm the liver's capacity to oxidize or export lipids, contributing to the development of steatosis. The fatty acid translocase FAT/CD36 mediates uptake of FFA into the liver and is upregulated in human and experimental NAFLD, which may contribute to steatosis (6,7,8).

Increased DNL

Hyperinsulinemia, often seen in the setting of obesity and the metabolic syndrome, can also contribute to DNL as the result of increased transcriptional activities of sterol regulatory element binding protein (SREBP) 1c- and peroxisome proliferator-activated receptor (PPAR)- γ (5,9,10). Increased circulating glucose levels also mediate lipogenesis via cholesterol regulatory element binding protein (ChREBP) activation (11). The increased synthesis of lipids within the liver can lead to accumulation within hepatocytes and can promote the development of steatosis.

Insufficient Export of Hepatic Triglycerides

Export of triglycerides from the liver requires the formation of VLDL and when VLDL formation is impaired steatosis can develop. VLDL are formed when triglycerides are complexed to apolipoprotein B100 (apoB100) via the action of microsomal triglyceride transfer protein (MTP). Steatosis can develop when any of the components of VLDL formation are missing or impaired. Genetic or pharmacologic alteration of MTP or the truncation or absence of ApoB100 can lead to steatosis (12-16). In addition, ApoB100 levels can be decreased by FFA accumulation. FFA accumulation within the liver can lead to chronic stress of the hepatocyte endoplasmic reticulum (ER). Increased ER stress results in increased ApoB100 degradation, decreasing the ability of the liver to export triglycerides and potentially worsen steatosis.

Complete VLDL assembly and secretion relies on several additional steps. Following the formation of nascent VLDL particles, further lipidation is needed to create mature VLDL particles. The process of this lipidation is not well understood but may rely on fusion with lipid droplets (17). Interruption of this process of lipid mobilization from lipids

droplets to VLDL may also contribute to the development of steatosis (18). Recent genetic studies have shown a strong link between a polymorphism in the gene patatin-like phospholipase domain-containing 3 (PNPLA3) and NAFLD. This coding region polymorphism (I148M) reduces hepatic VLDL secretion, possibly by interfering with triglyceride mobilization and results in hepatic steatosis (19-21). However, conflicting data indicates there may be a compensatory increase in VLDL export in some NAFLD patients, although this increase is insufficient to counterbalance the elevated hepatic triglyceride content (22). The transmembrane 6 superfamily 2 (TM6SF2) E167K variant results in decreased hepatic VLDL secretion and is associated with NAFLD, fibrosis and cirrhosis in the setting of decreased LDL and triglyceride levels. This variant is associated with progressive liver disease but a decreased risk of cardiovascular disease (23,24). Familial hypobetalipoproteinemia (FHBL) is a condition characterized by diminished levels of functional ApoB100, resulting in impaired VLDL export and the development of hepatic steatosis. Magnetic resonance spectroscopy studies have shown liver fat content in individuals with FHBL to be five times greater than in controls (25,26). Progress to steatohepatitis, cirrhosis and hepatocellular carcinoma (HCC) has been noted in this population (27,28,29,30).

Hepatic Accumulation of Free Cholesterol

The degree of hepatic free cholesterol accumulation in NAFLD correlates with presence and severity of cytologic ballooning (31). Decreased expression of ATP-binding cassette (ABC) A1 and ABCG8 cholesterol efflux proteins, may disrupt transfer of cholesterol from hepatocytes, driving up hepatocyte cholesterol (32,33). There is conflicting evidence regarding changes to hepatic uptake of LDL in individuals with NAFLD, with some studies indicating upregulation of LDL receptors resulting in cholesterol overloading (34).

CHANGES IN LIPID METABOLISM

Dyslipidemia is frequent in adults with radiographic and biopsy-proven NAFLD and is characterized by hypertriglyceridemia, increased LDL particle concentrations, decreased LDL particle size, and decreased HDL levels (35). High ratios of total cholesterol or triglyceride to HDL-cholesterol are associated with NAFLD (36). In addition, non-HDL-cholesterol (non-HDL-C), a composite measure of apolipoprotein-B containing lipoproteins and an important marker of CVD risk, is elevated in individuals with NASH (19). NASH is also characterized by alterations in lipoprotein subfractions.

Lipoprotein subfraction assays measure lipoprotein particle size, density and composition. NASH is characterized by large VLDL particle size and decreased LDL and HDL particle size (35). However, there is conflicting data on the association between NASH and VLD particle size (17,18). Furthermore, increased levels of LDL-III and IV particles, atherogenic forms of LDL, and reduced HDL2b levels, a cardioprotective lipoprotein, are observed in NASH (36,37). Fortunately, resolution of NASH is associated with increases in HDL, decreases in triglycerides, and increases in mean LDL particle diameter and the frequency of LDL phenotype A (39).

