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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

Table 1
Alcoholic dyslipidemia (Refs. [12–28]).

Lipid profile derangement		Liver disease		
		Acute AFL/ASH	Chronic AFL/mild ASH	Severe ASH/cirrhosis
Quantitative	TG	↑ (VLDL ± Chylomicrons)	↑ ≈ post-prandial hyperlipidemia	↓ ≈ (↑ rarely in cirrhosis)
	Chilom.	↑ ≈	≈ ↑	≈
	Tot-CH	↑ (F-CH)	≈ ↑	↓ (E-CH)
	VLDL	↑	≈ ↑	↓
	LDL	≈	≈ ↓	↓ ≈
	HDL	↓ (ASH)	↑	↓
	PL	↑	≈ ↑	↓
	PUFA	↑	↑	↓ (cirrhosis)
	Apo-AI	↓ (ASH)	↑ ≈	↓
	Apo-B	_	_	↓
	Apo-C	_	_	↓
	Lp(a)	↓	↓	↓
Qualitative	VLDL	↓ E-CH, Apo-E, Apo-C[a]	_	_
	LDL	↑ TG and ↓ E-CH[a]	_	↑ TG and ↓ E-CH
	HDL	↑ Apo-E and PL[a]	_	↑ TG and PL
		↓ Apo-AI and E-CH[a]		↓ E-CH
Recovery after withdrawal		Yes	Yes	No

[a] Reported in ASH.

cirrhosis and is characterized by elevated plasma TG resulting from VLDL accumulation or, rarely, by superimposed (fasting) hyperchylomicronemia [14–16]. Such a VLDL increase depends on the amount of ingested alcohol and patient features (genetics, body weight and metabolic comorbidity) [16–18]. LDL levels are usually unaltered [19,20]. HDL concentrations are reduced in acute ASH [21,22]. In addition to hypertriglyceridemia, increased concentrations of serum total CH and phospholipids (PL) have also been described [15,16]. (Table 1) [12,23–28]. Both AFL and alcoholic hyperlipidemia result from decreased mitochondrial FA oxidation and increased synthesis of TGs, which are partly secreted into the bloodstream and partly stored in the liver [15,16]. Alcoholic dyslipidemia is promptly reversible following alcohol withdrawal. TG clearance rapidly occurs, whereas the clearance of CH and PL takes longer. Serum CH reduction is accompanied by increased esterified fraction, reflecting improved liver function and plasma lecithin cholesterol acyl transferase (LCAT) activity [15,16,23].

During chronic alcohol abuse, fasting and postprandial hyperlipidemias tend to disappear because of enhanced lipoprotein lipase (LPL) activity and impaired capacity of the fibrotic liver to synthesize and export lipids into the bloodstream [15,16,20,24]. Therefore, decreased VLDL, may herald progressive fibrosis in the ALD course. Minor hypertriglyceridemia, however, may persist in advanced ALD, probably as a result of decreased hepatic TG clearance [15,25]. Plasma Lipoprotein(a) [Lp(a)] levels are reduced both in moderate and heavy alcohol drinkers, and Lp(a) levels are increased after ethanol withdrawal [20,26]. One study reported that alcoholics without cirrhosis had increased polyunsaturated fatty acids (PUFA) in serum PL, while in cirrhosis PUFA levels (mainly arachidonic acid) were decreased [27] as confirmed by a very recent study [28]. (Table 1) [12,23–28].

In the hepatocyte, mainly by action of alcohol dehydrogenase, ethanol is oxidized to acetaldehyde, a reactive metabolite that can produce liver injury, including enhanced fibrogenesis, via impaired mitochondrial β-oxidation of FA, glutathione depletion, lipid peroxydation, formation of oxygen-free radicals and acetaldehyde adducts in rat and mice models [29].

ALD and the effects of ethanol on cardiovascular system result from the balance of three different biological effects: *de novo* lipogenesis (DNL), anti-clotting effect and generation of lipid peroxidation products.

