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Review article

Statins and nonalcoholic fatty liver disease in the era of precision medicine: More friends than foes

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) describes a spectrum of alcohol-like hepatic histological changes, which occur in the absence of any competing causes of chronic liver disease, notably including significant alcohol consumption. A close and bi-directional relationship links NAFLD with the metabolic syndrome (MetS), and concurrent MetS will hasten the progression to more severe forms of NAFLD, including cirrhosis and hepatocellular carcinoma (HCC). Patients with NAFLD will typically exhibit atherogenic dyslipidemia and increased cardiovascular risk (CVR).

Statins are among the most widely prescribed lipid-lowering drugs. Their use has historically been hampered, in individuals with liver disease, owing to the fear of hepatotoxicity. However, studies suggest that statins are not only effective in reducing cardiovascular events, but may also exert multiple beneficial effects on the liver.

CVR in those with NAFLD has extensively been covered by our group and others. This updated clinical narrative review will critically examine the effects of statins on the pathogenesis of NAFLD, including the key elementary pathological lesions of NAFLD, i.e. steatosis, inflammation and fibrosis, and its liver-related complications, i.e. cirrhosis, portal hypertension and HCC.

1. Background

NAFLD stands for nonalcoholic fatty liver disease, an umbrella definition which identifies the gamut of alcohol-like clinico-pathological hepatic changes which are closely and bi-directionally associated with the metabolic syndrome (MetS) and its individual components in the absence of competing causes of liver disease, notably including alcohol, viral hepatitis and drug-induced liver steatosis [1].

The vast majority of NAFLD patients are asymptomatic and reach clinical attention based on either raised liver enzymes or the finding of hepatic steatosis at liver imaging performed for unrelated reasons [2]. A certain proportion of individuals live with steatosis without seemingly developing any inflammatory reaction to it (i.e. they are "*good storers*" of intrahepatic fat) [3]. However, owing to a variety of modifiers, notably including gender, lifestyle, oxidative stress, insulin resistance (IR), lipidomic signature and genetic polymorphisms, a minority of these NAFLD individuals will develop nonalcoholic steatohepatitis (NASH), which is deemed to be the most powerful predictor of fibrotic evolution. Liver fibrosis, in its turn, dictates the natural course of hepatic disease spanning steatosis to steatohepatitis, cirrhosis, portal hypertension, liver failure, end-stage liver disease and hepatocellular carcinoma (HCC) [4]. Together with its hepatic manifestations and complications, however, NAFLD patients are also exposed to excess cardio-metabolic risk and extra-hepatic manifestations, which are probably also

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; ChREBP, carbohydrate response element binding protein; CVD, cardiovascular disease; CVR, cardiovascular risk; DILI, drug-induced liver injury; ER, endoplasmic reticulum; FC, free cholesterol; HDL, high-density lipoprotein; HSCs, hepatic stellate cells; HVPG, hepatic venous pressure gradient; ICAM-1, intercellular adhesion molecule-1; IR, insulin resistance; KLF2, Krüppel-like Factor 2; LDL, low-density lipoprotein; LFA-1, lymphocyte function-associated antigen 1; MAPK, mitogen-activated protein kinase; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-kB, nuclear factor-kB; NO, nitric oxide; NgBR, Nogo-B receptor; PKA, protein kinase-A; Plin5, perilipin 5; PNPLA8, patatin-like phospholipase domain-containing enzyme 8; PPAR, peroxisome proliferator-activated receptor; SREBPs, sterol regulatory element-binding proteins; TGF-β1, transforming growth factor-β1; TNFα, tumour necrosis factor α

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associated with more advanced disease [5]. Notably, cardiovascular disease (CVD) is the leading cause of death in patients with NAFLD and NASH [6]. Therefore, owing to the close association with MetS and increased cardiovascular morbidity and mortality, statins are an important weapon in the treatment of NAFLD. The major current guidelines on NAFLD/NASH pointed out that statins can be safely used to treat dyslipidemia and prevent CVD in patients with NAFLD/NASH [7,8]. Moreover, highlighting that CVD is the main cause of death in NAFLD/NASH, an Expert Panel has recently suggested that, pending further studies, the use of statins, either alone or combined with a peroxisome proliferator-activated receptor (PPAR) γ agonist or ezetimibe, should be considered for the primary/secondary prevention of CVD and also to avoid the development of liver-related complications (cirrhosis, liver transplantation or HCC), in patients with NAFLD/NASH at high CVD or HCC risk [9].