Insulin Resistance

Insulin resistance is a fundamental aspect of NAFLD and can result in many of the alterations in lipid metabolism and circulating lipid levels seen in NAFLD.

INSULIN RESISTANCE INCREASES CIRCULATING LDL, VLDL AND TRIGLYCERIDES LEVELS

Insulin resistance can increase circulating VLDL and triglyceride levels via several mechanisms. Insulin resistance leads to a loss of suppression of MTP transcription, which increases the efficiency of VLDL assembly (40,41). Insulin resistance also impacts VLDL levels by decreasing lipoprotein lipase (LPL) levels. LPL is an enzyme found on the endothelial cells within muscle and adipose tissue. LPL hydrolyzes triglycerides from circulating VLDL and facilitates triglyceride delivery to muscle and adipose tissues. In the setting of insulin resistance, LPL is downregulated decreasing the clearance of VLDL from the circulation and increasing circulating VLDL levels (42).

Insulin resistance can also act via ApoCIII levels to increase circulating VLDL and triglyceride levels. ApoCIII, a lipoprotein found on VLDL, inhibits LPL and can decrease VLDL clearance from the circulation (43). In the setting of insulin resistance, ApoCIII levels are increased, leading to decreased VLDL/triglyceride clearance and resulting in hypertriglyceridemia and increased VLDL levels. ApoCIII also appears to modulate plasma triglyceride levels via LPL-independent mechanisms. In patients with LPL deficiency due to familial chylomicronemia syndrome, administration of an ApoCIII mRNA inhibitor for 13 weeks reduced plasma triglycerides by 56-86% (44).

Insulin resistance also impacts LDL metabolism via upregulation of hepatic lipase and increased LDL receptor degradation. Hepatic lipase is an enzyme that remove triglycerides from intermediate-density lipoproteins (IDL)

leading to the development of smaller, denser low-density lipoproteins. In NAFLD and insulin resistance, hepatic lipase levels are upregulated leading to increased levels of small, dense LDL (sdLDL) (45). Insulin can also increase circulating LDL levels via its effects on the LDL receptor. Insulin upregulates proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that can bind and degrade the LDL receptor (46). Upregulation of PCSK9 leads to decreased LDL receptor availability on hepatocytes and increased circulating LDL levels.

INSULIN RESISTANCE DECREASES CIRCULATING HDL LEVELS

Insulin resistance decreases circulating HDL levels by interfering with HDL particle assembly. HDL is formed within plasma at the surface of the hepatocyte and requires the interaction of ApoA-1 and ABCA1 (47). Nascent HDL particles are formed when ApoA-1, secreted by the liver or released from other lipoproteins, is lipidated by ABCA1 with phospholipids and free cholesterol. Insulin resistance hampers HDL formation by promoting the phosphorylation and degradation of ABCA1 and by reducing ABCA1 activity (48). In addition to hampering HDL production, insulin resistance may interfere with reverse cholesterol transport. Insulin resistance can result in the formation of particularly triglyceride-rich HDL particles via the action of cholesterol ester transfer protein (CETP) (49). Triglyceride-rich HDL are taken up more rapidly by the liver and may result in lower circulating HDL levels.

Management

Diet and exercise are the foundations of the management of both NAFLD and the dyslipidemia of NAFLD. Small studies have indicated that both a low carbohydrate diet as well as the Mediterranean diet may improve serum lipid levels and NAFLD (50-52). Further, adherence to a Mediterranean diet reduces the development of CVD (53). As CVD is a cause of considerable morbidity and mortality in NAFLD patients, adherence to a Mediterranean diet may have multiple benefits.

Routine aerobic exercise, defined as 30 minutes of moderate exercise most days of the week, can result in significant improvements in lipid levels and may improve hepatic lipid content (54,55). Individuals with NAFLD should be advised to participate in regular, aerobic exercise.

LIPID LOWERING MEDICATIONS

HMG-CoA Reductase Inhibitors

When diet and exercise are insufficient in individuals with NAFLD, HMG-CoA reductase inhibitors or “statins” are recommended. Statins play an important role in both the primary and secondary prevention of CVD and should be used in patients with NAFLD and dyslipidemia. Compared to placebo, statins have been shown, in a post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study, to significantly reduce cardiovascular events in individuals with NAFLD (56). Statins have also been shown to exert a protective effect on liver histology in patients with NAFLD/NASH, with dose-dependent reduction in steatosis, steatohepatitis and fibrosis stages F2-F4, although protection against steatohepatitis in the presence of the I148M PNPLA3 risk variant did not reach statistical significance (57).