Acetaldehyde is metabolized into acetic acid and finally acetyl-CoA, which can be converted to FA through DNL [30,31]. In healthy humans, although modest in absolute values, fractional DNL increases from 1% at baseline to 31% after a low-dose bolus of 24 g of ethanol.30 Moreover acetaldehyde, via stimulated SREBP-1c, activates the enzymes of DNL after acute and chronic ethanol feeding in rats and micropigs [32–34]. Both ethanol products and DNL impair mitochondrial FA oxidation 31 so further perpetuating DNL vicious circle. In mice, acute ethanol administration induces dose-dependent development of hepatic steatosis via induction of CYP2E1, oxidative stress, activation of JNK, lowered autophagy and increased lipogenic SREBP-1c and ChREBP, which promote DNL through up-regulation of PPARγ and DGATs mRNAs [33,35]. In these rodents, chronic alcohol exposure selectively stimulates lipolysis in white adipose tissue, most likely through IR, leading to an excess release of FA which, once transported to the liver, are stored as TGs [36].

Anti-clotting effect of ethanol result from deranged coagulation, increased fibrinolysis and decreased platelet count. Chronic, high dose alcohol consumption is associated with deranged coagulation parameters in humans. The mean value of prothrombin time and activated partial thromboplastin time are significantly higher in the chronic alcohol drinkers compared to nondrinkers and, in alcohol consumers, prothrombin time values are positively correlated with hepatobiliary enzymes [37]. Moreover, studies conducted on human liver tissue and acute alcohol mouse model have shown that alcohol itself directly (rather than as a result of ALD) alters hepatic expression of pro- and anti-fibrinolytic genes in hepatocytes and stellate cells in a dose-dependent manner, low dose promoting and, conversely, high dose inhibiting fibrinolysis [38]. Finally, excess alcohol drinking is associated with reversible, low-grade thrombocytopenia, (75,000–100,000/mm^3, often associated with macrocytosis) due to direct bone marrow toxicity [39].

Elevated alcohol blood concentrations increase systemic oxidant stress both in acute and in chronic conditions in humans. Correlating with rising ethanolemia, oxidant stress increases in a time and dosage-dependent manner in volunteers [40]. Moreover, oxidative stress is markedly increased in acute alcoholic hepatitis and in patients with cirrhosis, particularly of alcoholic etiology [40]. Therefore oxidant stress contributes to the development of ALD [40] as well as excess CVR in the alcoholic [41]. Vitamin C rather than aspirin reduces oxidative stress in chronic liver disease patients [40] but has no effect on cardiovascular events [42].

Alcoholic hyperlipidemia, together with its pro-inflammatory, thrombogenic and procoagulative effects, is a definite CVR factor

in drinkers [43,44]. The association between metabolic syndrome (MS), CVR, and alcohol consumption, however, is *U*- or *J*-shaped [45–47] indicating that moderate drinkers (30 g/day) may benefit from increased HDL-CH [15,17,27] and decreased platelet count [48,49]. A similar relation has been described for alcohol intake and incident T2D [50] or frank T2D due to chronic pancreatitis [51].

3. NAFLD

NAFLD displays a powerful atherogenic lipoprotein profile; serum TG, LDL-CH, and Apo-B are increased, while HDL-CH and LDL buoyancy are decreased [52–54].

A recent large multi-ethnic study demonstrated that NAFLD, diagnosed through the Liver/Spleen ratio, although unassociated with total CH or LDL-CH, was indeed associated with higher fasting serum TG, lower serum HDL-CH, LDL particle concentration, and negatively associated with LDL particle size. Such lipoprotein abnormalities persisted after correction for an impressive number of confounders indicating that they occur independent of IR [55].