The history of the discovery and development of statins was succinctly covered elsewhere [10]. It is now clear that statins are efficacious and cost-saving both for primary and secondary prevention of cardiovascular events; however, fear of medication toxicity and pill burden result in poor prescription and adherence rates to statin treatment, thus negatively impacting on public health [11].

As far as extra-cardiovascular indications of statins are concerned, this class of drugs has undergone an evolution from initially being under-prescribed in those with either suspected or definite liver disease [12], to being ever increasingly suggested as a potential tool for the treatment of hepatic fibrosis, portal hypertension and the chemoprevention of HCC in randomized clinical trials [13–16].

On this background, we aimed at critically reviewing the most updated lines of evidence regarding the double-edged sword of statins being either detrimental or beneficial to those with liver disease and, given that they are prone to excess CVR, particularly to those with NAFLD/NASH. The bibliographic research strategy was based on a PubMed database search using the following key words: *statins; NAFLD; fatty liver; NASH; cirrhosis; HCC; side effects,* updated as of 9th December 2018. Retrieved bibliographic material was analyzed by both AL and FN and only published articles which were unanimously worthy of consideration were included in the present review article.(See Box1 and Box2)

2. Are statins detrimental in patients with nonalcoholic fatty liver disease?

High doses of statins caused significant liver injury in animal toxicology studies, probably due to the depletion of mevalonate or its downstream metabolite [17]. However, the hepatotoxicity of statins in humans is rare and unpredictable [18].

The most common hepatic side effect of statins is asymptomatic raised aminotransferases. Safety data coming from clinical trials of statins have consistently reported that the incidence of persistent and significant elevation in alanine aminotransferase levels (as defined by levels $>$ 3 times upper limit of normal on at least two measurements), is less than 3% in patients treated with statins, which is not significantly different from that registered in patients receiving placebo [18]. Of note, a meta-analysis of 49275 patients from 13 placebo-controlled trials of statins used for the treatment of hyperlipidemia or for primary or secondary cardiovascular prevention confirmed that low-to-moderate doses of statins are not associated with raised liver enzymes [19]. However, the incidence of statin hepatotoxicity is dose-related. Indeed, another meta-analysis of randomized clinical trials comparing higher versus lower intensity statin therapy showed that higher intensity statin therapy was associated with an increased incidence of aminotransferases elevation [20]. Raised aminotransferases, usually occurs within the first year of treatment, is generally asymptomatic, and often resolves spontaneously [18].

Currently, six statins are available for clinical use: atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin. These compounds differ for pharmacokinetic characteristics which may affect their potential hepatotoxicity (Table 1) [21,22]. In particular, all statins are cleared by the liver, but the rate of hepatic excretion strictly depends on the lipophilicity of the individual statin. Three groups of statins based on lipophilicity have been described: simvastatin and lovastatin constitute the highly lipophilic group; the modestly lipophilic group include atorvastatin and fluvastatin; finally, rosuvastatin and pravastatin are the low lipophilic statins [20]. The more lipophilic compounds have a greater hepatic excretion rate, while the less lipophilic statins exhibit more pronounced active renal excretion [12,21]. Of note, it has been suggested that the relative hydrophilicity or lipophilicity of statins is associated with the type and frequency of adverse reactions [20]. In their meta-analysis, Dale et al. showed that only less lipophilic statins resulted in an increased relative risk of aminotransferase elevation: the relative risk of aminotransferase elevation was 3.54-fold [95% CI 1.83–6.85] greater in subjects treated with higher intensity hydrophilic statins than in those treated with lower intensity hydrophilic statins; in contrast, the use of higher intensity lipophilic statins did not significantly affect the risk of aminotransferase elevation (1.58 [95% CI 0.81–3.08]) [20].

Clinically apparent drug-induced liver injury (DILI) associated with statins has been reported in the literature but is very rare. In an analysis of occurences of adverse reactions received by the Swedish Adverse Drug Reactions Advisory Committee between 1988 and 2010, 73 cases of DILI attributed to statins were identified, corresponding to 1.2 episodes/100.000 users [23]. Large studies on patients with DILI reported that 1–3% of cases were considered to be due to statins [24–26]. A recent survey among 1188 cases of DILI enrolled between 2004 and 2012 in a prospective registry by the U.S. DILI Network described 22 cases (1.9%) which were definitely attributed to a statin [27]. Of note, the pattern of liver injury caused by statins lacks a common distinctive phenotype: cholestastic, hepatocellular and mixed patterns have all been described; moreover, a proportion of patients may develop features of autoimmune hepatitis. Liver injury is mainly mild-to-moderate in severity and reverses in most cases following statin withdrawal; however, irreversible liver damage leading to death or liver transplantation, though extremely rare, has been documented. No clear factors have been identified which increase the risk of statin-associated hepatotoxicity [18,27,28].