It is important to note that while there remains a concern among physicians about statin hepatotoxicity, the incidence of statin-induced hepatotoxicity in the general population is extremely low and is not increased in individuals with NAFLD or NASH (58-60). Apprehension among physicians may partly account for the current under prescribing of statins in patients with NAFLD (61,62).

Omega-3 Fatty Acids

Omega-3 fatty acids can be used in patients with NAFLD for the treatment of isolated hypertriglyceridemia or when statins alone are insufficient to control triglyceride levels. Omega-3 fatty acids act to reduce hepatic VLDL secretion and lower serum triglyceride levels. Doses of up to 4 grams daily can decrease triglycerides by 25-35% (63). Omega-3 fatty acids may reduce radiographic steatosis and several randomized controlled trials (RCTs) of omega-3 fatty acids are ongoing to determine their impact on NASH histology (64-66).

Cholesterol Absorption Inhibitors

A further class of drugs which may hold promise are the cholesterol absorption inhibitors, of which ezetimibe has been most extensively studied. A recently conducted RCT involving 32 NAFLD patients found that ezetimibe use led to significant improvement in fibrosis stage and ballooning score (67). Of note, Loomba et al. reported no significant impact of ezetimibe on liver fat content, as assessed by magnetic resonance imaging proton density-fat fraction and liver biopsy (68). The influence of ezetimibe on the various stages of NAFLD pathogenesis remains to be fully characterized. Further large-scale RCTs are warranted to explore ezetimibe’s potential as a component of NAFLD/NASH therapy alongside statins.

LIPID TREATMENT GOALS

We recommend that patients with NAFLD adhere to the Cholesterol Clinical Practice Guidelines from the American Heart Association and American College of Cardiology released in 2018. The guidelines recommend that all adults with any form of CVD or an LDL ≥ 190 mg/dL should be treated with high intensity statins for a goal 50% reduction in LDL. Patients aged 45-70 years with diabetes with LDL < 189 mg/dL or patients with > 7.5% global 10-year CVD-risk should receive moderate intensity statins for a goal 30-50% reduction in LDL. A specific target LDL is no longer formally recommended.

Return to Case

For our patient with NAFLD it would be both safe and important for her to take lipid-lowering medication to manage her dyslipidemia and reduce her risk of a CVD development. She would benefit from administration of a statin of either moderate or high intensity, based on the outcome of risk assessment.

Table 1. Key Points- Non-Alcoholic Fatty Liver Disease
NAFLD is associated with insulin resistance which results in atherogenic dyslipidemia characterized by increased small dense LDL and triglyceride levels and decreased HDL levels.
The dyslipidemia of NAFLD may contribute to the increased risk of CVD observed in individuals with NAFLD
Patients with NAFLD and NASH should be treated for their dyslipidemia to reduce their CVD risk.
Individuals with NAFLD can be treated with statins without increased risk of hepatotoxicity.

ALCOHOLIC LIVER DISEASE

Case Presentation

An obese 48-year-old man with a past medical history significant for coronary heart disease, hypertension, and diabetes mellitus presents for management of newly diagnosed hepatic steatosis. He has a family history of coronary artery disease. He admits to consuming 3 glasses of wine per night during the week and an additional two per evening on weekends. His fasting plasma triglyceride concentration is 350 mg/dl, his LDL cholesterol is 130 mg/dl, and HDL cholesterol is 55 mg/dl. The alanine aminotransferase level (ALT) is modestly elevated at 55 IU/ml. He would like to know whether he has NAFLD and whether you recommend continuing his current alcohol intake to protect against CVD, especially since he was told that his good cholesterol was elevated.

Introduction

Alcoholic liver disease (ALD) accounts for nearly half of cirrhosis-related mortality in the United States (69). A hallmark feature of ALD is hepatic steatosis, which develops in more than 90% of heavy drinkers. However, less than one third of these individuals develop complications that include alcoholic hepatitis, cirrhosis and HCC (69). Risk factors for disease progression include female sex, obesity, drinking patterns, dietary factors, non-sex-linked genetic factors, and cigarette smoking (70,71). Alcohol also synergizes with other etiologies of chronic liver disease, including NAFLD and viral hepatitis to accelerate progression (69). Hypertriglyceridemia is the primary dyslipidemia associated with alcohol ingestion (72), and a J-shaped association exists between alcohol intake and CVD (73), which may reflect a parallel effect of plasma triglycerides (72). Although its contribution to metabolic syndrome is unclear, alcohol intake appears to interact with obesity to further increase plasma triglyceride concentrations (72).

Changes in Lipoprotein Metabolism and Clinical Manifestations

DEVELOPMENT OF STEATOSIS

As with NAFLD, the development of steatosis in response to alcohol is multifactorial. Alcohol impairs the β -oxidation of fatty acids by mitochondria, promotes *de novo* lipogenesis in the liver, and increases fatty acid uptake. As is the case in NAFLD, VLDL secretion is also increased due to alcohol.

