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TOPIC HIGHLIGHT

2015 Advances in Nonalcoholic Fatty Liver Disease

Cardiovascular risk across the histological spectrum and the clinical manifestations of non-alcoholic fatty liver disease: An update

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is considered to be an independent cardiovascular disease (CVD) risk factor. However, simple steatosis has a benign clinical course without excess mortality. In contrast, the advanced form of NAFLD, non-alcoholic steatohepatitis (NASH) with liver fibrosis increases mortality by approximately 70%, due to an increase in CVD mortality by approximately 300%. Chronic kidney disease (CKD) may be caused by NAFLD/NASH and it substantially increases CVD risk, especially in the presence of type 2 diabetes mellitus. Moreover, CKD may trigger NAFLD/NASH deterioration in a vicious cycle. NAFLD/NASH is also related to increased arterial stiffness (AS), an independent CVD risk factor that further raises CVD risk. Diagnosis of advanced liver fibrosis (mainly by simple non-invasive tests), CKD, and increased AS should be made early in the course of NAFLD and treated appropriately. Lifestyle measures and statin treatment may help resolve NAFLD/NASH and beneficially affect the CVD risk factors mentioned

above.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Cardiovascular disease; Liver fibrosis; Statins; Chronic kidney disease; Arterial stiffness; Inflammation

Core tip: Non-alcoholic fatty liver disease (NAFLD) is an independent cardiovascular disease (CVD) risk factor. However, simple steatosis has a rather benign clinical course, while its advanced form, non-alcoholic steatohepatitis (NASH) substantially increases total mortality, mainly due to increased CVD events. In this review we propose the use of statin treatment for NASH, given its beneficial effect on NAFLD/NASH and CVD risk. There are data suggesting biopsy proven amelioration of NASH and normalization in liver ultrasonography and enzyme values as well as improvement of chronic kidney disease and arterial stiffness that usually accompany NASH and exacerbate CVD risk.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), a term describing the most common liver disease (affects approximately 15%-30% of the general population in Western Countries), is characterized by accumulation of fat (> 5%) in liver cells in the absence of excessive alcohol intake, chronic viral hepatitis or other liver disease[1,2].

NAFLD has a high prevalence (75%-100%) in populations with pre-existing metabolic conditions characterized by insulin resistance (IR) such as obesity, metabolic syndrome (MetS) or type 2 diabetes mellitus (T2DM)[1,2]. NAFLD prevalence continues to increase due to the obesity and T2DM pandemic[1].

Histological manifestations of NAFLD range from simple steatosis, non-alcoholic steatohepatitis (NASH; characterized by hepatocellular necroinflammation and ballooning), liver fibrosis and cirrhosis, which in some cases may progress to hepatocellular carcinoma[3]. Despite its high prevalence, the pathogenesis of steatosis and the progression to NASH with fibrosis/cirrhosis, and the natural history of NAFLD are not yet entirely clear (Figure 1)[4]. The evidence[3] suggests that NASH prevalence ranges from 3%-5% (> 20% of NAFLD cases) in the general population, however this rises to 37% in the morbidly obese[5].

NAFLD/NASH is considered as the hepatic manifestation of MetS, and are closely related to cardiovascular disease (CVD)[6], to the extent that NAFLD/NASH and CVD are viewed as two aspects of a shared disease[6]. More patients with NASH die from CVD than from liver disease[6,7]. Nevertheless, CVD risk level is not the same across the entire histological and clinical spectrum of NAFLD[8]. It seems that simple steatosis and NASH are considered disease states of different CVD risk involvement, each with different consequences, linked to environmental and genetic factors[9,10]. The multiple parallel hit theory suggests that NASH may occur directly in many individuals without previous simple steatosis[9,10]. It is possible that NASH can happen in the absence of simple steatosis because inflammation related to NASH pathogenesis might originate in the gut microbiota, in response to the prime neutrophil chemokines and macrophage-inflammatory protein-2, inflamed adipose tissue and to circulating inflammatory cells. In any case, the identification and management of high CVD risk patients with NAFLD/NASH remains a clinical challenge[8]. This narrative review considers this key issue, referring only to recent advances in diagnosis, risk stratification and treatment of NAFLD/NASH[9,10].

DEGREE OF LIVER FIBROSIS AND CVD RISK

The United States National Health and Nutrition Examination Survey (NHANES) was conducted in 1988-1994 and followed-up 11154 participants until the end of 2006 (mean follow up: 14.5 years). The findings suggest that the degree of liver fibrosis is related to clinical outcome in NAFLD/NASH patients[7]. The diagnosis of NAFLD was based on liver ultrasonography and the degree of liver fibrosis in NAFLD patients was determined without a biopsy by the NAFLD fibrosis score (NFS), the AST-platelet ratio index (APRI) and the FIB-4 score[7]. The ultrasonographic prevalence of NAFLD was 34% (if projected to the entire United States adult population this represents 43.2 million Americans), however, if only people with moderate to severe steatosis were included in NAFLD diagnosis its prevalence falls to 20.2%, projecting to 25.6 million United States adults[7]. The majority of NAFLD patients (71.7%) had simple steatosis, while 28.3% had NFS values suggesting an intermediate (25.1%) or high (3.2%) level of liver fibrosis[7]. These data project to 10.8 million United States adults with NAFLD with some evidence of advanced fibrosis, 9.4 million with an intermediate probability and 1.4 million with a high probability of fibrosis[7]. The 15 years follow-up showed that NAFLD in the form of steatosis was not related with higher total mortality compared with those without NAFLD (adjusted HR = 1.05, 95%CI: 0.93-1.19, *P* =