The safety of statins in patients with pre-existing elevated liver enzymes has been debated for several years. Many physicians are still worried about the risk of increased hepatotoxicity of statins in patients with elevated baseline aminotransferases or underlying liver disease, and concern also regards the use of statins in patients with NAFLD. A

Box 1
Are statins detrimental in patients with nonalcoholic fatty liver disease?

- Elevation in aminotransferases is the most common hepatic side effect of statins
- It is generally asymptomatic, occurs within the first year of treatment, and often resolves spontaneously
- It is more common with higher doses of hydrophilic statins
- Clinically apparent statin-induced liver injury leading to irreversible liver damage is rare and unpredictable
- Statins have proven hepato-safe also in patients with elevated aminotransferases and chronic liver diseases, including NAFLD

Box 2
Are statins beneficial in patients with nonalcoholic fatty liver disease?

- Statins reduce cardiovascular morbidity and mortality also in patients with elevated aminotransferases and chronic liver diseases, including NAFLD
- Statins may improve liver histology in patients with NAFLD
- Statins may ameliorate portal hypertension in patients with cirrhosis
- Statins may act as chemopreventive agents for hepatocellular carcinoma
- Further studies are warranted to determine whether statins should be used to specifically treat NAFLD and its liver-related complications

Table 1
Pharmacokinetic characteristics of statins [adapted from Refs. [21,22]].

	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Optimal time dosing	Any time	Bedtime	With meals morning and evening	Any time	Bedtime	Any time	Evening
Effect of food	Decreased bioavailability	Decreased bioavailability	Increased bioavailability	No effect	Decreased bioavailability	No effect	No effect
Bioavailability (%)	12	24	5	80	18	20	5
Elimination half-life (h)	14	1.2	3	11	1.8	19	2
Protein binding (%)	98	> 98	> 95	96	50	90	95–98
Solubility	Lipophilic	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic
Active metabolites	Yes	No	Yes	Minor	No	Minor	Yes
CYP450 metabolism	3A4	2C9	3A4	2C9	Glucuronidation 3A4	2C9 2C19	3A4
Hepatic excretion (%)	> 70	> 68	> 70	NA	46–66	90	78–97
Renal excretion (%)	< 5	6	10	< 2	20	10	13

survey of 937 primary care physicians from 138 academic centers in the United States showed that only 50% would prescribe statins if the baseline aminotransferases were elevated and this rate dropped to 40% in the presence of an underlying liver disease [29]. These figures were confirmed in recent studies from United States and Europe showing an under-prescription of statins in patients with NAFLD, even if they had dyslipidemia and were at high CVR [30–33].

This negative perception, which contributes to the underutilization of statins, conflicts with increasing evidence that statins are safe in patients with elevated aminotransferases or underlying liver disease, NAFLD included. In 2004 Chalasani et al. were first in showing that subjects with abnormal liver enzymes were not exposed to an increased risk of hepatotoxicity from using statins [34]. Notably, a post-hoc analysis of 437 patients with elevated baseline liver enzymes potentially attributable to NAFLD, from the Greek Atorvastatin and Coronary Heart Disease Evaluation study, found that treatment with statins was associated with a substantial improvement in liver enzymes and a significant reduction of cardiovascular events [35]. A study examining 2264 Dallas Heart Study participants further supported these findings by showing that statins were not associated with a higher risk of liver steatosis or abnormal liver enzymes, even among subjects with baseline liver steatosis [36]. Consistently, a population-based study recruiting 2578 subjects in Rotterdam demonstrated that in overweight individuals the use of statins for more than 2 years was independently associated with a lower prevalence of liver steatosis [37]. Moreover, a recent study enrolling 101 patients with NASH and pre-diabetes/type 2 diabetes clearly demonstrated that statins can safely be prescribed also in this category of patients at very high CVR [38].

In summary, statins are hepato-safe and reduce cardiovascular morbidity, even in patients with baseline abnormal liver enzymes and pre-existing NAFLD and NASH. Since hepatotoxicity of statins is rare and unpredictable, in 2012 the Food and Drug Administration revised statin safety labels by removing the need for routine periodic monitoring of liver enzymes and recommending liver enzyme testing only before starting statin therapy and as clinically indicated thereafter [39].