Excess FFA Delivery to the Liver

As is the case for NAFLD, fatty acids from extrahepatic sources appear to contribute to hepatic steatosis. In addition to increasing mobilization of fatty acids from adipose tissue (74), alcohol intake augments the supply of lipids to the liver from the small intestine in the form of chylomicron remnants (75).

Increased DNL

Increased DNL contributes to alcohol-related steatosis by direct and indirect mechanisms (69). The alcohol metabolite acetaldehyde increases transcription of SREBP1c, which upregulates transcription of lipogenic genes. Alcohol-induced endoplasmic reticulum stress and inflammation leads to increased processing of the SREBP1c protein within hepatocytes. Alcohol also inhibits proteins that suppress lipogenesis. The protein deacetylase Sirtuin 1 (SIRT1), plays a central role (76). Suppression of SIRT1 by alcohol leads to hyperacetylation of a group of molecules, including those that promote lipogenesis. Inhibition of adenosine monophosphate kinase (AMPK) contributes, because AMPK-mediated phosphorylation of SREBP1c reduces transcriptional activity. AMPK also phosphorylates and inhibits acetyl-CoA carboxylate (ACC), the rate-limiting step in lipogenesis.

Impaired Oxidation and Degradation of Fatty Acids

Alcohol decreases mitochondrial fatty acid oxidation principally by decreasing activity of the transcription factor peroxisome proliferator activated receptor (PPAR) α . This occurs in response to increased NADH/NAD⁺ ratios and decreased AMPK activity, among other factors (69). PPAR α promotes the transcription of genes that mediate fatty acid oxidation. Alcohol intake may also inhibit autophagy (69), which plays an important role removing lipids from the liver (77).

Insufficient Export of Hepatic Triglycerides

Alcohol increases VLDL secretion (72,78), apparently by increasing the transcription of MTP (74). The increased in export of hepatic triglycerides is insufficient to offset the accumulation due to increases in fatty acid uptake and synthesis in the setting of decreased oxidation.

HYPERTRIGLYCERIDEMIA

Increased VLDL secretion contributes to hypertriglyceridemia that is observed in the setting of alcohol consumption. This is exacerbated by decreased expression of LPL (79), which promotes clearance of VLDL triglycerides into muscle and fat tissue. There is also an interaction between alcohol consumption and genetic polymorphisms in apoCIII, which circulates in the plasma and functions to inhibit lipoprotein lipase activity (80).

CIRCULATING HDL LEVELS

Alcohol increases HDL lipids and apolipoproteins in patterns that depend upon amount of consumption: Moderate consumption tends to increase plasma concentrations of smaller HDL particles, whereas heavier consumption favors larger HDL particles (81). Alcohol interacts with HDL metabolism in multiple steps, which can ultimately lead to increased reverse cholesterol transport, the process by which cellular cholesterol is transported to the liver for elimination into bile (81,82). Heavier alcohol consumption impairs CETP activity, so the typical inverse relationship observed under circumstances associate with NAFLD is not necessarily observed in the setting of alcohol use and HDL may be increased as well (72,83). Moderate alcohol consumption also appears to enhance the anti-inflammatory and anti-oxidant properties of HDL particles (81).

CIRCULATING LDL LEVELS

The effects of alcohol on plasma LDL cholesterol concentrations is less consistent than observed for HDL, with different patterns observed in different populations, which may be attributable to genetic polymorphisms with these populations (81).

Management

Although considerable anecdotal evidence exists to support a CVD benefit of moderate alcohol consumption, insufficient data are available to translate this concept into a clinical recommendation. In the setting of alcohol-related hepatic steatosis, cessation of drinking, along with therapeutic lifestyle modifications, are the mainstays of therapy.

Return to Case

The diagnosis of NAFLD is based on the absence of significant alcohol consumption. For a man, the upper limit of alcohol intake is 2 drinks per day. This means that this patient cannot be categorized simply as NAFLD, although the coexistence of alcoholic liver disease and NAFLD is likely in this patient. He is at high risk for CVD, so should be managed accordingly, including lipid lowering therapy with statins. His alcohol consumption should be reduced to less than 2 drinks per day, which may help reduce his fasting triglyceride concentrations. He should not be falsely reassured by his elevated HDL cholesterol concentration.

Table 2. Key Points- Alcoholic Liver Disease

The consumption of alcohol is a common cause of excess fat accumulation in the liver.

There are multiple mechanisms by which alcohol promotes hepatic steatosis.

Alcohol can increase plasma HDL cholesterol concentrations and fasting triglyceride concentrations.

Although modest alcohol consumption is associated with reduced CVD risk, this cannot be recommended due to other potential adverse effects, including alcoholic liver disease.