Dyslipidemia in NAFLD is mainly related to the hepatic overproduction of VLDL particles and a dysregulated clearance of lipoproteins from the bloodstream [56]. Hyperinsulinemia, commonly present in NAFLD patients, drives excess hepatic *de novo* lipogenesis promoting increased expression of SREBP-1c in the liver [57]. Increased hepatic lipogenesis resulting in hypertriglyceridemia accounts for low HDL levels typically observed in NAFLD and associated with increased CVR and high hepatic fat content [58,59]. Whenever the impaired VLDL secretion is dissociated from IR, only histologically non-progressive pure steatosis occurs, as in familial hypobetalipoproteinemia (FHBL), a condition caused by mutations of the Apo-B gene [60]. Interestingly, FHBL patients, despite moderate to severe steatosis, are protected from CVR, probably as a result of the conserved hepatic and peripheral insulin sensitivity and the reduced exposure to Apo-B-containing lipoproteins [61–63].

The accumulation of diacylglycerol in typical NAFLD causes hepatic IR mediated by protein kinase C epsilon [64]. Accordingly, NAFLD becomes an amplifier of metabolic derangements, an early precursor in the chain of events eventually leading to full-blown MS [65,66] and a relatively novel independent CVR factor [10,53,67].

Small dense LDL, the most atherogenic subclass of LDL, is elevated in MS and NAFLD as a result of elevated VLDL and serum total CH [68].

Dyslipidemia of IR has close pathophysiologic and genetic links with the familial combined hyperlipidemia (FCHL) phenotype, a common genetic lipid disorder characterized by many features of MS independent of obesity [69]. Several genes have been described in FCHL which can affect lipid and glucose metabolic pathways and a common genetic background between FCHL and T2D has been reported [70]. Increased adipose tissue free FA overflooding the liver may contribute to IR and hyperlipidemia in FCHL, promoting liver disease progression [71].

A growing body of literature also suggests that patients with nonalcoholic steatohepatitis (NASH) are at higher CVR [72] compared to subjects with pure steatosis, because of the more atherogenic lipid profile [73,74]. Following an oral fat load NASH patients display a progressive increase in postprandial TG, VLDL, free FA and oxidized LDL, a deep fall in HDL and Apo-AI and a slow decrease in adiponectin levels. The physiological compensatory increase in adiponectin secretion, evoked by postprandial lipemia and aimed at restoring baseline plasma lipids by free FA oxidation and VLDL catabolism, is progressively blunted in NASH and may contribute to liver injury and cardiometabolic risk [74].

Lifestyle changes including diet and physical exercise reduce glucose and lipid abnormalities, IR and liver fat content, thus contributing to a substantial reduction in CVR [75–78]. The atherogenic lipid profile displayed by NAFLD benefits from the very same counseling offered to any high CVR patient [79]. Lipid-lowering agents have been proposed in patients with NAFLD associated dyslipidemia: the beneficial clinical effect will closely mirror the reversal of changes observed in lipoprotein profile [80]. Statins may improve several aspects of NAFLD pathogenesis and complications [8,81,82]. Insulin sensitizers have generated a certain degree of disappointment [83,84]. Novel drugs such as antisense nucleotides are under investigation [85].

4. Chronic hepatitis B

The interaction of hepatitis B virus (HBV) vital cycle with the host lipid metabolism is not characterized as fully as is the case for HCV infection.

Acute hepatitis B is associated with transient hypertriglyceridemia [86,87]. The biological basis underlying this reversible dyslipidemia, however, remains poorly characterized and given its transient course, it is probably of scarce concern for CVR.