Another potential adverse event associated with the use of statins worthy to be mentioned in the specific setting of patients with NAFLD is the risk of newly diagnosed type 2 diabetes mellitus [40]. Several meta-analyses of major statins trials have consistently reported a modestly increased (9–13%) risk of incident diabetes [41–45]. Although this diabetogenic property is a class effect, it appears that there is a gradient in the risk of newly diagnosed type 2 diabetes across different types and doses of statins [41,44]. In particular, it has been reported that the risk of incident diabetes is higher for intensive than for moderate-dose statin therapy [40,42,45]. The absolute risk of statin-induced diabetes in major trials was 0.2% per year and largely depended on the presence of baseline prediabetes or underlying diabetes risk factors [40]. Since several cardiovascular events are prevented for every new diagnosis of diabetes mellitus, statin use should not be discouraged in patients with NAFLD who are at both high CVR and high risk of diabetes mellitus. While it is mandatory to carefully monitor patients on statin therapy for newly diagnosed type 2 diabetes mellitus, the side effects of this class of drugs are overcome by the multiple cardiovascular and kidney-protective effects offered by statins [46].

3. Are statins beneficial in patients with nonalcoholic fatty liver disease?

Patients with NAFLD will typically have an atherogenic dyslipidemia and thus often have an increased CVR necessitating statin therapy. Data discussed above clearly demonstrate that statins are safe in patients with NAFLD and should liberally be used for primary and secondary cardiovascular prevention whenever clinically indicated in this patient population. Studies on NAFLD patients have shown that statins are effective in improving their lipid profile by reducing total cholesterol, LDL cholesterol and triglycerides, increasing HDL cholesterol and decreasing free fatty acids [47–50]. In addition, increasing evidence also suggests that treatment with statins may have beneficial effects on NAFLD and its liver-related complications, notably including cirrhosis, portal hypertension and HCC. Indeed, further to their lipid-lowering activity, statins also exert several systemic pleiotropic mechanisms, that collectively may concur in improving steatosis, sterile inflammation, fibrosis and tumorigenesis (Fig. 1) [10,12,51,52], which are NAFLD elementary histological changes and also recapitulate the hepatic natural history of NAFLD [53,54].