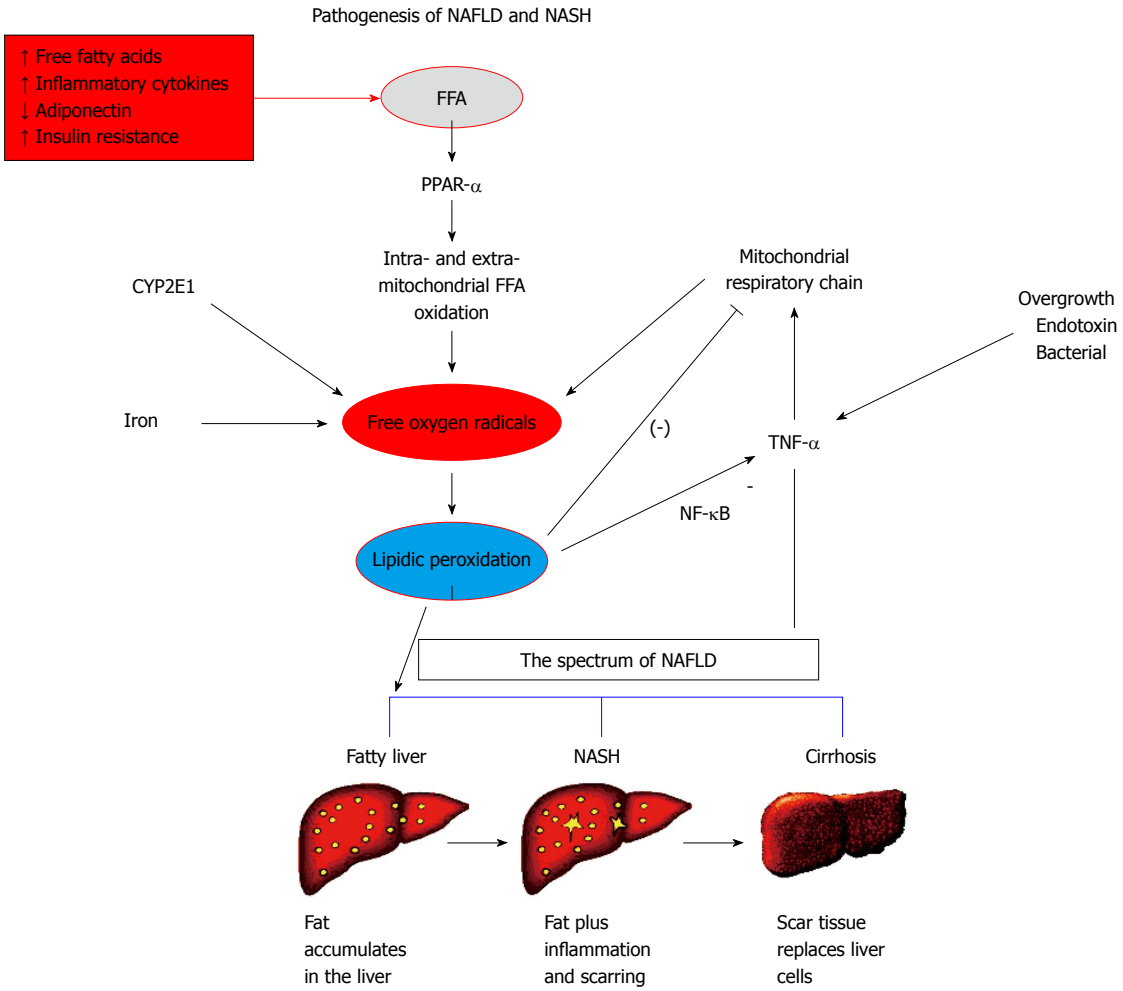

Figure 1 Factors that contribute to the pathogenesis of non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; TNF-α: Tumor necrosis factor-alpha; CYP2E1: Cytochrome P450 2E1; FFA: Free fatty acid; NF-κB: Nuclear factor kappa-light-chain-enhancer.

NS)[7]. In contrast, there was a progressive increase in total mortality with increasing levels of liver fibrosis scores [adjusted HR = 1.69, 95%CI: 1.09-2.63 for the NFS, 1.85 (1.02-3.37) for the APRI, and 1.66 (0.98-2.82) for the FIB-4], as compared with subjects without fibrosis[7]. The increase in mortality was mainly due to increased CVD mortality (HR = 3.46, 95%CI: 1.91-6.25 for NFS; 2.53, 1.33-3.83 for APRI; 2.68, 1.44-4.99 for FIB-4)[7]. Thus, prospective data from this US representative cohort suggest that steatosis per se, does not increase total and CVD mortality, while NASH, with advanced fibrosis as evaluated by non-invasive markers, was related to increased total and (mainly) CVD mortality[7].

The fact that NAFLD at the stage of simple steatosis has a benign clinical course without excess mortality has been reported 10 years ago[11]. Also, the fact that NASH with liver fibrosis was related to increased overall and CVD mortality was established by studies with a long-term follow-up (up to 28 years)[12,13]. Moreover, fibrosis or even cirrhosis was found in 15%-50% of NASH patients on their index biopsy, suggesting that a good portion of NASH patients develop progressive liver disease that could lead to liver-related mortality[14,15]. A study reporting survival of biopsy proven NAFLD or alcoholic fatty liver disease (AFLD) after 24 and 20 years of follow-up, respectively, showed that CVD was the most common cause of death (48%) in NAFLD patients, while liver-related death was recorded in 7% of these patients[16]. In contrast, AFLD patients had a liver-related death rate of 36% and CVD death rate of 32%[16]. NASH patients with moderate or severe fibrosis at baseline showed a worse survival rate than patients with none or mild fibrosis at baseline (adjusted HR = 2.09, $P = 0.01$)[16].