Chronic HBV infection is associated with reduced TG, total CH and HDL-CH and with significantly increased serum adiponectin levels [88–90], but is not associated with IR, MS and hepatic steatosis [91–93], in keeping with low CVR [94]. Wang et al., followed-up for 17 years 3931 HBsAg seropositives and 18,541 HBsAg seronegatives. At multivariate analysis, mortality from ischemic heart disease, cerebrovascular disease, atherosclerotic disease and all CVD were not statistically different between groups [94]. This finding is in sharp contrast with data in chronic HCV infection which, conversely, was associated with a significant excess of cardiovascular disease [95]. The difference may be explained by the different prevalence of steatosis: steatosis is associated with HCV infection 2.5–fold more frequently than expected by chance [96], whereas HBV infection protects from the development of hepatic steatosis [91,97]. Moreover, as opposed to chronic hepatitis C where hepatic steatosis and IR are positively correlated with HCV replication and negatively modulate the response to antiviral therapy [98], NAFLD might promote spontaneous HBsAg seroconversion [99,100], is negatively associated with HBV-viral load in human studies [97,101], and inhibits HBV related-antigens expression and HBV-DNA replication in a transgenic rodent model [102].

For all these reasons, it is tempting to speculate that steatosis represents both a marker and a cause of excess CVR in those with chronic viral hepatitis, with HCV being associated with both steatosis and atherosclerosis and HBV being spared by both.

5. Chronic hepatitis C

Chronic HCV infection is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) worldwide [103,104].

An altered metabolic profile is a peculiar extra-hepatic feature in HCV infection, acknowledged to be a “systemic disease” [105]. It includes IR, steatosis, hypocholesterolemia and visceral fat hypertrophy. This unique cluster of dysmetabolic conditions named *HCV-associated dysmetabolic syndrome* differs from the “typical” MS on the grounds of reduced plasma lipids levels [11,106,107]. The underlying mechanism of acquired, reversible, hypobetalipoproteinemia has been partly elucidated: the virus, particularly HCV genotype 3, is able to exploit the host lipoprotein metabolism, selectively perturbing the distal pathway of CH synthesis in order to advantage its vital cycle [108–110]. This metabolic

peculiarity has major clinical implications; acquired, reversible hypolipidemia, is positively correlated with the severity of hepatic steato-fibrosis and negatively with the response to antivirals [108,111,112] and that statin therapy is associated with increased sustained virological response rates following standard HCV antiviral regimens [107,113].

HCV infection is also associated with excess T2D risk [114], which confers an additive risk of developing cirrhosis and HCC [115] and may contribute to increased CVR. A recent meta-analysis examining 34 studies and more than 300,000 patients has shown that HCV patients have about 1.7-fold increased risk of T2D compared to non-infected controls both in retrospective and prospective studies. The mechanisms underlying such HCV-associated glucose metabolism derangements are complex and encompass the direct role of the virus in determining IR and probably beta-cell dysregulation, the host response to the virus and the consequence of HCV-induced liver damage. The 1.8-fold excess T2D risk in HCV infected patients with respect to HBV-infected controls, however, supports metabolic risk to occur independent of liver histological changes in a HCV-specific manner [116]. The protection from impaired fasting glucose and T2D which follows HCV eradication is further evidence for this view [117,118].

The risk of coronary and carotid atherosclerosis in those with HCV infection has been extensively investigated. For instance, HCV infection is an independent predictor of angiographically-detected coronary artery stenosis [119,120] and increased carotid intima-media thickness [121,122]. More recently, studies have focused on the relation between HCV infection, liver histology and carotid atherosclerosis. Petta et al. have reported that severe hepatic fibrosis was associated with increased risk of early carotid atherosclerosis in 174 patients with chronic HCV infection due to genotype 1 [123]. A subsequent study by Adinolfi comparing 326 treatment-naive chronic hepatitis C (175 with and 151 without steatosis) with 292 healthy subjects without steatosis and 185 age- and gender-matched NAFLD controls, found that both viral load and steatosis contribute to carotid atherosclerosis in chronic HCV infection [124]. Taken collectively, these two studies demonstrate that HCV infection exerts such profound metabolic implications as to radically reverse the old paradigm that "*liver disease protects from atherosclerosis*" [11].

The mechanisms of atherogenesis are however incompletely defined. Increased levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), hyperomocysteinemia, decreased adiponectin, steato-fibrosis might all contribute to premature vascular aging in HCV-infected patients [123–127]. More data are needed to confirm a reduced CVR following sustained virological response after antiviral regimens.