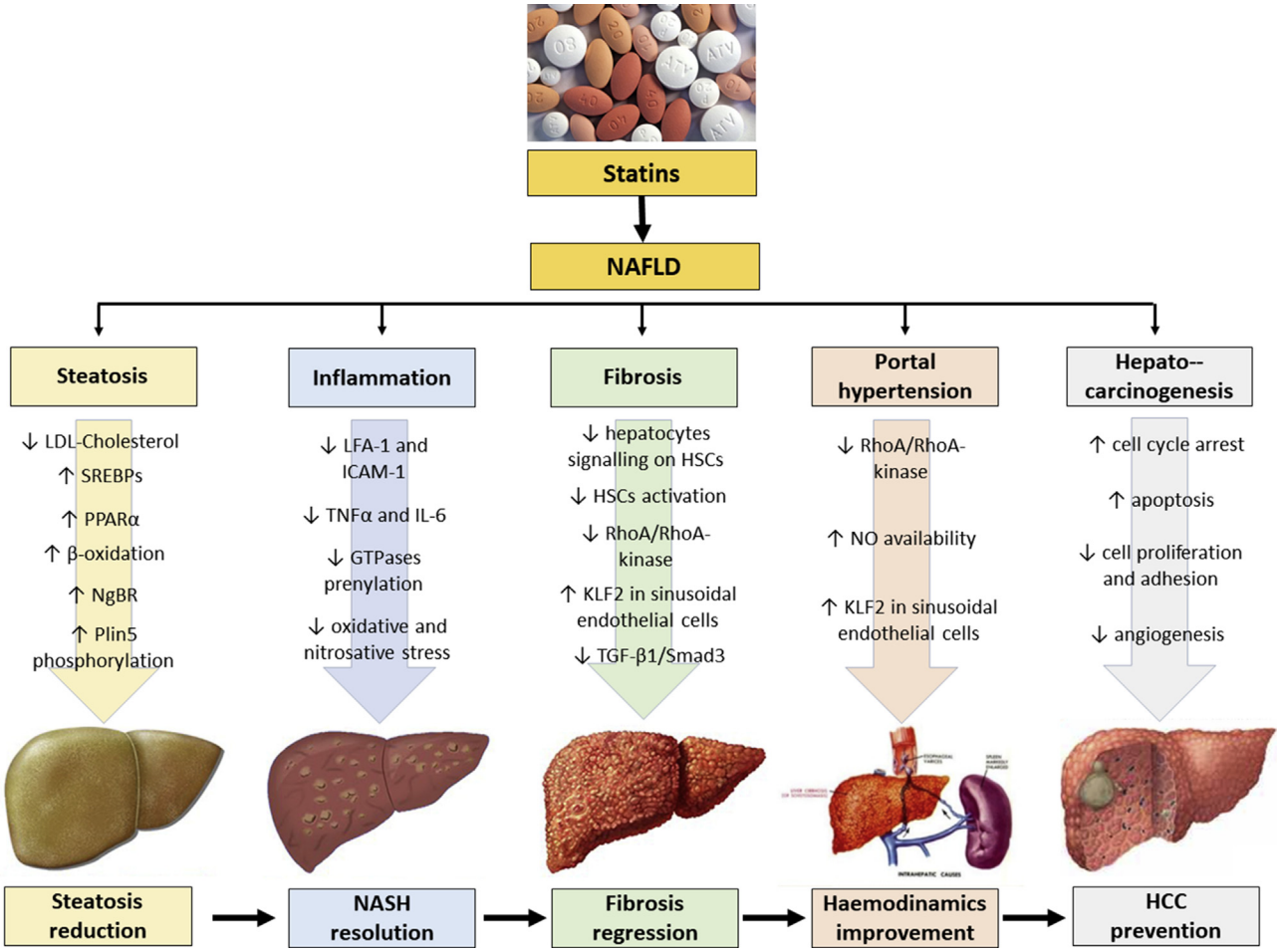

Fig. 1. Potential mechanisms by which statins may favorably affect liver histology and hepatic complications in NAFLD.
This cartoon highlights the pleiotropic effects of statins on the liver and the potential mechanisms that may concur in improving the key elementary pathological lesions of NAFLD, i.e. steatosis, inflammation and fibrosis, and its liver-related complications, i.e. portal hypertension and HCC [10,12,51,52].

3.1. Effects of statins on NAFLD elementary liver histology lesions

3.1.1. Clinical data

Several animal studies examining the impact of statins in NAFLD or NASH have shown promising results in the reduction of steatosis, inflammation and fibrosis [55]. The potential beneficial effect of statins on liver histology has also been investigated in some cross-sectional and interventional studies in humans (Table 2) [30,48,50,56–61]. Two recent cross-sectional studies, the first enrolling 346 patients with type 2 diabetes and biopsy-proven NAFLD and the second 1201 individuals who underwent liver biopsy for suspected NASH, yielded consistent results by showing that treatment with statins was associated with a reduced risk of NASH and fibrosis [30,61]. Of note, in both studies a dose-response effect of statin treatment intensity on liver damage protection was observed; in particular, higher intensity statins were associated with the greatest reduction in the risk of histological changes [30,61]. A longitudinal case-control retrospective study of 68 patients with NAFLD and elevated liver enzymes undergoing follow-up liver biopsies suggested that patients treated with statins exhibited a significant reduction of liver steatosis and stabilization of fibrosis stage despite a more severe metabolic profile compared to patients not taking statins [57]. Interventional trials testing the effect of statins on NASH would be difficult to design because patients with NAFLD commonly require treatment with statins to reduce CVR. Consistently, those few small, underpowered interventional studies of statins on NASH which have been conducted so far have yielded conflicting results. Several open label non-placebo controlled studies suggested that treatment with pravastatin, atorvastatin or rosuvastatin may significantly improve steatosis and inflammation in NASH [48,50,56]; conversely, other studies, including a small randomized placebo-controlled trial [58], failed to demonstrate a significant effect of simvastatin, pitavastatin or low-dose rosuvastatin on steatosis, necroinflammatory activity or stage of fibrosis in patients with NASH [58–60]. A Cochrane meta-analysis concluded that statins may improve aminotransferase levels and imaging findings in patients with NAFLD; however, data are insufficient to prove that statins are effective in improving NASH histology [62]. Sufficiently powered randomized controlled trials are needed to establish whether statins have a direct beneficial effect on liver histology. Meanwhile, a more recent large longitudinal study showing that statin use is associated with an independent and significant reduction in overall and liver-related morbidity and mortality in biopsy-proven NAFLD patients further supports the beneficial effects of statins [63].

