REVIEW

Is liver fat detrimental to vessels?: intersections in the pathogenesis of NAFLD and atherosclerosis

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Abstract

NAFLD (non-alcoholic fatty liver disease) encompasses the spectrum of fatty liver disease in insulin-resistant individuals who often display T2DM (Type 2 diabetes mellitus) and obesity. The present review highlights the pathophysiological basis and clinical evidence for a possible causal linkage between NAFLD and CVD (cardiovascular disease). The role of traditional and non-traditional CVD risk factors in the pathophysiology of NAFLD is considered in the first part of the review, with the basic science shared by atherogenesis and hepatic steatogenesis discussed in depth in the second part. In conclusion, NAFLD is not an innocent bystander, but a major player in the development and progression of CVD. NAFLD and CVD also share similar molecular mechanisms and targeted treatment strategies. On the research side, studies should focus on interventions aimed at restoring energy homoeostasis in lipotoxic tissues and at improving hepatic (micro)vascular blood supply.

Introduction

NAFLD (non-alcoholic fatty liver disease) encompasses the spectrum of fatty liver diseases seen in individuals with the MS (metabolic syndrome). Although the recognition of NAFLD as a precursor lesion to cirrhosis dates to the late 1970s [1], it was not until 1997 that a link between NAFLD and accelerated atherosclerosis was suggested by Lonardo [2]. In 1998, a paper from Japan reported that fatty liver clustered with traditional CVD (cardiovascular disease) risk factors in sedentary people [3]. Since these pioneering studies, our understanding of NAFLD as a potential novel risk factor for CVD has been rapidly expanding, leading to the reversal of the dogma that chronic liver disease usually protects from CVD.

In the present review, which critically examines evidence linking NAFLD and CVD, emphasis is given to the biological basis for a connection between fatty liver syndromes and atherosclerosis.

Role of CVD Risk Factors in the Pathophysiology of NAFLD

Many metabolic, haemodynamic, hormonal, prothrombotic and pro-inflammatory CVD risk factors [4–8],
Table 1  Possible pathophysiological bases for an association between NAFLD and accelerated atherosclerosis

The left-hand column lists the widely accepted genetic and environmental risk factors for atherosclerosis according to [4–8]. Interestingly, evidence is mounting that the same factors also play a role in the development and/or fibrosis evolution of NAFLD [9–36]. ALT, alanine aminotransferase; HCV, hepatitis C virus; VLDL, very-LDL.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Atherosclerosis</th>
<th>NAFLD</th>
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<tbody>
<tr>
<td></td>
<td>With a genetic predisposition</td>
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<tr>
<td></td>
<td>Atherogenic hyperlipidaemia</td>
<td>Associated with high LDL, VLDL and low HDL</td>
</tr>
<tr>
<td></td>
<td>Arterial hypertension</td>
<td>Associated and partially reversible with a decrease in hypertension</td>
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<td></td>
<td>Hyperhomocysteinaemia</td>
<td>Associated</td>
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<td></td>
<td>T2DM</td>
<td>Strongly associated</td>
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<td></td>
<td>Abdominal obesity</td>
<td>Strongly associated</td>
</tr>
<tr>
<td></td>
<td>Prothrombotic state</td>
<td>Association with fibrinogen, PAI-1, Factor VII, Factor VIII, platelet reactivity and others</td>
</tr>
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<td></td>
<td>Systemic inflammation</td>
<td>Associated with CRP and other acute-phase proteins</td>
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<td></td>
<td>MS and IR</td>
<td>Strongly associated</td>
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<tr>
<td></td>
<td>Male gender</td>
<td>Men &lt; 60 years of age are twice as likely to be affected compared with women</td>
</tr>
<tr>
<td>Environmental</td>
<td></td>
<td></td>
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<td></td>
<td>High-fat diet</td>
<td>Strong association with lifestyle</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
<td>Strongly associated and reversible by stopping</td>
</tr>
<tr>
<td></td>
<td>Low antioxidants</td>
<td>Findings not conclusive</td>
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<tr>
<td></td>
<td>Sedentariness</td>
<td>Independent association</td>
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</table>

often clustering in the broader spectrum of the MS, play a major role in the complex pathophysiology of NAFLD (Table 1) [9–36].