Liver biopsy is the gold standard for the diagnosis of NAFLD or NASH[16]. The classification in liver biopsy is as follow: Steatosis should have a > 5% fat content in the liver biopsy. Fibrosis stage was defined as follows: 0 = none, 1 = perisinusoidal or periportal fibrosis, 1A = mild perisinusoidal fibrosis, 1B = moderate perisinusoidal fibrosis, 1C = portal/periportal fibrosis, 2 = perisinusoidal - portal/periportal fibrosis, 3 = bridging fibrosis, and, 4 = cirrhosis[17]. However, it is not possible to perform a liver biopsy in all patients with NAFLD (a considerable proportion of the general

population); not all patients need a liver biopsy and many will not consent. Thus, non-invasive tests can be used instead to evaluate the stage of fibrosis and consequently the overall risk of these patients[18]. A recent study evaluated the usefulness of 4 validated non-invasive scoring systems that were originally designed to distinguish patients from those without advanced liver fibrosis in comparison with the results of liver biopsy[18]. Thus, 310 biopsy proven NAFLD/NASH patients were followed for median period of 105 mo. The 4 tests were the 3 used in the United States National Health and Nutrition Examination Survey[7], NFS, APRI, and FIB-4[19,20], plus the more recently introduced BARD score[21]. These are calculated using the original published formulas[19-21]. The score of these simple non-invasive tests were useful for the identification of NAFLD patients in this study who are at increased risk for total and liver-related mortality and predicted clinical outcome successfully[18]. These results were confirmed by a meta-analysis of 32 studies evaluating the diagnostic accuracy of these 4 non-invasive tests in comparison with the results of liver biopsy[22]. Results of this evaluation suggested an excellent sensitivity and specificity of these tests[22]. Thus, with the use of these 4 simple tests NAFLD patients can be evaluated for both CVD risk and progressive liver disease risk[22]. These tests can also divide NASH patients into those with and those without advanced fibrosis and therefore increased overall risk, indicating which patients need more intensive therapy[22]. It seems that these data were lost in the large number of papers on NAFLD, which has dramatically increased during the last 5 years. The vast majority of the papers or the majority of studies analyzed in a review on the NAFLD and CVD association, include NAFLD patients diagnosed by ultrasonography or alanine aminotransferase (ALT) levels[23,24]. These usually report an increased CVD risk in NAFLD patients, however it is not clear which NAFLD patients shape this risk: all NAFLD patients or those with (advanced) fibrosis? Only a few studies identify this association and also indicate NAFLD patients at risk of systemic complications, based on the 4 simple tests mentioned above to distinguish NAFLD patient with liver fibrosis[25]. One of these studies used the NFS and the FIB-4 scores to separate 1559 NAFLD patients that included those with high possibility of liver fibrosis (group 1) and those with a low probability (group 2)[25]. In group 1 the prevalence of CVD at baseline was 7.7% *vs* 2.3% (NFS, $P = 0.002$) and 9.0% *vs* 2.3% (FIB-4, $P = 0.0012$)[25]. The prevalence of T2DM at baseline was in group 1 in comparison with group 2, 31.5% *vs* 3.1% (NFS, $P < 0.0001$) and 17.0% *vs* 4.7% (FIB-4, $P < 0.0001$)[25]. New onset diabetes (NOD) prevalence was 4.5% *vs* 1.2% (NFS, $P = 0.034$) and 3.6% *vs* 1.2% (FIB-4, $P = 0.11$), and of CVD in these patients was 5.0% *vs* 0.9% (NFS, $P = 0.0019$) and 5.4% *vs* 0.9% (FIB-4, $P = 0.0034$)[25]. This study brings forward another issue: that of pre-existing T2DM and the risk of NOD according to the degree of liver fibrosis in NAFLD patients; diabetes further increases the risk of CVD morbidity and mortality in NAFLD and MetS patients[26]. This can also be seen from the other way around: in T2DM patients the prevalence of NAFLD is 75%-100%, of NASH 63%-87%, liver fibrosis 22%-60%, and advanced liver fibrosis (4%-9%)[27], according to the number of MetS components, visceral obesity, older age, increased duration of T2DM, and the presence of family history of T2DM[27]. This is a vicious cycle leading from NAFLD/NASH to T2DM and vice versa. In any case the presence of NAFLD, and especially with (advanced) liver fibrosis, in T2DM patients is associated with increased overall (CVD and liver-related) mortality[27]. Given that an increase in the adherence to multiple interventions in patients with T2DM is feasible and effective in better controlling the disease, as shown in a best practice study[28], and that similar measures may improve NAFLD/NASH[26] this is an interesting implication for the treatment of both diseases[28-31].

We need to abandon the idea that elevated liver enzymes and steatosis on ultrasonography alone could define CVD and liver-related risk; we need to calculate the overall risk of NAFLD/NASH patients with the use of the 4 simple tests, routinely available in clinical practice[32]. We need a pragmatic approach to diagnosis and staging of NAFLD so that patients at risk of complications can be identified[32]. This approach has implications for both diagnosis and treatment[33].

