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EXPERT OPINION

Statins and nonalcoholic fatty liver disease: a bright future?

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease affecting up to 30% of adults in Western countries. NAFLD and mainly nonalcoholic steatohepatitis (NASH) are independent cardiovascular disease (CVD) risk factors; more of these patients are expected to die from CVD rather than from liver disease. The effect of statins on newer risk factors that may influence the pathobiology of liver damage in NASH is considered. These include microparticles, inflammasomes, gut–liver axis abnormalities and dietary lipids. Evidence suggests that statins induce NAFLD/NASH resolution and substantially improve symptom-free survival from CVD to a greater extent than in patients without NAFLD. However, large randomized clinical trials are needed to verify these findings.

Keywords: cardiovascular disease, inflammasomes, microparticles, nonalcoholic fatty liver disease, statins

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Non-alcoholic fatty liver disease (NAFLD) is the commonest chronic liver disease affecting adults (20 – 30% and 75 – 100% in patients with metabolic syndrome [MetS] or diabetes mellitus [DM]) and children (up to 10%) [1]. In NAFLD, > 5% of liver tissue consists of triglycerides (TGs), in the absence of excessive alcohol consumption or other liver disease [1]. Lipotoxicity has been implicated in the development of several obesity-related diseases, including NAFLD [2]. NAFLD is a spectrum of conditions with histological findings varying from steatosis to steatosis with inflammation (nonalcoholic steatohepatitis [NASH]; represents 20% of the NAFLD population), necrosis, fibrosis or cirrhosis that can, rarely, progress to hepatocellular carcinoma [2]. NAFLD and NASH are viewed as the hepatic manifestations of MetS and are closely related to cardiovascular disease (CVD) [3], to the extent that NAFLD/NASH and CVD are considered as two aspects of a shared disease [4]. More patients with NASH die from CVD than from liver disease [3,4]. Existing data suggest that the accumulation of excessive TGs and hepatic injury occur in parallel but independently.

Inflammation plays a role in the progress of NAFLD to NASH, suggesting a pathophysiological mechanism similar to that of atherosclerosis [4]. The common mechanisms between NAFLD and CVD relate to a contribution of the inflamed liver to the pathogenesis of CVD [4]. Thus, several factors which promote atherosclerosis, vascular inflammation, endothelial dysfunction and insulin resistance are present in NASH patients and correlate with histological severity, independently of the traditional CVD risk factors and components of MetS; these include low adiponectin levels and increased levels of fibrinogen, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), resistin, plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6) and angiotensin [4].

The National Registry of Myocardial Infarction IV, based on 174,635 patients with acute coronary syndromes, showed that those who received statin therapy

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within the first 24 h of hospitalization had a significantly lower rate of early complications and in-hospital mortality compared with those who did not receive this treatment [5]. It was hypothesized that this early benefit could be attributed to the pleiotropic effects of statins (e.g., on the inflammatory process, endothelial function or coagulation-fibrinolysis) [5]. In the same review, we presented data relating to various mediators, either derived from the immune system or adipose tissue, that seem to play an important role in the development of NAFLD and related inflammation [4]. At a clinical level, we had shown that 1-year multifactorial intervention in MetS patients with NAFLD diminishes the biochemical and ultrasonographic evidence of NAFLD and substantially reduces CRP levels [5]. These data suggested that statins are an option for the treatment of NAFLD/NASH and CVD. However, this approach has not been widely adopted and requires additional supportive evidence.

Recently, more detailed data on the pathogenesis of NASH were reported implicating microparticles (MPs), inflammasomes, abnormalities of the gut–liver axis and dietary lipids [1]. Given that NAFLD/NASH and CVD share some pathogenetic features, the question arises as to whether there are common treatments (e.g., statins).

MPs are small heterogeneous membrane-bound particles released from dying or activated cells [1]. Patients with NASH had significant increases in circulating MPs from natural killer T cells, macrophages-monocytes (CD14) and hepatocyte-derived MPs (released as a response to lipotoxicity). These MPs act as a link between hepatocyte lipotoxicity, inflammation, pathological angiogenesis and fibrosis [1]. MP numbers are related to the severity of inflammation and the histological status of NASH [6].

Circulating MPs from patients with CVD (myocardial infarction [MI]), DM, MetS or obstructive sleep apnea induce endothelial dysfunction by decreasing nitric oxide (NO) activity and bioavailability [1]. MPs are present within atherosclerotic plaques, promoting coagulation after plaque erosion and rupture [1]. Moreover, plaque MPs, exhibit proteolytic, angiogenic and inflammatory effects which are potential players in plaque vulnerability and rupture. MPs display several properties that can contribute to CVD initiation, progression and its clinical manifestations. Statins decrease circulating MPs and this could, at least in part, explain their anti-inflammatory and anticoagulant role [7]. In this context, a dose-related response of atorvastatin was recorded on endothelial-derived MPs (EMPs) in patients with dilated cardiomyopathy [8]. Atorvastatin reduced the levels of circulating EMPs independently of its action on lipids, oxidized low density lipoprotein and CRP [8]. Furthermore, statins may inhibit initiation of thrombin generation partly through a MP-dependent mechanism [8]. Thus, statins could ameliorate hepatic inflammation in patients with NAFLD/NASH, while also tackling a CVD risk factor [8]. More work is needed to confirm or refute such a relationship.