6. Cirrhosis

Cirrhosis represents the stereotyped end-stage histologic lesion resulting from unopposed chronic action of a variety of liver injuring agents. ALD, HCV infection and NASH are the most common causes of cirrhosis in Europe and North America, whereas HBV infection is the prevailing cause in most parts of Asia and sub-Saharan Africa [128].

Liver cirrhosis is characterized by an abnormal plasma lipid and lipoprotein profile due to impaired liver biosynthetic capacity. In non-cholestatic hepatocellular diseases, the decrease in plasma apolipoprotein and lipid levels is positively correlated with the severity of liver failure [129]. Quanti-qualitative lipid and lipoprotein derangements commonly include: a) low serum levels of lipids and lipoproteins: CH, TG, VLDL, HDL, Apo-AI, Apo-B, apoprotein-C (Apo-C), Lp(a) and b) altered composition of lipoproteins: LDL enriched in TG and deficient in esterified CH; HDL enriched in TG, PL and free CH [129–133]. LDL levels have been variably reported as unchanged [129,134] or lowered [135–137]. Few studies compared serum lipid and lipoprotein levels in cirrhosis to non-cirrhotic chronic hepatitis [131,135,138]. Cicognani et al. found a significant decrease in LDL, HDL, and total CH serum levels compared with both chronic active hepatitis and control patients, while VLDL-CH was only lower compared to controls [135]. LDL, HDL, and total serum CH were progressively lower from Child class A to class C, suggesting an association between hypocholesterolemia and poor prognosis, as confirmed by many other studies [135,138–141]. A recent study confirmed that both HBV and HCV cirrhosis subgroups had total CH, CH esters, LDL- and HDL-CH lower than controls without liver disease, whereas TG and VLDL-CH were similar; there was no significant difference between the two cirrhosis subgroups [142]. Another study found that subjects with alcoholic cirrhosis had significantly higher total and LDL-CH concentrations than nonalcoholic cirrhosis and that cirrhotic patients with comorbidities (T2D and hypertension) had higher serum lipid concentrations than those without it [137].

Specific enzymes deficiency account for those specific plasma lipid and lipoprotein changes usually observed in cirrhosis.

LCAT activity is directly related to plasma albumin values [143]. Therefore it may often be depressed in advanced cirrhosis with paralleling increased values of free CH and lecithin and corresponding decreases in CH ester and lysolecithin [129,143]. As a further consequence of reduced activities of LCAT and hepatic lipase [129,134], remodeling of VLDL to LDL is impaired, esterified/free CH ratio is reduced, HDL and LDL are poor in CH ester and proportionally enriched in TG and PL [15,129,143,144]. *In vitro* studies in cirrhotic patients have shown low HTGL activity, which account for impaired hepatic removal of TG and PL from lipoproteins [15].

Table 2
Serum lipid profile, insulin resistance, steatosis and cardiovascular risk in chronic liver diseases.

	ALD (Refs. [12–36,40,41,45–48])	NAFLD (Refs. [10,52–54,65–68,72–74])	Chronic HBV (Refs. [88–94,97])	Chronic HCV (Refs. [11,105–107,111,116,119–124])	PBC (Refs. [160,164–179,182–184])	Cirrhosis – HCC (Refs. [115,129–138,149,150,158–163,190,191,198–201])
Tot-CH	≈ ↑	≈ ↑	↓	↓↓	↑↑	↓
LDL	≈ ↓	↑	↓	↓	↑↑	≈ ↓
HDL	↑	↓↓	↓	↓	↑↑	↓
TG	↑ ≈	↑	↓	≈ ↓	↑↑	↓
IR/T2DM	↑[a]	↑	↓	↑	↓	↑
Steatosis	↑	↑	↓[c]	↑[b,c]	↓	↑[d]
CVR	↑[a]	↑	↓	↑	↓	?, ↑[d]

[a] Predominantly for heavy alcohol consumption.
[b] Predominantly in genotype 3 HCV infection.
[c] Liver steatosis has deleterious effects on viral outcomes in HCV infection, whereas has positive effects in HBV infection.
[d] Associated with NASH- and ALD-cirrhosis.