NAFLD, chronic kidney disease and CVD risk

The prevalence of chronic kidney disease (CKD) among the general population in the United States is 13% (that of early stages of CKD, including stage 3, is 11%)[34], in Europe it is similar[35], while in Japan it is much higher; 20% of the adult population is estimated to have CKD stage 3-5 [glomerular filtration rate (GFR) < 60 mL/min per 1.73 m^2][36]. In total, there seem to be more than 1.1 million patients with end-stage-renal disease (ESRD) worldwide[37]. CKD is an independent CVD risk factor substantially increasing its morbidity and mortality, to the degree that it is considered as a coronary heart disease (CHD) risk equivalent[38]. CVD is the leading cause of morbidity (40% of hospitalizations) and mortality (50% of deaths) in CKD patients[37,38]. Less than a half of CKD patients have develop ESRD, because most of them die from CVD before they develop ESRD[37,38].

NAFLD is considered to be a risk factor for CKD and is associated with an increased prevalence and incidence of CKD[37,39]. In a community-based study involving 2103 patients with T2DM the prevalence of stage 3 or higher of CKD was 15% among patients with ultrasound-diagnosed NAFLD *vs* 9% ($P < 0.001$) among T2DM patients without NAFLD, after adjustment for numerous baseline confounding factors and

independent traditional CKD risk factors[40]. Another study evaluated 1361 subjects with an abnormal oral glucose tolerance test (OGTT) on routine screening[41]. Participants with ultrasound-diagnosed NAFLD had a higher prevalence of microalbuminuria compared with patients with impaired glucose tolerance who did not have NAFLD (19% *vs* 6.3% in abnormal OGTT subjects; 32.6% *vs* 4.5% in newly diagnosed T2DM patients; $P < 0.0001$) after adjusting for several classical risk factors[41]. These results suggest that NAFLD is a predictor of another CKD manifestation, microalbuminuria, in patients with prediabetes or T2DM[41].

Two studies from the NHANES 2001 through 2006 investigated the association between serum surrogate markers of NAFLD, gamma-glutamyl-transpeptidase (GGT) and bilirubin concentrations, and CKD in a (United States) nation-wide representative sample of 13188 adults[42,43]. Serum GGT elevation was associated with an increased odds of CKD (OR = 2.38, 95%CI: 2.02-2.80, $P < 0.0001$)[42], while total bilirubin levels were independently related with both decreasing estimated-GFR and increasing albuminuria in United States adults[43].

A recent review suggests that NAFLD, and mainly NASH, is related with an increased and independent risk of developing CVD, T2DM, CKD, and colorectal cancers[44]. Finally, in a meta-analysis, which included 33 studies with 63902 participants, NAFLD was associated with an increased risk of prevalent (OR = 2.12, 95%CI: 1.69-2.66) and incident (HR = 1.79, 95%CI: 1.65-1.95) CKD[45]. NASH was related to a higher prevalence (OR = 2.53, 95%CI: 1.58-4.05) and incidence (HR = 2.12, 95%CI: 1.42-3.17) of CKD than simple steatosis[45], and advanced fibrosis in NASH was associated with an even higher prevalence (OR = 5.20, 95%CI: 3.14-8.61) and incidence (HR = 3.29, 95%CI: 2.30-4.71) of CKD than NASH without advanced fibrosis[45]. These data suggest that the presence and the severity of NAFLD/NASH and advanced fibrosis are clearly related with an increased risk and the severity of CKD[45].

Recent studies suggest the NAFLD/NASH is characterized by inflammation of the liver which may secrete proinflammatory, pro-fibrogenic, and anti-fibrinolytic substances, including fetuin-A, tumor necrosis factor-alpha (TNF-α), and plasminogen activator inhibitor-1 (PAI-1), all causing kidney injury[46]. The above mentioned meta-analysis also found that even mild renal impairment may promote NAFLD generation, within a vicious cycle, with unfavourable CVD and metabolic consequences[45], suggesting that CKD *per se* may contribute to the pathogenesis of NAFLD[45,47]. It has been shown in male Sprague-Dawley rats that nephrectomy results in a substantial dysregulation of hepatic fatty acid metabolism, steatohepatitis, IR, glucose and lipid metabolism aberrations, early even prior to glomerulosclerosis and CKD development[47].

Moreover, in liver transplant recipients the odds of developing CKD is high, while the risk of death in these patients increases exponentially when GFR is < 30 mL/min per 1.73 m^2 (HR = 2.67 and 5.47; 95%CI: 1.80-9.65, for stage 4 and 5, respectively)[48]. Given that available therapeutic options to reverse CKD are restricted, it should be emphasized that there is a need for hepatologists to diagnose CKD early in patients with chronic liver disease, mainly NAFLD, to optimize management aimed at delaying CKD progression[49]. In a large registry including 1120295 adults it was estimated that the adjusted HR for hospitalizations is high and for death in stage 5 CKD patients reaches 5.9 (95%CI: 5.4-6.5), while that for overt atherosclerotic CVD is 3.4 (95%CI: 3.1-3.8) compared with subjects with normal renal function[50], suggesting a low quality of life and a reduced life expectancy[50]. It has also been shown that stage 3 or higher diabetic nephropathy is related to an annual mortality rate of 20%, similar only to that of cancer[51]. If a patient has T2DM and CKD plus NAFLD/NASH (clinical practice suggests that almost all patients with diabetic nephropathy have NAFLD) the CVD burden is even greater[45,52,53].