VIRAL HEPATITIS-- C

Case Presentation

A 65-year-old woman with a past medical history of CVD and untreated genotype 1 chronic hepatitis C presents for management of CVD. Her lipid levels are notable for an LDL of 99. She has read that since her LDL is below the recommended level for patients with CVD she would not benefit from lipid lowering therapy. What would you advise her?

Introduction

Hepatitis C virus (HCV) is a positive-strand RNA virus of the family *Flaviviridae* that can lead to chronic infection as well as the development of cirrhosis, HCC, and the need for liver transplantation. Chronic HCV (CHC) infection impacts between 130 and 170 million individuals worldwide (84).

Changes in Lipoprotein Metabolism

HCV replication is intricately linked with host cell lipids and impacts host lipid metabolism. Circulating HCV virions complex with host lipoproteins and form lipovirions (85). This lipid composition is a prerequisite for maintenance of viral particle morphology and HCV infectivity (86,87,88,89). For example, lipids on the virion surface shield viral envelope epitopes, protecting them from antibody engagement (90). Lipovirions can enter hepatocytes via multiple receptors including the hepatocyte LDL receptor (which may also facilitate the replication step of the HCV cycle (91)) and utilizes cell surface molecules including Niemann-Pick C1-like 1 (NPC1L1), a receptor for cholesterol resorption, and scavenger receptor class B member 1 (SRB1), which acts to promote cholesterol uptake from lipoproteins, and interacts with HCV envelope glycoprotein E2 to promote HCV entry (92,93,94). LDL receptor and SRB1 appear to have a redundant role in HCV entry (95). Several apolipoproteins influence HCV uptake: apoC1 interacts with HCV glycoproteins to promote infection, and apoE mediates initial attachment between virus and hepatocyte. Hepatocyte VLDL receptor mediates an additional HCV entry mechanism, involving E2 and apoE, with increased VLDL receptor expression conferring greater susceptibility to infection (96). Formation of the HCV core protein involves interaction with host cytosolic lipid droplets and interaction with diacylglycerol O-acetyltransferase 1, a host enzyme involved in triglyceride synthesis. HCV replication also interacts with host cholesterol synthesis within hepatocytes. The host protein FBL2 undergoes geranylgeranylation, an intermediate of the cholesterol synthesis pathway (97). When this pathway is interrupted, the HCV replication complex is extinguished (98). Finally, HCV secretion from hepatocytes involves complexing with apoE-containing host lipoproteins in the form of VLDL or HDL (99).

Clinical Manifestations

Like NAFLD, HCV infection is associated with the development of hepatic steatosis. However, unlike NAFLD, HCV is also associated with hypolipidemia. CHC infection is associated with significantly lower host LDL and total cholesterol levels than in uninfected controls (100). Treatment is associated with increases in both LDL and cholesterol levels in patients with HCV who achieve a cure, defined as a sustained virologic response (SVR). Changes in host serum lipids are also seen in patients with acute HCV. Acute HCV infection is associated with a decrease in total cholesterol, LDL and non-HDL-cholesterol from pre-infection levels. In addition, total cholesterol, LDL, triglycerides and non-HDL-C progressively decline over a 10-year period following HCV seroconversion, after

adjusting for BMI and FIB-4 score (101). In patients who achieved viral clearance, either spontaneous or treatment-induced, total cholesterol, LDL and non-HDL-C increased significantly from infection levels. In an important proportion of patients with both acute and chronic infection, post-viral clearance lipid levels exceed pre-infection levels (102).

While HCV infection is associated with a decrease in LDL and non-HDL-C, important CVD risk factors, HCV infection is associated with an increased overall risk of CVD (103,104). When non-HCV infected individuals with similar lipid levels are compared to those with CHC, HCV infection independently confers an increased risk of acute myocardial infarction (AMI), with a more pronounced increase seen in younger individuals (105). Further, lipid-lowering therapy among individuals with CHC was associated with a greater reduction in AMI risk than uninfected persons with similar lipid levels. Therefore, lipid levels may not accurately reflect CVD risk in patients with CHC.