3.1.2. Experimental data

Although data regarding the beneficial effects of statins in experimental steatosis are conflicting [52], the mechanisms through which statins may potentially reduce liver fat and triglycerides accumulation include: decreased LDL-cholesterol, triglycerides and free fatty acids; activation of sterol regulatory element-binding proteins (SREBPs), PPARα and β-oxidation [64]; protein kinase A (PKA)-mediated promotion of carbohydrate response element binding protein (ChREBP) nuclear exclusion and ChREBP DNA-binding activity reduction [65]; PKA-mediated increased expression of liver-type carnitine palmitoyltransferase 1 [65]; activation of Nogo-B receptor (NgBR) expression

Table 2
Studies assessing the impact of statins on liver histology in patients with nonalcoholic steatohepatitis.

Author, Year	Type of Study	Subjects studied	Statin used	Main results	Comments
Rallidis, 2004 [56]	Open label non-placebo controlled interventional study	5 patients with biopsy-proven NASH and abnormal liver enzymes	Pravastatin (20 mg daily) for 6 months	Among the 4 patients who gave consent to be re-biopsied at the end of the study, 3 had an improvement in the grade of inflammation and the fourth in the degree of steatosis	Pravastatin may have some beneficial effect on inflammation and steatosis in NASH
Ekstedt, 2007 [57]	Longitudinal retrospective case-control study (follow-up 10.3–16.3 years)	68 patients with NAFLD and abnormal liver enzymes undergoing follow-up liver biopsies, 17 of whom treated with statins	Different types and doses	Patients treated with statins exhibited a significant reduction of liver steatosis and stabilization in fibrosis stage despite a more severe metabolic profile with respect to patients not taking statins	Statins may stabilize fibrosis in NAFLD patients at high risk of progression
Hyogo, 2008 [48]	Open label non-placebo controlled interventional study	31 patients with biopsy-proven NASH and hyperlipidemia	Atorvastatin (10 mg daily) for 24 months	Among the 17 patients with follow-up liver biopsy, there was a significant improvement of liver steatosis and NAFLD activity score, whereas 4 patients had fibrosis worsening	Atorvastatin may have some beneficial effect on steatosis and activity in NASH
Nelson, 2009 [58]	Double-blind randomized placebo-controlled trial	16 patients with biopsy-proven NASH	Randomization to simvastatin (40 mg daily) (10 patients) versus placebo (6 patients) for 12 months	Among the 10 patients who completed the study and underwent the follow-up liver biopsy, no significant improvement in steatosis, necroinflammation and fibrosis was found between groups	Simvastatin does not seem to be an effective treatment for NASH
Hyogo, 2011 [59]	Open label non-placebo controlled interventional study	20 patients with biopsy-proven NASH and hyperlipidemia	Pitavastatin (2 mg daily) for 12 months	Among the 13 patients with follow-up liver biopsy, NAFLD activity score and fibrosis stage did not change significantly	Pitavastatin does not seem to be an effective treatment for NASH
Nakahara, 2012 [60]	Open label non-placebo controlled interventional study	19 patients with biopsy-proven NASH and hyperlipidemia	Rosuvastatin (2.5 mg daily) for 24 months	Among the 9 patients with follow-up liver biopsy, NAFLD activity score and fibrosis stage did not change significantly	Low-dose rosuvastatin does not seem to be an effective treatment for NASH
Kargiotis, 2015 [50]	Open label non-placebo controlled interventional study	20 patients with biopsy-proven NASH and metabolic syndrome	Rosuvastatin (10 mg daily) for 12 months	Complete resolution of NASH in 19 patients	Moderate-dose rosuvastatin may favour NASH resolution
Dongiovanni, 2015 [61]	Cross-sectional study	1201 individuals who underwent liver biopsy for suspected NASH, 107 of whom treated with statins	Different types and doses	Patients treated with statins were protected from steatosis, NASH and fibrosis. The use of higher intensity statins was associated with the greatest reduction in the risk of histological lesions. The protective effect of statins on NASH was stronger in subjects not carrying the I148 M PNPLA3 risk variant.	High-intenisty statins are associated with a reduced risk of steatosis, NASH and fibrosis. PNPLA3 genotype may influence the effect of statins on NAFLD histology.
Nascimbeni, 2016 [30]	Cross-sectional study	346 patients with biopsy-proven NAFLD and type 2 diabetes, 154 of whom treated with statins	Different types and doses	The use of statins was independently associated with a reduced risk of NASH (OR 0.57 [95% CI 0.32–1.01]) and significant fibrosis (OR 0.43 [95% CI 0.26–0.84]). The use of higher intensity statins was associated with the greatest reduction in the risk of histological lesions.	High-intensity statins are associated with a reduced risk of NASH and fibrosis in patients with diabetes mellitus

[66] and PKA-mediated phosphorylation of perilipin 5 (Plin5) [67]; increase in SREBP-2 driven autophagy through activation of patatin-like phospholipase domain-containing enzyme 8 (PNPLA8) expression [68].