Thus, NAFLD and CKD share some key cardiometabolic risk factors and it is suggested that they have common pathophysiological mechanisms; one can lead to the other and their co-existence leads to a geometrically increased CVD risk in patients that have both conditions, especially in those with metabolic disorders such as T2DM[37,39,45,52,53]. Given that there is available treatment of NAFLD[54-56] and CKD (up to stage 3)[57], that also prevents CVD or its complications[58,59], especially in patients with T2DM with increased CVD risk[60,61], hepatologists, nephrologists, and cardiologists should place additional emphasis on the early diagnosis of both NAFLD and CKD[62,63].

Another issue is that elevated serum uric acid (SUA) levels, related to renal function and T2DM[64-66], may play a role in the pathogenesis of NAFLD. There seems to be a link between elevated SUA levels and MetS/NAFLD[67-69]. Given that NAFLD, CKD, and elevated SUA levels are implicated in increased CVD risk, attention should be given to SUA within the treatment of NAFLD[68-71]. It has been reported that some lipid and blood pressure lowering treatments that decrease CVD risk and improve/preserve renal function, while improving NAFLD, reduce SUA levels with their off-target effects[68-73]. These specific drugs should be preferred for the treatment of NAFLD risk factors, such as arterial hypertension or dyslipidaemia.

NAFLD, ARTERIAL STIFFNESS AND CVD RISK

NAFLD was found to be an independent predictor

of faster progression of arterial stiffness (AS), even after adjusting for other CVD risk factors, thus further increasing CVD risk. Pulse Wave Velocity (PWV), a measure of AS, is independently associated with increased CVD risk across several patient groups and even in the general population, in both genders[74-76]. NAFLD is associated with AS, as evaluated by PWV, even in a non-obese, non-hypertensive, and non-diabetic young and middle-aged (Chinese) population[77]. NAFLD patients with severe liver fibrosis have the higher increase in AS[78]. Moreover, in patients with stage 3-5 CKD, PWV is much higher than in patients with CKD stage 1-2 and constitutes a major clinical determinant of CVD event rate and severity, independently of traditional CVD risk factors[79,80]. The pathogenesis of AS in NAFLD is not clear. One mechanism might be related to the systemic inflammation linked to NAFLD, and mainly NASH with fibrosis[78], which seems to have an adverse effect on arterial compliance; high-sensitivity C-reactive protein (hsCRP) and pro-inflammatory cytokines may have adverse effects on the elastic properties of the wall of large arteries[81]. Arterial compliance was low in NAFLD patients with elevated hsCRP, while NAFLD with low hsCRP had no effect on arterial compliance[81]. Central obesity was a vital determinant for both increased AS and elevated hsCRP levels in NAFLD patients[81]. Another issue is whole blood viscosity (WBV), a predictor of CVD events[82]. WBV was shown to be increased in NAFLD and to be independently related with AS, even after adjusting for other CVD risk factors[82]. This association between WBV and AS has been shown in T2DM patients also, which comprise a great portion of NAFLD patients[83]. Thus, detection of abnormal WBV and AS should be performed early within risk stratification in NAFLD patients[82].

There are data suggesting that the older theory on AS pathogenesis (AS is a result of large artery atherosclerosis) is not correct[84]. Stiff arteries suffer from arteriosclerosis, which is different from atherosclerosis, and this is also verified by the fact that there is little or no association between PWV and traditional CVD risk factors, except for age and arterial hypertension[84]. Additionally, PWV does not increase during the early stages of large artery atherosclerosis, but it is increased during the advanced atherosclerotic plaque period, probably due to arterial (aortic) calcification (AC)[84]. AC is a common complication of CKD and ESRD, and the extent of AC in the general population and in patients with CKD is predictive of subsequent CVD mortality beyond traditional CVD risk factors[85]. Thus, late atherosclerosis and CKD both promote AC and increase AS[84,85].

There is evidence that lifestyle changes, antidiabetic drugs, inducible nitric oxide synthesis, antihypertensive agents [mainly inhibitors of the renin-angiotensin-aldosterone system (RAAS)], and statins improve arterial elasticity in patients with a wide spectrum of diseases, such as CVD, CKD, T2DM, MetS, obesity, primary biliary cirrhosis, NAFLD, heart failure with preserved ejection fraction, arterial hypertension and dyslipidaemia[86-100]. Moreover, anti-inflammatory drugs, such as corticosteroids and anti-TNF-α therapy have been shown to improve arterial compliance in patients with chronic inflammatory conditions[101]. Overall a multifactorial approach appears to be the optimal solution for the management of increased AS due to NAFLD[26-31,89,90,93,97]. However, differences appear to exist within classes of agents, with some statins and RAAS inhibitors having a more favourable effects on AS[94-96,99,100].

NAFLD, STATINS (AND OTHER HYPOLIPIDAEMIC AGENTS) AND CVD RISK

Safety of statins in patients with NAFLD

Data from the Third NHANES (1988-1994) that included 15676 subjects from the United States suggest that the prevalence of ALT elevation was high in the United States, ranging from 7%-15% according to race[102]. In the majority of those with increased ALT levels this could be attributed to NAFLD, in the absence of alcohol abuse, viral hepatitis or hemochromatosis[102]. Moreover, unexplained ALT elevation (61% of cases) was strongly associated with adiposity and other features of MetS[102]. NHANES data collected from 1988 to 2008 showed that the prevalence of major causes of chronic liver disease remained stable, except for NAFLD, which increased steadily, alongside with the increase of the prevalence of metabolic diseases (MetS, T2DM)[103]. Given the increasing rates of obesity, NAFLD prevalence is expected to contribute substantially to the increased burden of chronic liver disease (and CVD) in the United States[103].