In contrast, there is no evidence for deficiency of other enzyme activity in cirrhosis. For example, plasma activity of Cholesterol Ester Transfer Protein (CETP), a key enzyme in reverse cholesterol transport, in patients with liver cirrhosis is normal [134]. Similarly is Lipoprotein lipase (LPL) activity [134], mirroring the extrahepatic origin of this enzyme. Normal LPL, together with the adequate apoC-II and apo C-III in VLDL from these patients, may guarantee the rapid catabolism of plasma VLDL-TG. High atherosclerosis risk has been associated with high plasma levels of phospholipid transfer protein (PLTP), which plays an important role in HDL remodeling [145] whereas PLTP deficiency protects lipoproteins from oxidation [146,147]. Reduction of PLTP protein mass and mRNA has been reported in mice with ALD [148].

The severity of CVR in cirrhosis is controversial; it probably has evolved over time as a result of a shift in the etiology of cirrhosis. Recent studies describing a high prevalence of major risk factors for atherosclerosis and coronary artery disease in NASH- and ALD-cirrhosis [149,150] challenge previous investigations suggesting a protective effect of (at that time mostly viral) cirrhosis on CVD [151–154], possibly due to reduced CH, fibrinogen and platelet count [155].

Low LCAT levels have been described in cirrhosis implying low HDL and altered lipoprotein composition [15,129,143,144]. In patients with primary LCAT deficiency, in spite of low HDL-CH levels, CVD is uncommon [156]. In LCAT-deficient patients compared to healthy controls, LDL contains more TG and less cholesteryl ester; however LDL size is normal. LDL-associated radioactivity is cleared from plasma more rapidly than in healthy subjects, suggesting LDL catabolism to be increased and LDL receptor pathway up-regulated [156]. These changes will eventually result in a decreased uptake of LDL by vessel wall [129,156].

Conversely, patients with cirrhosis show reduced Apo-AI and paraoxonase-1 activity which may adversely affect the protective role of HDL against oxidative stress and inflammation [157].

Not negligibly, cirrhosis is a diabetogenic condition, given that up to 30% of cirrhotic patients have T2D. Diabetes develops as a complication of cirrhosis itself ("hepatogenous diabetes"), primarily due to IR in peripheral tissues and chronic hyperinsulinemia [51,158], which improve following liver transplantation [159].

NAFLD-, ALD-, HCV-related cirrhosis and hemochromatosis are more frequently associated with T2D, whose risk, conversely, is not increased in patients with cirrhosis due to cholestatic liver disease [160]. In turn, T2D is an emerging risk factor for the development and progression of liver disease, increases liver-related morbidity and mortality in cirrhotic patients and is a potential menace of increased CVR in this population of patients [115,161]. Cardiovascular events are extremely common after liver transplantation and patients with post-transplant T2D and MS are at higher risk of developing cardiovascular complications [162]. Interestingly, CVR is function of the etiology of liver disease also in liver transplant recipients, being lower for patients with cholestatic liver disease and higher for those with NASH-cirrhosis [163].

7. Primary biliary cirrhosis

As part of chronic cholestatic liver diseases, primary biliary cirrhosis (PBC) is often associated with mixed hyperlipidemia (hypercholesterolemia with markedly elevated TG, LDL and HDL serum concentrations) [164]. Reduced plasma LCAT activity, biliary lipids secretion and functional LDL receptors in hepatocytes, as well as increased hepatic CH synthesis are all deemed to concur to the development of the altered lipid profile [165,166]. Two different patterns of serum lipoproteins are identified according to PBC stages. Total- and HDL-CH are progressively reduced with the severity of disease, suggesting that reduced hepatic synthesis and intestinal absorption in end-stage PBC outweigh the lipid raising effect of impaired biliary secretion [167,168]. Also high levels of