Oxidative stress defines a prevalent pro-oxidant status resulting from an increased production of reactive oxygen species associated with impaired antioxidant defense; macromolecular damage and disruption of cellular redox signaling will ensue [69,70]. Statins are believed to exert beneficial effects against inflammatory-fibrotic liver changes which are pathogenically associated with increased oxidative stress [30,71]. Statins exert their anti-inflammatory activity thanks to multiple mechanisms [52,72–75], e.g. by: (a) decreasing the adhesion of leukocytes to endothelial and epithelial cells by inhibiting expression and binding of lymphocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule-1 (ICAM-1); (b) decreasing pro-inflammatory cytokines [such as tumour necrosis factor α (TNFα) and interleukin-6 (IL-6)] through impaired nuclear factor-kB (NF-kB) synthesis; (c) blocking the prenylation of key proteins necessary to the formation of lipid rafts and activation/growth of immune cells; (d) inhibiting the prenylation of small GTPases which results in decreased downstream signaling. Statins also decrease the level of oxidative and nitrosative stress by decreasing the serum concentration of LDL-cholesterol and its oxidation, and reducing the synthesis of inducible nitric oxide (NO) [52,76,77].

In experimental models, statins have antifibrotic effects via multiple mechanisms [75,78–82], which are partly indirect, through their anti-inflammatory activity and by restoring the sinusoidal endothelial function, and partly direct, via inhibiting the activity of hepatic stellate cells (HSCs) by: (a) blocking their activation and fibrogenic activity by affecting the paracrine signaling of hepatocytes on HSCs; (b) inducing their senescence; (c) inhibiting the RhoA/Rho-kinase pathway through Krüppel-like Factor 2 (KLF2) induction; and (d) regulating the transforming growth factor-β1 (TGF-β1)/Smad3 pathway [83].

3.2. Effects of statins on portal hypertension and hepatocellular carcinoma

3.2.1. Clinical data

Statins may possibly confer a certain level of protection not only from fibrosing NASH, but also against the development of cirrhosis and liver-related complications, such as the progression of portal hypertension, hepatic decompensation and HCC [51,55,84].

There is increasing experimental and interventional evidence that statins may significantly ameliorate portal haemodynamics by decreasing hepatic venous pressure gradient (HVPG) and improving liver perfusion in patients with cirrhosis [13,85,86]. A seminal controlled trial randomized 59 patients with cirrhosis and portal hypertension to simvastatin or placebo; simvastatin significantly reduced HVPG irrespective of treatment with beta-adrenergic blockers [85]. Of note, in a recent randomized trial of 158 cirrhotic patients receiving standard prophylaxis to prevent re-bleeding, the addition of simvastatin to standard therapy was not able to significantly reduce re-bleeding, but was associated with a survival benefit [87]. To further confirm the potential benefit of statins on the natural history of cirrhosis, two recent large meta-analyses consistently demonstrated that the use of statins was associated with a significant reduction of the risk of fibrosis, decompensated cirrhosis, and all-cause mortality in chronic liver diseases [88,89].

Data also suggest that statins may act as chemopreventive agents for HCC. Two meta-analyses consistently reported that statin use is associated with a 37–42% risk reduction of liver cancer [90,91]. Interestingly, another meta-analysis, which aimed to compare the chemopreventive effect of different statins, suggested that fluvastatin is probably superior to other treatment strategies in reducing the risk of HCC [92]. A very recent nationwide, nested case-control study from Korea confirmed the beneficial effect of statins on the development of HCC both in the general population and in individuals at high risk for HCC, particularly those affected by type 2 diabetes mellitus and those with liver cirrhosis [93]. However, randomized clinical trials in populations at high risk for HCC are warranted to confirm these important findings. Finally, statin use has also been associated with improved outcomes and survival in patients with HCC undergoing either surgical or non-surgical treatments [94,95]. Since HCC is a very heterogeneous condition owing to both diverse etiologies and molecular signatures which result in different biological profiles, before specific recommendations on the use of statins as chemopreventive agents for HCC are issued, studies accounting for all these modifiers are eagerly awaited.