An observational study included 342 hyperlipidaemic patients with elevated transaminases who were prescribed a statin, 1437 hyperlipidaemic patients with normal transaminases who were prescribed a statin and 2245 patients with elevated liver enzymes but who were not prescribed a statin[104]. Patients with elevated transaminase levels were given atorvastatin or simvastatin at a median dose of 10 and 20 mg/d[104]. The incidence of further elevation in transaminase levels was similar in the two groups[104]. Among patients treated with a statin, the incidence of mild-moderate elevation in transaminase levels [< 10 times the upper limit of normal (ULN) or < 10 times the baseline transaminase levels] was higher in patients with elevated transaminases at baseline than in those with normal transaminase levels (n = 1437)[104]. However, the incidence of more marked elevation in transaminase levels (> 10 times the ULN) did not differ between the two groups[104]. Another observational study (n = 3399) in patients with elevated transaminase levels who were treated with lovastatin reported similar findings[105]. Moreover, >

112000 person-years of 5 year-exposure in double-blind randomized trials comparing placebo and pravastatin (40 mg once daily) showed low risk for hepatotoxicity[106].

Effect of statins on NAFLD

In clinical practice up to 10 years ago it was "forbidden" to prescribe statins, even in high CVD risk patients, if they had a chronic liver disease, including NAFLD, and modestly elevated serum transaminases.

Eight years ago, given that there was no proven effective therapy for NAFLD, atorvastatin (10-80 mg/d) was tested in 25 NAFLD patients for the treatment of their dyslipidaemia; 22 patients completed the study[107]. After 6 mo of atorvastatin treatment, 8 patients (36.3%) had normal transaminase levels, while the remaining patients continued treatment for 12 more months[107]. During that period 20% of patients presented with normal transaminase levels, while the rest of the patients demonstrated a 10% reduction in baseline levels[107]. These results suggested that treatment with atorvastatin in NAFLD patients with dyslipidaemia resulted in a normalization of lipid profile and a significant reduction in serum ALT and this treatment was both effective and safe[107].

Seven years ago a study evaluated the efficacy of atorvastatin (10 mg daily) for 24 mo in the treatment of 31 patients with biopsy proven NASH and dyslipidaemia[108]. Follow-up liver biopsy was performed in 17 patients[108]. After treatment, 23 patients (74.2%) had normal transaminase levels, adiponectin levels were noticeably increased, and the levels of TNF-α were significantly reduced[108]. These results suggest that atorvastatin may have acted *via* a reduction in markers of systemic inflammation, such as TNF-α, as well as increased adiponectin levels[108], while another study suggested a beneficial effect of atorvastatin on NASH due to the reduction in serum levels of advanced glycosylated end products (AGEs), implicated in the pathogenesis of NASH[109]. However, 4/17 patients had progression of fibrosis in the repeat biopsy after 2-years and 3 of them progressed to stage 3[108]. The authors could not explain these divergent results and attributed them to sampling error, heterogeneity of the population, or untreated postprandial rise in triglyceride (TG) levels[108].

Six years ago a pilot study with 16 NASH patients showed that monotherapy with simvastatin does not seem to be an effective treatment for NASH[110]. From the 16 patients with biopsy proven NASH, 14 completed the study and 10 underwent follow-up biopsy after one year. Although there was a 26% low-density lipoprotein cholesterol (LDL-C) reduction in the simvastatin group as compared with placebo, there was no significant improvement in serum transaminases, hepatic steatosis, necroinflammatory activity or stage of fibrosis[110].

Five years ago, the *post hoc* analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) survival study (n = 1600; 437 patients had moderately abnormal liver tests at baseline probably due to NAFLD as indicated by liver ultrasonography and after exclusion of other liver diseases)[111] showed that 227 participants who were treated with statins (mainly atorvastatin, mean dose 24 mg/d) had a substantial improvement in liver tests, ALT, aspartate aminotransferase (AST), and GGT (P < 0.0001), whereas 210 not treated with a statin had a further increase of liver enzyme concentrations[111]. Statin treatment was safe in patients with CVD and NAFLD; only 1% discontinued treatment[110]. Thus, atorvastatin did not have any adverse effect on liver enzymes; on the contrary, it reduced them substantially and improved liver ultrasonography within the 3-year duration of the study[111].

Four years ago a study with pitavastatin (2 mg/d for 12 mo) in 20 patients with biopsy-proven NASH with dyslipidaemia was reported[112]. Liver enzymes and lipid profile were significantly improved, however NAFLD/NASH activity score and fibrosis stage did not change significantly in all patients (they improved in 54% and 42%, respectively) and 3 of the 13 patients with a repeat biopsy had progression of fibrosis during the treatment[112].

Three years ago a study included 42 biopsy-proven NASH patients treated with atorvastatin 10 mg/d for 12 mo. Atorvastatin significantly decreased liver transaminase, GGT, LDL-C, TGs, type Ⅳ collagen, and TNF-α levels, while it improved NAFLD activity score and increased liver to spleen density ratio[113].