**Patient characteristics**

**Age**

Age represents a definite gender dimorphic traditional risk factor for CVD. NAFLD also occurs in children, but it increases in early adulthood, peaking in the 40–60-year age group and declining progressively afterwards [37]. The significance for this advanced age-related decline in NAFLD is still unclear, but it might mirror the selective mortality of these individuals [38].

**Gender**

Female gender is relatively spared CVD in the reproductive age range. Basic and clinical studies support the hypothesis that oestrogens might also protect from the development of NAFLD [25,26].

**Cigarette smoking**

Although smoking has a definite role in promoting CVD, its role in NAFLD has not been fully evaluated. A recent case-control family study found that NAFLD patients were more likely to be smokers [29]. This finding needs to be confirmed in larger epidemiological studies.

**Sedentariness**

Hsieh et al. [3] were the first to observe a strong association between sedentariness, sum of coronary risk factors scores and ultrasonographic fatty liver. A recent study has confirmed further that physical fitness, evaluated through maximal treadmill test, is inversely related to the prevalence of NAFLD [34].

**MS and its correlates**

**MS**

The MS is a cluster of interrelated risk factors promoting the development of CVD [39]. Visceral obesity and IR (insulin resistance) are thought to be the two major underlying risk factors for the MS, with gallstones being a ‘fellow traveller’ [40]. Currently, the MS has also been found to be a strong predictor of NAFLD [41], and NAFLD is widely accepted to be the hepatic manifestation of the MS [21,42]. Subjects with the MS have a 4-fold increased hepatic fatty content [43], and the presence of the MS among NAFLD patients increases the likelihood of having more advanced forms of liver disease [44]. Consistent with this, a large Japanese study found NAFLD to be more likely to develop and less likely to regress in those subjects with the MS at baseline [23].
Visceral obesity and IR
Increased abdominal fat and IR play a pivotal role in the pathophysiology of NAFLD [21,42]. Visceral adipose tissue is a dynamic endocrine organ that secretes a number of factors, such as NEFAs (non-esterified fatty acids; ‘free fatty acids’), hormones and cytokines (for example, IL-6 (interleukin-6), TNF-α (tumour necrosis factor-α), PAI-1 (plasminogen activator inhibitor-1), leptin, adiponectin and angiotensinogen) that are involved in the regulation of vascular/systemic inflammation and IR [45]. Quantitative metabolic findings have documented that elevated peripheral NEFA flux, mainly derived from visceral fat depots, is the major determinant of the accumulation of hepatic and lipoprotein fat in NAFLD [46]. Moreover, patients with NASH (non-alcoholic steatohepatitis) have significant increases in plasma markers of inflammation and endothelial dysfunction that are primarily mediated through underlying IR and increased visceral fat [18,45]. Conversely, adiponectin, an adipose-tissue-secreted protein with anti-inflammatory and anti-atherosclerotic properties, is decreased in insulin-resistant states, CVD [47] and NAFLD [26]. Furthermore, low adiponectin levels have been found in NASH compared with simple steatosis [48] and in NAFLD associated with steatosis and necroinflammation but not fibrosis [49].

Gallstones
In NAFLD, there is a trend towards a higher prevalence of gallstones compared with the general population. In addition, the likelihood of having gallstones in NAFLD significantly increased with increasing serum uric acid concentrations in men, and total cholesterol, apoB (apolipoprotein B) and triacylglycerol (triglyceride) concentrations in women [50].