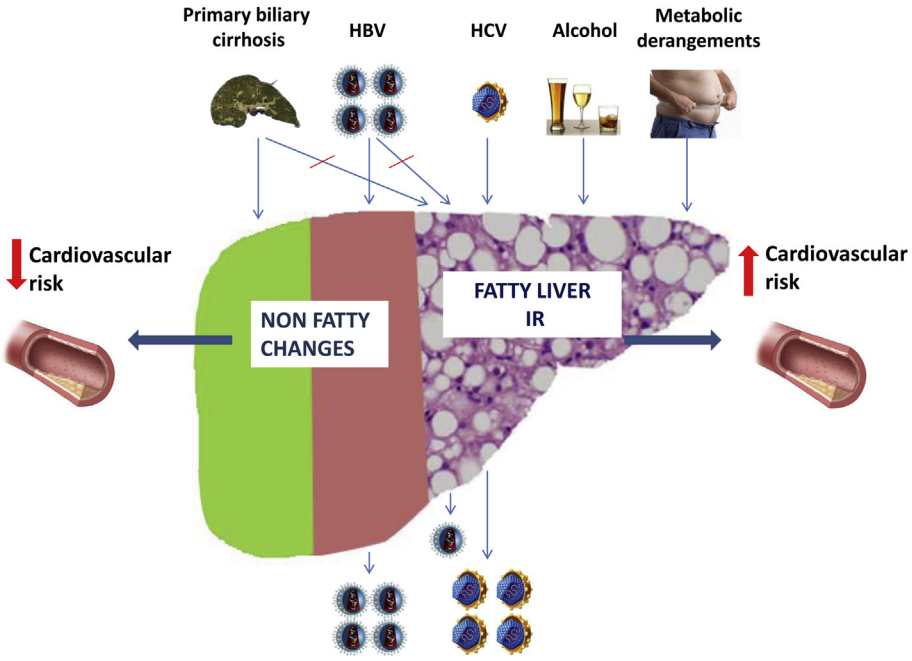

Fig. 1. Fatty liver as a chief effector of increased cardiovascular risk and a modulator of infection with major hepatotropic viruses. Hepatic steatosis, which results from alcohol abuse, metabolic derangements and chronic HCV infection [29,36,60,65,66,96,111], is associated with insulin resistance and appears to be the chief effector of increased cardiovascular risk [10,11,45–47,53,67,72,119–124,149,150,163]. Chronic HBV infection and primary biliary cirrhosis, which are not directly associated with fatty liver and insulin resistance (unless in case of concurrent host's additional steatogenic risk factors), appear to be spared from CVR [91–93,97,164]. With regard to the replicative cycle of two major hepatotropic viruses, however, hepatic steatosis seems to exert opposite influences: while HCV is strongly associated with steatogenesis and thrives on fatty substrates, HBV is not steatogenic and its replication seems to be inhibited by fatty liver [96–102,106–113].

lipoprotein-X (Lp-X), an abnormal LDL rich in PL and free CH, characterize advanced PBC [169].

Hypercholesterolemia is associated with increased CVD morbidity and mortality from in the general population; in PBC a threefold higher mortality rate than that of the general population has been reported, but the contribution of cardiovascular events to such an excess mortality remains controversial [170,171]. Intriguingly, the few cohort studies investigating this topic failed to demonstrate an increase in fatal and/or non-fatal cardiovascular events in PBC [168,172–175]. A possible bias of these studies is the competing effect of liver-related morbidity and mortality; nevertheless, studies using early markers of CVD as surrogate end points for atherosclerosis also failed to demonstrate a clinically significant impact of hypercholesterolemia in PBC [176–179]. The mechanistic explanation for the absence of the expected remains poorly defined. If oxidative stress, endothelial dysfunction and impaired autonomic cardiovascular function may suggest that vascular alterations are indeed present in PBC [179,180], the prevalence of female sex, the anti-atherogenic lipid profile (high HDL levels, low Lp(a) levels, Lp-X antioxidant effect), the low visceral fat and the high adiponectin concentrations observed in PBC may explain the conflicting results [165,166,169,181,182].