In patients with cirrhosis awaiting liver transplantation, the use of statins is safe and is not associated with hepatic decompensation [96]. Following liver transplantation, proatherogenic hyperlipidemia is common (affecting up to 66% of patients) owing to genetic factors, changes in diet, development of metabolic syndrome and its components, cholestasis and immunosuppressants (e.g. cyclosporine) [97]. Consistently, liver transplant recipients are more exposed than the general population to cardiovascular events, warranting a personalized cardiovascular risk assessment in these individuals [97]. A combined treatment strategy including lifestyle changes and use of lipid-lowering agents can improve the lipid profile in these patients [97]. As specifically regards statins, few studies have clearly shown that they are safe and effective in improving the lipid profile also in the setting of liver transplantation [98,99]. Since NAFLD is a rapidly growing indication for liver transplantation and CVD is among the leading causes of death in liver transplant recipients, future studies will have to address the impact of statins on liver graft outcomes and patients survival.

3.2.2. Experimental data

Further to their effects on the structural, i.e. fibrotic components of chronic liver disease which eventually lead to portal hypertension, statins also affect the dynamic components of portal hypertension by modulating those pathways, such as RhoA/Rho-kinase and NO, which regulate vasomotor tone and the expression of KLF2 [71,81,85,100–103].

The risk of developing HCC also in non-cirrhotic stages of disease is one of the most dreadful features of the natural history of NAFLD [104]. In this regard, the notion that statins might also exert specific properties in the setting of NAFLD-HCC is of particular interest [105]. The mechanisms of this pleiotropic antineoplastic activity are multiple and complex and include: interference/inhibition of Myc, Akt; K-ras NF-kB and TNFα-mediated IL-6 production, as well as Hippo pathway effector TAZ, and extracellular signal–regulated kinase 1/2 (ERK1/2) and prevention of p21 and 27 breakdown in malignant cells followed by induction of cell cycle arrest; activation of the adenosine monophosphate-activated protein kinase (AMPK) and p38/mitogen-activated protein kinase (MAPK) pathways, and induction of p53-dependent apoptosis; inhibition of cell proliferation and adhesion through interference with cell membrane integrins and Rho-kinase; anti-angiogenic effect which is dependent on the context of chronic liver disease; effects on TGF-β1 and thyroid hormones regulation [105–108].

4. Conclusions

Confuting previous paradigms, which tended to over-emphasize the responsibility of statins in association with raised or worsened liver enzymes, recent data showing the low risk of DILI owing to statins, are reassuring and potentially disprove this notion by showing that NAFLD histology will often benefit from treatment with statins. Unfortunately, those data regarding the beneficial effect of statins on NAFLD histology mainly derive from experimental basic studies and limited evidence from cross-sectional studies or small underpowered interventional trials in humans. Epidemiological and experimental studies have identified statins among the few available candidate chemopreventive agents for HCC [10]. However, the clinical testing of statins has been hampered by the difficulties involved in conducting lengthy and costly studies [105].

Although the profile of efficacy remains uncertain, data on safety are reassuring and additional studies are eagerly awaited [109]. These should investigate the role of statins on hepatic outcomes in patients with NAFLD and determine whether statins should be used specifically to treat NAFLD and its liver-related (and potentially extrahepatic) complications [110]. This would probably lead to a modification of those currently available guidelines which are not including statins in the algorithm of management of patients with NAFLD/NASH [55]. In the meanwhile, we believe that, based on existing studies, statins should be used more liberally in NAFLD patients with dyslipidemia and increased CVR. Indeed, statins have proven safe in patients with raised liver enzymes and chronic liver diseases, including NAFLD, while retaining a specific and enhanced effectiveness for CVD prevention particularly among those patient populations with NAFLD and raised liver enzymes. In this regard, although pragmatic approaches to the diagnosis of NAFLD and its inherently associated CVR have been proposed [6], we urgently need to define whether CVR scoring systems which we currently use may reasonably be applied to individuals with NAFLD or if, alternatively, more specific scoring systems should be used to assess CVR in NAFLD.

In conclusion, future studies should firmly establish how the choice of the individual statin and the dose to be prescribed to the individual NAFLD patient might be tailored based on each patient's unique metabolic profile, the risk of developing primary or recurrent CVD and the risk of fibrosing NASH or liver-related complications.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

F.N. and A.L. conceived the paper, retrieved bibliographic material and wrote the manuscript; E.P., S.L., A.M., S.B., G.O. and F.C. participated in drafting the manuscript and revised the manuscript critically for important intellectual content; all Authors gave approval of the final version of the manuscript.

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