During the same year a prospective study investigated the effect 2.5 mg/d rosuvastatin for 24 mo in 19 patients with biopsy-proven NASH with dyslipidaemia[114]. Transaminase levels, relatively low at the beginning, were not significantly changed during the treatment, while the lipid profile was significantly improved[114]. At the same time NAFLD activity score and fibrotic stage did not change significantly in all patients; they were improved in 33% and 33% of patients, and remained stable in 33% and 56% of patients, respectively, while 1 of 9 patients had progression of fibrosis during rosuvastatin treatment[114]. This result was attributed to the very low dose of rosuvastatin administered (2.5 mg/d)[114]. During the same year a *post hoc* analysis of the survival study Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT)[115] with an atorvastatin- (34 or 24 mg/d) based multifactorial treatment approach in patients and MetS and NAFLD showed that attaining multiple treatment targets is safe and beneficial in primary prevention patients with MetS and NAFLD[115]. Lipid levels and liver enzymes were normalized and ultrasonographic evidence of NAFLD resolved during the 42 mo duration of the study in both intensive (mean dose 34 mg/d) and standard (mean dose 24 mg/d) atorvastatin treatment groups[115].

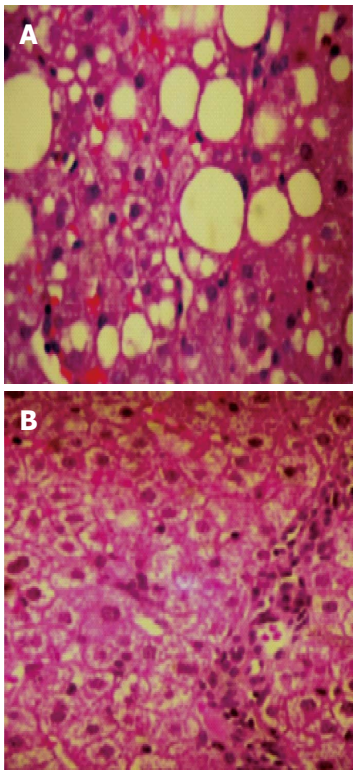

Figure 2 Liver biopsy of a patients with non-alcoholic steatohepatitis at baseline (A) and one year after 10 mg/d of rosuvastatin monotherapy (B) [unpublished data from personal archive].

In 2013 the *post hoc* analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial (n = 8863) showed that high dose atorvastatin treatment (80 mg) in 1081 (12.2%) patients, who had an ALT ⩾ ULN resulted in normalisation of ALT values[116]. The higher the atorvastatin dose (80 mg/d) the greater the reduction in liver enzyme levels[116].

In 2014 a pilot study (n = 6) with 10 mg/d of rosuvastatin monotherapy in biopsy proven NASH patients with MetS, showed within one year of treatment a normalisation of lipid profile, all liver enzymes, and complete resolution of NASH in the repeat biopsy (fibrosis, necroinflammation, ballooning, and steatosis were totally absent and histology revealed a normal liver tissue) in 5 out of 6 patients[117]. In 2015 we completed the study, for which the pilot was designed (unpublished data), with 20 biopsy proven (repeat biopsy after 12 mo of treatment) NASH patients with MetS treated with rosuvastatin 10 mg/d as monotherapy. The results remained as impressive as in the pilot study (Figure 2) and this study confirmed that the patients did not have MetS any longer, due to the reduction in TGs, the increase in high density lipoprotein cholesterol (HDL-C), and a paradoxical (substantial by 20 mg/dL) reduction in fasting plasma glucose. Waist circumference and body mass index did not change, thus, the improvement could not be attributed to reduction of (abdominal) obesity.

As stated in the above data there has been a gradual and hesitant attempt during the last 8 years to investigate the efficacy of statins in the treatment NAFLD/NASH. The results of these studies suggest that the effect of statins on NAFLD/NASH is intensity of compound and dose dependent[107-117]. The *post hoc* analyses of GREACE, ATTEMPT and IDEAL studies are hypothesis generating and there is a need for randomized controlled prospective studies on this issue. However, with all statins, except rosuvastatin, out of patent no pharmaceutical company is eager to finance a prospective study on this issue. This has to be done by independent researchers. We did our part, let others continue. In any case, we all know that several years are needed in order for guidelines to state a new indication for a drug. However, the information provided may help clinicians make decisions for patients with a highly prevalent disease**.**

From all the above the conclusion with practical implications was described by a Hepatologist: "Yes! Statins can be given to liver patients"[118].

Effect of other hypolipidaemic drugs on NAFLD/NASH

Ezetimibe can be added to statin treatment in patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of a high intensity statin[119]. The effect of ezetimibe on NAFLD was studied in a few, mainly uncontrolled studies with rather small number of patients. Serum ALT levels significantly decreased within 6 mo and in 4 patients levels reached the normal range (< 30 U/L), which was accompanied with at least a 10% decrease in serum total cholesterol and LDL-C. However, ezetimibe had no effect on liver steatosis as assessed with ultrasonography[120]. In another uncontrolled study in 10 patients with NASH, treatment with ezetimibe for 6 mo[121], NASH score and steatosis grade were also significantly improved in the repeat liver biopsy. The fibrosis stage did not change significantly, but 6 of the 10 patients exhibited an improvement in their fibrosis stage[121]. In another uncontrolled study 45 patients with liver biopsy-proven NAFLD were treated with ezetimibe for 24 mo[122]. Histological features of steatosis and necroinflammation improved, but fibrosis stage was not significantly changed[122]. In a recent randomized controlled study in NAFLD patients (16 on ezetimibe and 12 controls), ezetimibe improved hepatic fibrosis but increased hepatic long-chain fatty acids and HbA1c in NAFLD patients[123]. Thus, it is not clear yet which is the long term effect of ezetimibe on NAFLD/NASH (Table 1).