Management

Lipid treatment goals for individuals with CHC are not well established. We recommend that patients with CHC adhere to the Cholesterol Clinical Practice Guidelines from the American Heart Association and American College of Cardiology released in 2018 (106). Retrospectively-collected data links statin use to improved liver-related outcomes, with higher likelihood of achieving SVR, and lower rates of fibrosis progression, cirrhosis development, HCC incidence, and mortality amongst patients with CHC (107,108,109,110). Simon et al. identified that atorvastatin and fluvastatin have the most significant anti-fibrotic benefit, compared with simvastatin, pravastatin, lovastatin or no statin use (111). It is important to note that for individuals who have achieved an SVR after HCV treatment, lipid levels often increased to or above pre-infection levels. Induction of SVR using DAA therapy led to pro-atherogenic lipid changes (increased total cholesterol, LDL, LDL/HDL ratio, and non-HDL-C), irrespective of DAA regimen or fibrotic stage, with a parallel reduction in insulin resistance. The balance of these effects with respect to CVD risk remains to be determined (112). Hashimoto et al. found greater increases in serum LDL-cholesterol (LDL-C) levels in patients undergoing therapy with ledipasvir/sofosbuvir compared to daclatasvir/asunaprevir. Decline in HCV core protein was also independently associated with rises in LDL-C (113). Thus, practitioners should be mindful to monitor post-treatment lipid levels and treat appropriately.

Return to Case

For our patient with CHC and CVD it would be important for her to take a lipid-lowering medication to reduce her risk of

a second CVD event. Based on the guidelines, she would benefit from high intensity statin therapy, with a goal of decreasing LDL cholesterol by >50%.

Table 3. Key Points- Hepatitis C

The hepatitis C virus interacts with host lipids for hepatocyte entry, viral replication and secretion.
HCV infection decreases host serum LDL and total cholesterol levels.
HCV infection is still associated with an increased risk of AMI and treatment with statins reduces this risk.
Treatment of HCV results in increase in serum lipid levels to at least pre-infection levels.

VIRAL HEPATITIS –HEPATITIS B

Introduction

Approximately 240 million individuals are chronically infected with the hepatitis B virus (HBV) (114). Like HCV, chronic HBV infection can lead to cirrhosis and hepatocellular carcinoma.

Lipoprotein Metabolism in Hepatitis B

HBV interacts with host lipid metabolism in several important ways including during viral cell entry and formation of a vital viral protein, the HBV surface antigen. HBV uses the Na⁺-taurocholate cotransporting polypeptide (NTCP), a peptide that normally allows for hepatocyte uptake of host bile acids, to gain access to hepatocytes (115). HBV binding to NTCP impairs the ability of NTCP to promote hepatocyte uptake of bile acids. This results in an increase in conversion of cholesterol to bile acids.

The formation of the HBV surface antigen within hepatocytes relies in part on host cell cholesterol (116). The surface antigen particle is synthesized in the membrane of the hepatocyte endoplasmic reticulum (ER) and is associated with the host ER lipid bilayer. Association with the lipid bilayer helps make the particle resistant to degradation by cellular proteases. The surface antigen is then transported to the ER lumen and exported from the hepatocyte as a lipoprotein particle. Approximately 25% of the surface antigen complex is composed of host lipids including phosphatidylcholine, triglycerides, cholesterol and cholesterol esters (116).

HBV infection may also alter lipogenic gene expression. Two studies have demonstrated increased in lipogenic gene expression in HBV-infected transgenic mice compared to

uninfected mice. HBV-infected transgenic mice have increased gene expression of SREBP2, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, LDL receptor, fatty acid synthase, and ATP citrate lyase, all of which play a role in either cholesterol metabolism or fatty acid synthesis (117,118). Oehler et al also found that in HBV infected humanized mice, gene expression of human apolipoprotein A1, a lipoprotein found in HDL which plays a role in reverse cholesterol transport and PPAR-gamma which regulates adipocyte differentiation and fatty acid storage, was significantly enhanced.

HBV-infected transgenic mice also demonstrate elevated levels of 7 α -hydroxylase (hCYP7A1), which promotes bile acid formation from cholesterol. In liver biopsy samples from patients with chronic HBV infection, hCYP7A1 was significantly induced when compared to uninfected controls. These findings suggest that HBV replication may impact cholesterol metabolism.

Clinical Manifestations

Data on the impact of HBV infection on circulating lipid levels in humans is limited. HBV infection may be associated with lower triglyceride levels than in uninfected patients (119), however its influence on HDL remains ambiguous. Hsu et al performed a case control study comparing 322 individuals with chronic HBV infection to 870 age-matched, uninfected controls. Individuals with HBV infection were found to have significantly lower triglyceride and HDL levels when compared to controls. In a second retrospective cohort of 122 individuals with chronic HBV, HBV DNA levels was inversely proportional to serum triglyceride levels but no relationship was seen with HDL levels (119). Amongst a cohort of non-diabetic patients, HBsAg-seropositivity was inversely correlated with hypertriglyceridemia and low serum HDL cholesterol. Hence, chronic HBV infection may favorably impact lipid profiles, which could partly account for the inverse

relationship between HBsAg-seropositivity and metabolic syndrome seen in this cohort (120). Similarly, Joo et al. demonstrated that in patients who were initially free of dyslipidemia, HBsAg-positivity was associated with lower risk of developing dyslipidemia during an average follow up of 4.46 years (121).