T2DM (Type 2 diabetes mellitus)
Mortality from coronary heart disease in patients with T2DM is markedly increased [51], and impaired glucose homoeostasis also plays a pivotal role in the development of NAFLD. Indeed, T2DM is a strong risk factor for NAFLD, possibly through the underlying IR that provides substrates and molecular machinery necessary to promote hepatic steatogenesis [52]. Once developed, fatty liver will contribute further to systemic IR. Surrogate markers for NAFLD, such as raised LFTs (liver function tests), independently predict new-onset T2DM [33]. NAFLD and T2DM are a dangerous combination given that approx. 20% of patients with T2DM with NAFLD develop cirrhosis [54], and NAFLD increases the risk of incident myocardial infarction/coronary revascularization, ischaemic stroke or cardiovascular death in patients with T2DM, independent of other prognostic factors [55].

Hyperlipidaemia
Hyperlipidaemia, an established risk factor for CVD, is strongly associated with hepatic triacylglycerol content, as shown in Figure 1 [9,56]. Moreover, the severity of hepatic steatosis may increase atherogenesis in patients with T2DM by increasing plasma triacylglycerol and small-dense LDL (low-density lipoprotein)-cholesterol concentrations and by decreasing HDL (high-density lipoprotein)-cholesterol concentrations [57]. Further discussion of this major determinant of fat accumulation in the adipose and extra-adipose tissue is described below.

Oxidative stress and chronic inflammation
Established CVD risk factors mirroring the level of oxidative stress and chronic inflammation, such as plasma uric acid, CRP (C-reactive protein) and homocysteine concentrations, are important determinants for NAFLD. The pathogenic role of uric acid in CVD is mediated by endothelial dysfunction and systemic vascular inflammation [58]. Interestingly, increased plasma uric acid and insulin concentrations are independent predictors of NAFLD [59].

CRP, a risk factor for CVD [60], together with IR, is also a major determinant for the development of NAFLD [19]. Both the liver and visceral adipose tissue may contribute to increased CRP levels in NAFLD.

Mild hyperhomocysteinaemia is another metabolic factor shared by CVD and NAFLD. Hyperhomocysteinaemic animals have endothelial dysfunction and
accelerated atherothrombosis [61]. With regard to the liver, hyperhomocysteinaemia may cause NASH in mice [62] and helps to differentiate NASH from simple steatosis in humans [63]. Interestingly, specific genetic polymorphisms have also been observed to be a risk factor in human NASH [11].

Prothrombotic state
The association of liver steatosis with increased plasma levels of several prothrombotic factors is primarily mediated by visceral adiposity and/or IR [18,65]. However, recent observations have suggested that NASH can predict a prothrombotic state (specifically increased PAI-1) in a manner that is partly independent of the contribution of visceral adiposity and IR [66]. Of interest, the haemostatic system may also play a role in liver fibrogenesis [67].

Dietary habits and postprandial lipaemia
Studies support a close relationship between dietary habits, postprandial lipaemia and CVD [68,69]. ApoB is a strong predictor of NAFLD [70], and IR is coupled with a depressed postprandial atherogenic metabolism of triacylglycerol-rich lipoproteins in NASH [71]. Dietary habits and genetic determinants including MTP (microsomal transfer protein) polymorphisms may promote NASH and atherogenesis via hypoadiponectinaemia [27,30,72].

Hypertension and hypoxia

Hypertension
Owing to their increased IR and BMI (body mass index), patients with hypertension have a higher prevalence of fatty liver [10]. Being strictly involved in the pathogenesis of hypertension and IR, AngII (angiotensin II) is a key mediator in the interdependency of haemodynamic and metabolic pathways of the MS [73]. IR is frequently present in essential hypertension, and chronic treatment with RAAS (renin–angiotensin–aldosterone system) inhibitors may reduce new-onset T2DM [74], possibly through improved IR and PPAR (peroxisome-proliferator-activated receptor)-γ agonism [73]. Interestingly, treatment for 12 months with losartan in patients with hypertension with NASH significantly improved LFTs and liver histopathology [75].

Hypoxia
There may be a causal link between primary sleep abnormalities and CVD and metabolic disease [76]. Nearly 50% of NAFLD patients had symptoms of OSA (obstructive sleep apnoea) [77], and 20% of non-drinking patients with a clinical suggestion of OSA had raised LFTs [78]; moreover, those with severe OSA were more insulin-resistant and had a worse liver histology, suggesting that OSA, possibly through IR, is a strong risk factor for NASH, independently of BMI.