Both in animal models and in humans, there is evidence for a key role for bile acids in modulating TG and glucose homeostasis. Expansion/enrichment of the bile acid pool resulted in reduced hepatic TG content, improved liver steatosis and low IR through activation of farnesoid X receptor (FXR) pathway, which regulates bile acid, lipid and glucose metabolism [183,184]. Steatosis is not a typical feature of PBC and in general chronic cholestatic liver diseases are not associated with T2D, thus reducing CVR in PBC [160].

Lipid lowering agents reduce cardiovascular morbidity and mortality in the general population and ursodeoxycholic acid, statins and fibrates are both safe and effective in reducing serum CH levels in PBC [166,185–188]. However, given the complex background detailed above, it comes as no surprise that no studies have so far demonstrated that the administration of CH-lowering agents will eventually result into reduced CVR in PBC patients. A recent prospective study has suggested that low-dose, long-term atorvastatin treatment improves endothelial function in early-stage PBC [189]. Whether such intervention is justified in advanced disease remains to be ascertained.

8. Hepatocellular carcinoma

HCC frequently arises from cirrhosis and, much more rarely, from chronic, viral or metabolic, hepatitis [81]. While these predisposing conditions *per se* are often associated with deranged plasma lipid and lipoprotein profile [135], HCC patients will typically display slightly to significantly decreased TG, CH, free FA, HDL, LDL, Lp(a), Apo-AI and Apo-B plasma levels, which mirror a poorer prognosis [190,191].

Lipid and lipoprotein metabolism is regulated by cytokines; HCC is associated with the synthesis of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-2 (IL-2), IL-6 and TNF-alpha, which impair lipid synthesis, LCAT activity and MTP expression, reducing TG and CH serum levels [192–195].

Little is known on CVR in HCC, a disease with a poor prognosis having liver-related death as short or medium term outcome. In the future, cardiovascular complications will become increasingly prevalent in HCC patients as a result of the increasing burden of MS- and NAFLD-related HCC and the improved survival, following radical treatments and liver transplantation [196,197].

Preliminary studies have shown a worse prognosis due to infections, renal failure and cardiovascular complications in those subjects who had experienced newly onset T2D post-transplantation for HCC [198–201], as a result of host-related (age, ethnicity, obesity, family history of T2D), donor-related, hepatic (typically HCV infection) or iatrogenic factors (surgery, tacrolimus or corticosteroids) [202–205].

9. Conclusions

Liver diseases due to various etiologies are associated with varying serum lipid and lipoprotein phenotypes. Noteworthy, the two major hepatotropic viruses, HBV and HCV, display different lipid profiles.

At variance with what observed in the general population, patients with liver disease fail to display the strict and proportional association between increasing (total and LDL-) CH and TG levels and cardiovascular morbidity, suggesting that other factors, such as steatosis and IR, further to lipid profile, may be important.

Three common steatogenic liver diseases (NAFLD, AFL and HCV-related disease) are associated with premature atherosclerosis despite varying or even opposite lipid phenotypes, whereas PBC and chronic HBV infection are protected from both steatosis and CVR (Table 2) [10,12–36,40,41,45–48,52–54,65–68,72–74,88–94,97,105–107,111,115,116,119–124,129–138,149,150,158–179,182–184,190,191,198–201]. These findings support the paradigm that steatosis *per se*, almost invariably associated with IR, prothrombotic and pro-inflammatory liver and systemic milieu, sets the stage for increased CVR (Fig. 1). We should then move our belief from a simplistic equation "*the more circulating lipids, the higher the cardiovascular risk*" to another paradigm "*patients with steatosis are at cardiovascular risk unless proven otherwise*".

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