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Review

Cardiovascular risk, lipidemic phenotype and steatosis. A comparative analysis of cirrhotic and non-cirrhotic liver disease due to varying etiology

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ABSTRACT

Background: Liver regulates lipid metabolism in health and disease states. Nevertheless, the entity of cardiovascular risk (CVR) resulting from dysregulation of lipid metabolism secondary to liver disease is poorly characterized.
Aim and methods: To review, based on a PubMed literature search, the features and the determinants of serum lipid phenotype and its correlation with hepatic steatosis, insulin resistance (IR) and CVR across the wide spectrum of the most common chronic liver diseases due to different etiologies.
Results: Alcoholic liver disease (ALD) is associated with steatosis, IR and a typical lipid profile. The relationship between alcohol intake, incident type 2 diabetes (T2D) and CVR describes a J-shaped curve. Non-alcoholic fatty liver disease (NAFLD), and probably nonalcoholic steatohepatitis (NASH) in particular, is associated with IR, atherogenic dyslipidemia and increased CVR independent of traditional risk factors. Moreover, NASH-cirrhosis and T2D contribute to increasing CVR in liver transplant recipients. HBV infection is generally free from IR, steatosis and CVR. HCV-associated dysmetabolic syndrome, featuring steatosis, hypocholesterolemia and IR, appears to be associated with substantially increased CVR. Hyperlipidemia is an almost universal finding in primary biliary cirrhosis, a condition typically spared from steatosis and associated with neither subclinical atherosclerosis nor excess CVR. Finally, little is known on CVR in patients with hepatocellular carcinoma.
Conclusions: CVR is increased in ALD, NAFLD and chronic HCV infection, all conditions featuring IR and steatosis. Therefore, irrespective of serum lipid phenotype, hepatic steatosis and IR may be major shared determinants in amplifying CVR in common liver disease due to varying etiology.

Contents

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Abbreviations

AFL	alcoholic fatty liver
ALD	alcoholic liver disease
Apo-AI	apoprotein-AI
Apo-AII	apoprotein-AII
Apo-B	apoprotein-B
Apo-C	apoprotein-C
Apo-E	apoprotein-E
ASH	alcoholic steatohepatitis
CETP	cholesterol ester transfer protein
CH	cholesterol
ChREBP	carbohydrate response element binding protein
CVR	cardiovascular risk
CYP2E1	cytochrome P450 2E1
DGATs	diacylglycerol acyltransferases
DNL	*de novo* lipogenesis
E-CH	esterified cholesterol
FA	fatty acids
FXR	farnesoid X receptor
F-CH	free cholesterol
FCHL	familial combined hyperlipidemia
FHBL	familial hypobetalipoproteinemia
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
HMG-CoA	hydroxy methyl glutaryl-Coenzime A
HTGL	hepatic triglyceride lipase
IL-1	interleukin-1
IL-2	interleukin-2
IL-6	interleukin-6
IDL	intermediate-density lipoprotein
IR	insulin resistance
JNK	c-Jun N-terminal kinase
LCAT	lecithin cholesterol acyl transferase
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
LPL	lipoprotein lipase
Lp-X	lipoprotein-X
LXR	liver-X receptor
mRNAs	RNA, Messenger
MS	metabolic syndrome
CVD	cardiovascular disease
MTP	microsomal triglyceride transfer protein
NAFLD	nonalcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
PBC	primary biliary cirrhosis
PL	phospholipids
PUFA	polyunsaturated fatty acids
PPAR	peroxisome proliferator-activated receptors
SREBP-1c	sterol regulatory element binding protein-1c
TG	triglyceride
TNF-alpha	tumor necrosis factor-alpha
T2D	type 2 diabetes
VLDL	very-low-density lipoprotein

1. Background and aims

Liver, a major regulator of lipid metabolism through the synthesis of apoprotein and lipoprotein and *de novo* lipogenesis [1], is also a chief modifier of cardiovascular risk (CVR). This occurs through the synthesis of atherogenic apoprotein-B (Apo-B), and the remodeling of HDL and apoB containing lipoproteins by action of Cholesterol Ester Transfer Protein (CETP) and liver-X receptor (LXR) [2,3]. The activation of CETP gene expression by LXR is deemed to be pro-atherogenic [3], and certain polymorphisms of the CETP gene seem to be more common in subjects with coronary artery disease than in healthy subjects [4,5]. Moreover, CETP-mediated triglyceride (TG) enrichment of HDL is followed by the degradation of HDL by hepatic triglyceride lipase (HTGL), dissociation by apoprotein-AI (Apo-AI) and subsequent renal catabolism [6]. Finally, the pharmacological inhibition of cholesterol (CH) synthesis in the liver, through blockade of hydroxy methyl glutaryl-Coenzime A (HMG-CoA) reductase promotes the over-expression of LDL-receptors on the hepatocyte cell membrane and the reduction of CVR will ensue as a result of lowered LDL-CH plasma levels [7,8].

CVR linked with individual primary hyperlipidemias phenotypes is well defined [9]. In contrast, the presence and severity of CVR resulting from deranged lipid serum profile and metabolism secondary to liver disease is far from being fully defined and interpreted. This is of interest given that the prolonged life expectancy resulting from better cures in many liver diseases may eventually unveil the true impact of lipo-metabolic derangements in the natural history of liver disease. In particular, recent data from the non-alcoholic fatty liver disease (NAFLD) and the hepatitis C virus (HCV) areas have challenged the old paradigm that "*chronic liver disease protects from atherosclerosis*" [10,11].

The idea behind the present review is that the altered serum lipoprotein phenotype of liver disease of infective, metabolic and cholestatic origin might affect CVR. However, no systematic studies are available comparing lipoprotein profile and CVR in different liver disorders. This review aims to analyze the relation between serum lipid phenotype, liver steatosis and CVR across the spectrum of cirrhotic and non-cirrhotic liver diseases due to different etiologies: alcoholic and nonalcoholic, viral and autoimmune.

To this aim, a literature search was conducted in September 2013 on PubMed. The following search terms were used: alcoholic liver disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, hepatitis B, hepatitis C, primary biliary cirrhosis, cirrhosis, hepatocellular carcinoma, hyperlipidemia, lipoproteins, insulin resistance, steatosis.

2. Alcoholic liver disease

Excess alcohol intake is a common cause of non-familial hyperlipidemia [12,13]. Alcoholic hyperlipidemia, which follows binge drinking and is often associated with alcoholic fatty liver (AFL) and steatohepatitis (ASH), rarely occurs in established