Chronic intermittent hypoxia up-regulates several lipid biosynthesis genes and may induce dyslipidaemia, lipid peroxidation and hepatic inflammation in mice fed a high-fat diet [79–81]. Fatty liver in mice is generally hypoperfused, possibly due to mechanical obstruction of sinusoidal lumen by hepatocyte cytoplasm engulmed with triacylglycerols [82]. Although it may result in decreased oxygen and nutrient exchange and in an escalating cycle of chronic liver injury and vascular insufficiency [82], hepatic hypoperfusion in NAFLD patients may also be reversible after dietary/pharmacological therapy [83]. Evidence for a ‘hepato–coronary reflex’ has come from a study evaluating patients with T2DM with CVD using PET (positron emission tomography) [84]. Liver fat content was the most significant explanatory variable for myocardial IR among these patients. Furthermore, those with high liver fat content had markedly lower coronary flow reserve than those with low liver fat content. These findings suggest that, in patients with T2DM with CVD, liver fat content is a strong determinant of myocardial IR and decreased coronary functional capacity [84].

Deranged endocrine system
Endocrine derangements may be a non-traditional risk factor of CVD, also playing a significant role in the pathogenesis of NAFLD [26].

GH (growth hormone) deficiency
Untreated GH deficiency/insufficiency and subsequent low IGF-1 (insulin-like growth factor-1) concentrations in adults resemble the MS phenotype and are associated with increased CVD risk [85]. GH replacement therapy may decrease the global CVD risk of these patients principally by reducing visceral fat and improving the glycolipidic profile and chronic inflammatory state [86].

HPA (hypothalamic–pituitary–adrenal) dysfunction
Increased prevalence of progressive forms of NAFLD (NASH with or without cirrhosis in most cases) has been reported in patients with hypothalamic/pituitary dysfunction [87]. Cirrhosis developed via progressive NASH in these patients and was largely mediated by excessive weight gain and impaired glucose tolerance. Several studies have confirmed the link between neurosurgery and progressive NASH to be principally mediated by GH deficiency/insufficiency [26].

Visceral obesity is commonly associated with subclinical endocrine abnormalities, especially mild hypercortisolism [88]. Chronic cortisol hypersecretion causes the MS, thus determining an increased CVD risk in patients with Cushing’s syndrome [89]. In NAFLD, a subtle chronic overactivity in the HPA axis is closely associated with the severity of liver histopathology,
Table 2  Similarities in treatment strategies between NAFLD and atherosclerotic vascular disease (CVD)

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>CVD</th>
<th>NAFLD</th>
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<tbody>
<tr>
<td>Lifestyle changes with significant weight loss</td>
<td>Reduces CVD events</td>
<td>Improves LFTs and liver histology</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Reduces CVD events in morbidly obese patients</td>
<td>Improves LFTs and liver histology in morbidly obese patients</td>
</tr>
<tr>
<td>Insulin sensitizers (metformin, rosiglitazone and pioglitazone)</td>
<td>Reduces CVD events in patients with T2DM (metformin)</td>
<td>Improves LFTs and liver histology, especially in patients with T2DM and impaired glucose tolerance</td>
</tr>
<tr>
<td>Anti-hypertensive agents</td>
<td>Reduces CVD events in patients with T2DM and non-diabetic patients</td>
<td>Improves LFTs and liver histology in patients with hypertension (preliminary evidence and limited to losartan)</td>
</tr>
<tr>
<td>Statins</td>
<td>Reduces CVD events in patients with T2DM and non-diabetic patients</td>
<td>Improves LFTs and liver histology in patients with dyslipidaemia (preliminary evidence and limited to pravastatin and atorvastatin)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Reduces CVD events in patients with T2DM and non-diabetic patients</td>
<td>Improves LFTs and liver histology in patients with hypertriglyceridaemia (preliminary evidence and limited to gemfibrozil and bezafibrate)</td>
</tr>
<tr>
<td>Antioxidants/vitamins</td>
<td>Findings not conclusive</td>
<td>Findings not conclusive</td>
</tr>
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</table>

leads to subclinical hypercortisolism and might also be implicated in the development of NAFLD [49].