Inflammasomes are large caspase-1-activating multiprotein complexes that sense exogenous and endogenous danger signals through pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Inflammasomes regulate the cleavage of effector proinflammatory cytokines (pro-IL-1β and pro-IL-18) [9]. Most DAMPs trigger the generation of reactive oxygen species, which activate the nucleotide-binding oligomerization-domain protein-like receptors protein 3 (NLRP3) inflammasome, and this in turn activates IL-1β and IL-18 [9,10]. IL-18, the NLRP3 and the NLRP6 inflammasomes directly promote NAFLD to NASH progression, as well as aspects of MetS (e.g., weight gain and glucose homeostasis) via modulation of the gut microbiota; this results in accumulation of bacterial products in the portal circulation [9]. The immune system regulates colonic microbiota via a mechanism that requires an inflammasome, involving NLRP6, apoptosis-associated speck-like protein and caspase-1, and leads to the cleavage of pro-IL-18 [11]. All the above suggest that there is a regulatory sensing system in the colon, dependent on the NLRP6 inflammasome. Alterations of this sensing system may affect the composition of the microbiota leading to a shift toward inflammation [11]. The liver, being a first-pass organ, is exposed to the highest concentration of portal system products such as PAMPs and is vulnerable to these effects, particularly when preconditioned by lipid accumulation in hepatocytes [9]. This 'gut–liver axis', driven by alterations in gut microbial ecology, may be another mechanism for progression of NAFLD to NASH. Moreover, IL-1β activated by NLRP3 inflammasome promotes insulin resistance, atherosclerotic plaque formation and β-cell death. Finally, IL-1β is implicated in (liver) fibrosis [9]. Caution is needed not to over-interpret these findings in the context of the pathogenesis of NAFLD.

Inflammasome activation can also contribute to CVD pathogenesis [12]. Cholesterol esters within the necrotic core of an atheromatic plaque are related to lesion development. However, recent data suggest that crystals within very early plaques cause membrane rupture, leading to NLRP3 inflammasome activation, IL-1β release and progression of atherosclerosis [12]. As described above, IL-1β is a potent proinflammatory cytokine mainly produced by macrophages. It causes upregulation of adhesion molecules on endothelial cells, which recruit immune cells, and induces a plethora of additional proinflammatory mediators. IL-1β is activated by inflammasomes, which through the activation of caspase-1 activates IL-1β, IL-18, or both, thus leading to their secretion. During atherogenesis, chronic inflammation and infiltration of the developing plaque by monocytes lead to accumulation of macrophages. IL-1β expression is related to CVD severity, and as a mediator of the inflammatory cascade, it induces secretion of other pro-atherogenic cytokines, chemokines and endothelial expression of adhesion molecules and NO synthase (NOS) [12].

In a recent study on mice with MetS and fibrotic NASH, cholesterol-lowering drugs (atorvastatin + ezetimibe) reduced stress-activated c-Jun N-terminal kinase activation, hepatocyte injury/apoptosis, inflammation and fibrosis, thus achieving histological reversal of NASH in about 80% of mice and near complete reversal of liver fibrosis [13]. This was also accomplished by decreased liver injury, hepatocyte apoptosis, nuclear factor kappa β activation, adhesion molecule expression, monocyte chemotactic protein 1 levels and macrophage infiltration [13]. The ezetimibe + atorvastatin combination also reduced serum insulin levels and increased serum adiponectin levels – factors that could impact on the reduction in liver weight associated with removal of hepatic lipids [13].

Statins can block the activation of monocytes and their conversion to macrophages [4]. They also attenuate intracellular adhesion molecule-1, independent of any effects on NO bioavailability, at a level of inflammation earlier than that of inflammasome generation, and thus block the synthesis of atherogenic ILs (e.g., IL-6) [4,14]. Further to the reduction of proinflammatory cytokines expression, statins upregulate the expression of anti-inflammatory cytokine IL-10 and improve the balance between TNF-α/IL-10 post-MI in animal models [14].

The anti-inflammatory effect of statins on the vasculature is widely accepted [15]. Statins increase endothelial NOS and plasminogen activator activity, decrease PAI-1 and peroxisome proliferator-activated receptors expression, while reducing endothelin-1 synthesis and vascular smooth muscle migration/proliferation as well as inhibiting platelets. Statins also inhibit monocyte/macrophage proliferation and activity as well as matrix metalloproteinases [15]. Thus, statins seem to have a beneficial effect on both NASH and CVD pathogenesis (the stone that kills two birds?).