Circulating lipid levels may be predictive of clinical outcomes in HBV-infected patients. Chen et al. found that average plasma apolipoprotein A-V level was decreased amongst 209 non-survivors of HBV-acute on chronic liver failure versus 121 survivors (122).

Like HCV, chronic HBV infection is frequently associated with hepatic steatosis. Between 25% and 51% of patients with HBV are found to have steatosis on imaging or biopsy (123). However, while concurrent steatosis is common in HBV infections, steatohepatitis is not frequently described. Further, the pathogenesis of steatosis in HBV is not well understood and may be related to co-existing metabolic factors such as body mass index (BMI) and insulin resistance rather than the viral infection itself (124).

Management

As data on the impact of HBV infection on circulating lipids is limited there are no formal guidelines for dyslipidemia management in this population. Clinicians should be mindful of a possible decrease in HDL in this population and follow standard guidelines from the American Heart Association and American College of Cardiology on lipid management. Recent studies have shown reduced risk of cirrhosis development (125), decompensation (125, 126, 127, 128), mortality (126, 127) and portal hypertension (126) amongst statin users compared to non-users with chronic HBV- and HCV-related hepatitis. Furthermore, statin use was associated with a 32% reduced HCC risk. Concomitant use of statin and nucleos(t)ide analogue led to an additive chemopreventive effect (129). Large-scale RCTs to comprehensively evaluate statins as a means of protection against disease progression in patients with viral hepatitis are warranted.

Table 4. Key Points- Hepatitis B

HBV infection may interact with host lipids and enhance lipogenic gene expression
The clinical manifestations of HBV on host lipids are not well studied but HBV infection may decrease serum triglyceride and HDL levels.
Management of patients with HBV and dyslipidemia should be guided by standard recommendations for the treatment of dyslipidemia.

CHOLESTATIC DISEASES

Case Presentation

A 58-year-old woman is referred with primary biliary cirrhosis (PBC) for the management of an elevated plasma total cholesterol of 450. She reports symptoms only consistent with mild and intermittent pruritis. She is currently taking ursodeoxycholic acid. Her physical is notable for xanthelasma under the eyes.

Introduction

Bile is the route for cholesterol elimination from the body. Plasma cholesterol is taken up by the liver in the form of apolipoprotein B-containing lipoproteins (i.e. remnant lipoproteins and LDL) by receptor-mediated endocytosis or by selective uptake of HDL cholesterol (130). Cholesterol is eliminated by conversion to bile salts and by biliary

secretion. Biliary obstruction, notable when due to cholestatic diseases, can interfere with cholesterol elimination leading to hypercholesterolemia. This occurs most commonly in the setting of primary biliary cirrhosis (PBC), which is an autoimmune-mediated destruction of intrahepatic bile ducts. It can also occur in primary sclerosing cholangitis (PSC), in which there is inflammatory stricturing of larger bile ducts by poorly understood mechanisms.

Lipoprotein Metabolism in Cholestasis

Hypercholesterolemia associated with cholestasis is largely attributable to the formation of lipoprotein X, an atypical lipoprotein particle. Lipoprotein X comprises principally unesterified cholesterol and phospholipids (131), resembling the cholesterol-phospholipid vesicles that are secreted by the liver into bile (132). The principal proteins associated with lipoprotein-X are apoC and albumin contained within the core (133,134). The lipids of the

particle comprise a sphere, with an aqueous core. Lipoprotein-X is devoid of apoB. It appears to be formed due to the secretion of biliary-type particles into plasma in the setting of obstruction to bile flow (135), although defects in plasma cholesterol esterification may also contribute (131). Lipoprotein X has similar characteristics as LDL including density, so that its presence in plasma requires electrophoretic separation (136).

Plasma total cholesterol concentrations are increased in PBC in proportion to disease severity, with elevations that can be striking and exceed 1,000 mg/dl, and can be a rare cause of pseudohyponatremia (133). Where these elevations are primarily attributable to lipoprotein-X, apolipoprotein B concentrations may also be elevated due abnormal lipoprotein metabolism associated with liver disease (131,133). Serum metabolomics analysis of patients with PBC revealed elevated levels of VLDL and LDL compared to controls (137). HDL cholesterol concentrations are elevated in the early stages of PBC and tend to decline as the disease progresses (138), apparently because of increased circulating hepatic lipase activity that promotes HDL catabolism (131). Patients with more advanced PBC exhibit increased plasma triglycerides (131), presumably attributable to decreased hepatic lipase activity (138).

Plasma lipids in PSC have been less well characterized than in PBC. In a small series (139), the hypercholesterolemia was more modest than generally observed in PBC, but did increase in concert with disease severity. HDL cholesterol levels tended to be high, and triglyceride elevations were uncommon.