**Sex hormones**

Women are protected from the occurrence of CVD and NAFLD [26,90]; however, similarly to atherosclerosis, the oestrogen-related ‘hepato-protective’ effect wanes after menopause [25].

Normal sex hormone levels keep a healthy balance between lean and fat mass and affect glycolipidic metabolism. Hypoandrogenism in men and hyperandrogenism in women lead to NAFLD, possibly through visceral obesity and IR. Studies correlate the age-related decline of testosterone levels with increasing CVD [90]. In aging men, the decline in testosterone correlates with muscle mass loss and with increased fat mass [91]; conversely, higher testosterone levels are associated with higher insulin sensitivity and reduced incidence of the MS [92], suggesting that this hormone may protect against the development of the MS. Treatment with leuprorelin, a drug inhibiting LH (leutinizing hormone) release and suppressing testicular steroidogenesis, has been reported to induce the development of the MS and NAFLD [93].

Young patients with PCOS (polycystic ovary syndrome) have hyperandrogenism, irregular menses, components of the MS, increased carotid IMT (intima-media thickness) and elevated LFTs, often due to fibrosing NASH [94]. These findings suggest that patients with PCOS should be screened for NAFLD and CVD at an earlier age than the general population.

There appears to be growing evidence that multiple haemodynamic/hypoxic, endocrine/metabolic and prothrombotic/inflammatory factors play a major role in the development/progression of both CVD and NAFLD, which also share similar treatment strategies (Table 2) [39,95,96].

**THE LIVER–VESSEL AXIS: PHYSIOLOGICAL AND MOLECULAR BASIS FOR A LINK BETWEEN FATTY LIVER AND VASCULAR DISEASE**

Epidemiological observations providing direct and indirect evidence for a close link between fatty liver and vascular disease in cross-sectional and prospective studies have been reviewed elsewhere recently [97–99]. In the present review, we specifically address the biological principles for a link between fatty liver and (cardio)vascular disease.

**Role of fat deposition in organs other than the liver**

NEFAs can be generated through the de novo synthetic pathway or imported intracellularly [100]. Excess NEFAs are esterified and stored as triacylglycerols in adipocytes. Adipose tissue has a unique capacity to store large amounts of excess NEFAs. In contrast, when the limited lipid storage capacity of non-adipose tissues is exceeded, cell dysfunction/death will result, a phenomenon termed lipotoxicity [101,102]. Mechanisms of lipotoxicity include apoptosis, decreased cardiolipin content, increased membrane permeability and cytochrome c release in mitochondria, NF-κB (nuclear factor κB) activation and oxidative stress [102]. Adverse biological consequences of lipid overload occur in many organ systems, including the arterial wall, pancreas, myocardium and muscle.

**Arterial wall**

Pathological arterial lipid accumulation, an important contributor to atherogenesis, is linked to various pathways involving CD36 or other scavenger receptors that bind to normal or modified LDL to promote the progression of atherosclerosis [103–106]. LDL cholesteryl
esters can be independently delivered to cells without concurrent LDL particle uptake, a process named 'selective uptake' [107–109]. Saturated dietary NEFAs may modulate cholesterol delivery to the arterial wall, thus hastening atherogenesis [110].

Pancreas
Lipid overload in pancreatic β-cells leads to dysregulated insulin secretion and changes in the expression of PPARα, glucokinase, the GLUT2 glucose transporter, prepro-insulin and PDX-1 (pancreatic duodenal homeobox-1) [111]. Moreover, accumulation of excess NEFAs also causes β-cell apoptosis. In ZDF (Zucker diabetic fatty) rats, triacylglycerol accumulation in islets is associated with decreased β-cell mass and a decline in insulin production with DNA laddering [112]. In vitro, excess NEFAs lead to apoptosis in primary rat pancreatic β-cells and β-cell lines [113,114] and in isolated human islets [115]. Of interest, a synergistic effect in the toxic effects of glucose and NEFAs has been reported [116].
A significant association of pancreatic fat with β-cell dysfunction, independent of BMI, fasting plasma glucose and triacylglycerols, is only present in non-diabetic subjects, suggesting that, once diabetes occurs, factors additional to pancreatic fat account for a further decline in β-cell function [116].