The incretins glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) are released by the gastrointestinal tract which increases glucose-mediated insulin secretion, while decreasing hepatic glucose production [1]. Dipeptidyl peptidase-4 (DPP-4) cleaves GLP-1 and GIP leading to their rapid deactivation [1]. GLP-1 agonists and DPP-4 inhibitors are used for the treatment of type 2 DM [1]. Atorvastatin has been shown to be a competitive inhibitor of porcine DPP-4 *in vitro* [16]. This effect appears to be structure-specific and therefore not every statin may exert this action. It follows that structure optimization could lead to novel statin-like DPP-4 inhibitors [16].

A significant increase in the n-6:n-3 fatty acid ratio was reported in patients with NAFLD [1]. It seems that NAFLD and NASH have a distinct plasma lipidomic signature [17]. A stepwise increase in lipoxygenase (LOX) metabolites characterizes the progression from normal to NAFLD and then to NASH [17]. Although increased lipogenesis, desaturases and LOX activities characterize NAFLD and NASH, impaired polyunsaturated fatty acid metabolism and non-enzymatic oxidation are further associated with progression of NAFLD to NASH [17]. However, once NASH is established, a diet rich in n3 fatty acids and a combined weight loss of ≥ 9% can improve steatosis and have a modest effect on hepatic inflammation but does not appear to reduce the stage of fibrosis [18].

All the above-mentioned evidence mainly refers to mechanisms of disease. These need to be supported by clinical evidence. The Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) study (n = 1600) randomized patients with coronary heart disease (CHD) into two groups: the usual care group, treated by physicians chosen by patients and the structured care group (treated with all other secondary prevention treatments, similar with those of usual care) plus atorvastatin (with dose titration to achieve the low-density lipoprotein cholesterol (LDL-C) goal of < 100 mg/dl; 2.6 mmol/l) [19]. In a *post hoc* analysis of GREACE, 227 patients with NAFLD at baseline were treated with a statin (mainly atorvastatin) and 210 patients were not treated [19]. Those treated with a statin had a substantial reversal of NAFLD, as demonstrated by ultrasonography and serum transaminases, during a 3-year period [19]. Moreover, statin treatment reduced CVD morbidity/mortality in NAFLD patients to a greater extent than in those without NAFLD (68 vs 39%, p = 0.007) [19]. In GREACE, we observed three statin-related benefits: resolution of NAFLD, significant CVD reduction and overcoming the fear that may deprive patients with elevated liver enzymes from life-saving treatment with statins. A similar benefit of statin treatment was recorded in primary prevention (mainly with MetS) in the Assessing the Treatment Effect in Metabolic Syndrome without Perceptible Diabetes (ATTEMPT) study [20]. This treatment was atorvastatin-based, but included a multifactorial intervention character, controlling other NAFLD risk factors (MetS, obesity, arterial hypertension), besides dyslipidemia. However, in the control group with similar treatments, but without atorvastatin therapy, there was a deterioration of NAFLD (expressed as increased liver enzyme activity and steatosis on liver ultrasonography) [20]. In this study, CVD events were practically nonexistent in patients on atorvastatin treatment reaching LDL-C target [20]. In an earlier small study (n = 186), it was reported that multifactorial treatment (including a statin) simultaneously improved the features of the MetS and NAFLD [21]. This led to the suggestion that NAFLD is the hepatic manifestation of MetS [21].

In a preliminary report involving five patients with biopsy-proven NASH, rosuvastatin (10 mg/day) gradually improved (by the third month) liver enzymes which returned to normal. There was a complete resolution of NASH in the second biopsy in four patients [18]. The CVD risk status was considered as low after treatment [18].

Expert opinion

NAFLD, NASH and CVD share common risk factors. Until recently, the pathogenesis of NASH was not entirely clear. Recently, a review presented evidence that MPs,

inflammasomes, gut–liver axis and serum lipid composition play a role in the pathogenesis of NASH. Statins can improve some of these risk factors and thus might prevent or treat NASH. Furthermore, statins improve symptom-free survival from CVD in patients with NAFLD to a greater extent than in those with normal liver structure and function. Such a 'double' benefit would be clinically relevant since patients with NAFLD may be deprived from statin treatment due to elevated transaminase activity. For example, prescribers may feel that statins will worsen liver function. This potential new indication for statins needs to be validated in large randomized controlled trials.

Declaration of interest

VG Athyros has no disclosures. D Mikhaildis has given sponsored talks for MSD and Genzyme. N Katsiki has attended conferences sponsored by Novartis, Genzyme and Pfizer. A Karagiannis has given sponsored talks for Novartis, Pfizer, Menari and Astra Zeneca.

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