Clinical Manifestations

An important consideration has been whether the lipid abnormalities associated with cholestatic diseases confer increased CVD risk. This has been studied more extensively in PSC in the form of prospective trials (138,140). Although each had limitations, collectively there

was no suggestion of increased atherosclerotic events, which is in keeping with the relative absence of elevations in atherogenic particles. There is also evidence *in vitro* to suggest that lipoprotein-X may be atheroprotective by reducing oxidation of LDL (136). In patients with PBC, the presence of xanthelasma does not appear to connote an increased CVD burden (138).

As with PBC, the cholesterol elevations associated with PSC do not tend to confer CVD risk. None was observed in the small series cited previously, but it was acknowledged that patients were young enough that excess CVD complications would not have been expected (139). Lipid levels ultimately fell in patients who had progressed to cirrhosis and hepatic failure.

Management

Due to the overall lack of clinical evidence, the management of hypercholesterolemia associated with cholestasis lacks formal recommendations. In PBC, ursodeoxycholic acid (UDCA) slows the progression of disease and prolongs survival (141). Chronic UDCA administration also reduces plasma LDL concentrations. In PBC patients, statin therapy is generally safe and is effective at lowering LDL cholesterol in PBC patients (58,142-144). At present, UDCA is generally not recommended in the management of PSC (145), and data are lacking regarding lipid-lowering therapies in these patients. Of note, some patients with obstructive jaundice are treated with bile acid binders to reduce pruritus and not primarily to reduce plasma cholesterol concentrations.

Return to Case

For our patient with PBC, the presence of lipoprotein-X may be confirmed by lipoprotein electrophoresis. The possible contribution of atherogenic particles may be estimated by the measurement of the plasma apoB concentration. The institution of statin therapy should be based on standard estimates of CVD risk.

Table 5. Key Points- Cholestatic Disease

Plasma total cholesterol concentrations are commonly elevated in the setting of cholestasis.
Lipoprotein-X is an abnormal lipoprotein that circulates in patients with cholestasis and is primarily responsible for the elevations in plasma total cholesterol concentrations.
Elevations in plasma cholesterol concentrations due to cholestasis do not appear to confer excess CVD risk.
Patients with cholestatic disorders may be candidates for lipid lowering therapy if they are otherwise at risk for CVD.

CIRRHOSIS

Introduction

Cirrhosis is the common advanced histologic endpoint for chronic liver diseases in which the formation of fibrotic nodules in the liver often obscured the etiology of the responsible disease process. The clinical correlates range widely from well-compensated liver function with no apparent clinical manifestations to advanced decompensated liver disease with portal hypertension, with complications that include hepatic encephalopathy, esophageal varices, and ascites. Moreover, the development of cirrhosis confers increased risk of HCC.

Changes in Lipoprotein Metabolism and Clinical Manifestations

The changes in lipoprotein metabolism associated with cirrhosis generally reflect the degree of impairment of hepatic function. In one study (146), plasma concentrations of total cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol varied with increases in prothrombin time and decreases in albumin, which reflect hepatic synthetic function. These findings are in general agreement with other studies (147). Lipoprotein compositions are also altered in the setting of cirrhosis, with LDL particles enriched with triglycerides and deficient in cholesteryl esters, and HDL particles enriched with triglycerides, free cholesterol and phospholipids (147). These changes are secondary to

characteristic abnormalities in plasma enzymes that remodel lipoproteins, including lecithin-cholesterol acyl transferase (LCAT), hepatic lipase, and phospholipid transfer protein (PLTP) (147). HDL-C and enzymes involved in HDL maturation and metabolism are decreased in patients with cirrhosis. There is a shift in the composition of HDL in those with cirrhosis towards the larger HDL2 subclass, with a reduction in small HDL3 particles. The latter is associated with diminished cholesterol efflux capacity which in turn independently predicts 1-year mortality (148).

Hepatocellular carcinoma can occur in the setting of cirrhosis and may be associated with alterations in plasma lipids (149-151). In instances of hypercholesterolemia, the increase may be driven by elevated rates of cholesterol synthesis and cellular levels of 3-hydroxy-3-methylglutarylcoenzyme A. It is unclear whether this hypercholesterolemia confers increased CVD risk (152,153).

CVD risk is dependent upon the etiology of cirrhosis, at least in part due to the association of type 2 diabetes. Cirrhosis due to NASH, HCV, and alcoholic liver disease increases the risk of type 2 diabetes, which is not observed in cholestatic liver diseases and presumably contributes to CVD risk (147,154). Statin therapy may be safely administered in patients with compensated cirrhosis and increased CVD risk (58). In patients with non-cholestatic cirrhosis, low HDL cholesterol serves as a liver function test that is an indicator of poor prognosis, increasing the risk of cirrhotic death (155).

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