Heart
Systemic metabolic alterations that result in cardiac lipid accumulation are associated with cardiomyopathy. Rodent models show that such cardiac lipid accumulation can lead to systolic ventricular dysfunction [102]. In humans, cardiac lipid overload in patients with inherited defects in the mitochondrial fatty acid oxidation pathway is associated with heart failure and sudden death [117]. There might be a specific association between fatty liver and cardiac fat. Triacylglycerol accumulation in and around the myocardium seen in moderately obese individuals precedes left ventricular overload and hypertrophy [118]. In particular, in those with fatty liver, fat is accumulated in the epicardial area and myocardial energy metabolism is decreased [119].

Skeletal muscle
Increased plasma NEFAs leading to IMCL (intramyocellular lipid) accumulation could play a major role in IR and T2DM in humans [120]. Intracellular NEFAs or their metabolites activate a serine/threonine kinase cascade ultimately resulting in the decreased tyrosine phosphorylation of IRS-1 (insulin receptor substrate-1) and PI3K (phosphoinositide 3-kinase) activity and in a failure to promote insulin-dependent translocation of the GLUT4 glucose transporter [121]. IMCL accumulation is associated with the activation of PKC (protein kinase C)-θ [121] and PKC-ε [122], and the activation/translocation of PKC-β and PKC-δ isoforms from the cytosol to the cell membrane [123]. Moreover, decreased activation of atypical PKC isoforms (ζ/δ/ɛ) has also been reported [124]. In turn, alterations in PKC activation may impair insulin signalling and activate the NF-κB pathway [123,125].
Regarding their physiological role, IMCLs represent valuable energy stores during prolonged exercise, which, however, in the absence of regular physical activity and with overconsumption of fat, can have detrimental effects on muscular insulin sensitivity [126].

Mechanistic aspects of pathogenesis intersecting steatogenesis and atherogenesis
Various pathogenic pathways could interact in such a way that the inflamed liver in NASH might promote atherogenesis. The specific roles of hyperdyslipidaemia and inflammation are discussed below.

Hyperdyslipidaemia
The liver plays a central role in the maintenance of systemic lipid homoeostasis in health and, conversely, primary hyperlipidaemic states are associated with hepatic steatosis (Figure 1) [9,56]. What is the biological basis for the role of the liver in the development and complications of atherosclerosis?
Although hyperlidaemias represent an obvious common precursor to both atherosclerosis and NAFLD, the qualitative composition of dietary fatty acids and the lipogenic molecular machinery shared in the vessel and in the liver may be of no lesser importance. For instance, although the beneficial effects of n-3 fatty acids on cardiovascular disease have a strong physiological and clinical foundation [127,128] and have poured from the boundaries of the scientific literature into the lay press, only more recently have scientists appreciated that n-3 fatty acids exert beneficial effects on vascular dysfunction and inflammation in macrosteatotic mouse liver [129,130]. The mechanisms of these beneficial effects are to be found in the effects of n-3 fatty acids on cell membrane composition, resulting in improved signalling, in their capability to serve as natural ligands for nuclear receptors affecting gene expression and in their anti-inflammatory properties [131].

Several transcription factors in the SREBP (sterol-regulatory-element-binding protein) family govern the activation of lipogenic genes [132]. Although in healthy conditions hepatic lipogenesis is tightly coupled to lipoprotein secretion, which prevents steatosis developing, in transgenic mice all the three SREBPs isoforms (α, γ and δ) induce a severe fatty liver phenotype, suggesting an imbalance between lipid synthesis and secretion [133]. The hyperlipidaemic effects of dietary saturated fats are mediated through PGC-1β (PPAR-γ co-activator-1β) coactivation of SREBP [134].
Liver fat: intersections in the pathogenesis of NAFLD and atherosclerosis

Figure 2 The liver–vessel axis
Atherosclerosis and NAFLD share similar biological precursors that affect the development and progression of both. On the basis of the literature reviewed in the text, we hypothesize that there might be a similar histological evolution, with liver changes paralleling atherogenesis. Morphogenetic similarities in the liver and vessels justify the hypothesis of a similar pathogenesis and of reciprocal influences in these two organs, hence the concept of a ‘liver–vessel axis’.

The evolving view of atherosclerosis as a metabolic complication has directed attention towards PPARs as transcriptional regulators involved in lipid metabolism, inflammation and atherosclerosis [135]. With its distribution in the liver, heart, vasculature and immune cells, PPAR-α mediates cross-talk between liver, inflammation and vessels. In particular, PPAR-α activation modulates the hepatic acute-phase response and vascular endothelium reactivity, local vascular inflammatory responses and atherosclerosis plaque formation [135]. Interestingly, PPAR-α −/− mice have impaired lipid metabolism and obesity, consistent with the clinical HDL-increasing and triacylglycerol-decreasing effects of the PPAR-α agonists fibrates [136].

PPAR-γ is distributed in adipose tissue, skeletal muscle, liver, heart, vascular system and immune system: the serendipitous discovery of their synthetic agonists thiazolidinediones proved an invaluable tool in studying this nuclear receptor [137]. PPAR-γ has anti-inflammatory/anti-atherosclerotic activities through direct actions on macrophages [138] and prevention of hepatic steatosis [139] in rats and the MS in humans [140,141].

Inflammation
Inflammation may induce IR which, in turn, could amplify inflammatory responses [142]. The macrophage has emerged as an important player in the pathogenesis of both atherosclerosis and IR [142]. Studies have demonstrated increased accumulation of macrophages in adipose tissue of obese animals and humans, suggesting a direct role in the development of IR [143,144]. Experimental evidence suggests that the emerging interplay between cellular IR, persistent ER (endoplasmic reticulum) stress and apoptotic death in cells of the arterial wall may be a common denominator in the development of macrovascular complications in T2DM [142]. The recruitment of inflammatory cells in the intima is an essential step in the development and progression of atherosclerosis. This process is triggered by local production of chemokines and chemokine receptors from activated endothelial cells and inflammatory cells. [145] Various members of the CC chemokine family, notably including MCP-1 (monocyte chemoattractant protein-1)/CCL2, have been implicated in atherogenesis [145]. Similarly to the inflamed vessel and adipose tissue, macrophage infiltration is also a feature in the liver in patients with NASH [146]. Moreover, adipose tissue inflammation and increased ceramide content characterize subjects with high liver fat content, independent of obesity [147].

MCP-1 and its receptor are of major importance for monocyte recruitment and activation of inflammatory cells at the site of inflammation [148,149]. Expression of MCP-1 is increased in atherosclerotic lesions [150,151] and inhibition of its expression impairs atheroma formation in hypercholesterolaemic mice [152,153], supporting it as a major player in atherogenesis.

Increased MCP-1 expression in adipose tissue contributes to macrophage infiltration into this tissue, IR and obesity-associated hepatic steatosis in mice [154]. Patients with NAFLD are characterized by a low-grade systemic inflammation [155]. MCP-1 could be of importance for the persistent inflammation in NAFLD, particularly in patients with NASH, possibly playing a role in the progression from simple steatosis to NASH, at least partly...
by promoting infiltration of leucocytes into the liver [155].

CONCLUSIONS

In conclusion, many well-defined CVD risk factors play a major role in the pathophysiology of NAFLD. The existence of cross-talk between the liver and vessels might account for increased CVD risk in patients with NAFLD, and there appears to be a close link between deranged energy homeostasis, inflammatory changes in adipose and liver tissues and molecular mediators of atherogenesis.

Future studies should focus on interventions aimed at restoring energy homeostasis in lipotoxic tissues and at improving hepatic (micro)vascular blood supply.

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