Omega-3 fatty acid supplementation has also been used for the treatment of NAFLD/NASH. Omega-3 fatty acid administration is safe and effective for NAFLD patients with dyslipidaemia and can improve their ALT, serum lipid (mainly TG) levels and normalize the ultrasonographic image of the liver[124]. A recent meta-analysis, that included 9 studies (5 randomized

Table 1 Studies evaluating the effect of hypolipidaemic drug treatment on non-alcoholic fatty liver disease or non-alcoholic steatohepatitis

Ref.	Year	*n* of all	*n* with NAFLD/ NASH	Method of diagnosis of NAFLD/NASH	Drug	Dose/d	Duration of treatment	Results-main findings
Gómez-Domínguez *et al*[107]	2006	25	22	ALT levels	Atorvastatin	10-80 mg	12 mo	Normalization of ALT and lipid profile
Hyogo *et al*[108]	2008	31	31	Biopsy-proven NASH	Atorvastatin	10 mg	24 mo	Liver steatosis and NAFLD activity score were significantly improved; in 4 increase in fibrosis stage.
Kimura *et al*[109]	2010	45	45	Biopsy-proven NASH	Atorvastatin	10 mg	12 mo	The steatosis grade and NAFLD activity score were significantly improved.
Nelson *et al*[110]	2009	16	10	Biopsy-proven NASH	Simvastatin	20 mg	12 mo	No statistically significant improvement in serum ALT, hepatic steatosis, necroinflammatory activity or stage of fibrosis within or between groups.
Athyros *et al*[111]	2010	1600	437	ALT levels -ultrasonography	Atorvastatin	24 mg	3 yr	Improved ALT, AST, GGT, AP, and ultrasonography. Reduced cardiovascular events more than those without NAFLD (P = 0.007).
Hyogo *et al*[112]	2011	20	13	Biopsy-proven NASH	Pitavastatin	2 mg	12 mo	Improved NAFLD activity score and fibrosis stage In 54% and 42%, respectively, improved histology, however, 3/13 patients progression of fibrosis.
Hyogo *et al*[113]	2012	42	42	Biopsy-proven NASH	Atorvastatin	10 mg	12 mo	Improved NAFLD activity score, normalization of liver enzymes and TNF-α, and increased liver to spleen density ratio.
Nakahara *et al*[114]	2012	19	19	Biopsy-proven NASH	Rosuvastatin	2.5 mg	24 mo	NAFLD activity score and fibrotic stage did not change significantly in all patients, they were improved in 33.3% and 33.3% of patients, and stayed stable in 33.3% and 55.6%, respectively.
Athyros *et al*[115]	2011	1123	326	ALT levels -ultrasonography	Atorvastatin	20-30 mg	42 mo	Improved ALT, AST, GGT, AP, and ultrasonography. Eradicated cardiovascular events in high dose group.
Tikkanen *et al*[116]	2013	8863	1081	ALT levels	Atorvastatin Simvastatin	80 mg 20-40 mg	5 yr	Normalization of liver enzyme values and greater CVD benefit with atorvastatin in the elevated ALT group.
Kargiotis *et al*[117]	2014	6	6	Biopsy-proven NASH	Rosuvastatin Monotherapy	10 mg	12 mo	Complete resolution of NASH in 5 patients. Normalization of liver enzyme values in all patients.
Park *et al*[122]	2011	45	45	Biopsy-proven NASH	Ezetimibe	10 mg	24 mo	Steatosis grade, necroinflammatory grade, ballooning, and NAFLD activity score were significantly improved from baseline. Fibrosis stage was not significantly changed.
Zhu *et al*[124]	2008	72	72	ALT levels -ultrasonography	n-3 PUFA	6 g	6 mo	ALT was reduced but other liver enzymes not. Ultrasonography improved in 53% of patients

NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AP: Alkaline phosphatase; CVD: Cardiovascular disease; GGT: Gamma-glutamyltransferase.

controlled trials- RCTs), involving 355 NAFLD patients, tested omega-3 *vs* control treatment for a period from 8 wk to 12 mo[125]. Results showed that omega-3 fatty acids were beneficial *vs* placebo in reducing liver fat and decreasing AST, but not ALT activity[125]. Sub-analyses of only the 5 RCTs showed a significant benefit for omega-3 fatty *vs* control on liver fat, but not for ALT or AST[125]. The pooled data suggest that omega-3 polyunsaturated fatty acid (PUFA) supplementation may decrease liver fat, however, the optimal dose could not be found[125].

Recently, several high quality reviews on NAFLD/ NASH and CVD risk have been published[126-129]. These recent reviews focused on the relation of NAFLD/NASH or other ectopic fat deposition with CVD risk or even more specific with the risk of arrhythmic complications in these patients, focusing mainly to pathophysiological mechanisms and dedicated a rather small portion to treatment[126-129]. In contrast, our review focused on specific NASH characteristics (degree of liver fibrosis and CVD risk) or confounding factors (NAFLD-chronic kidney disease and CVD risk as well as NAFLD-arterial stiffness and CVD risk) that could all be treated with a single drug, a statin. However, given that improvement of NAFLD/NASH with concomitant reduction in CVD risk may not be a drug class effect, we had to analyze the

effect of specific regiments at specific doses for specific treatment periods on the progression, amelioration or even reversal of NAFLD/NASH. This is the main difference between our review and the excellent recent analyses on this issue mentioned above.

Effect of statins on CVD morbidity and mortality in NAFLD patients

There are no prospective RCTs that investigated the effect of statins on CVD morbidity and mortality in NAFLD/NASH patients. Existing data come from *post hoc* analyses of 3 survival trials: GREACE[111], ATTEMPT[115], and IDEAL[116].

The GREACE *post hoc* analysis showed that in patients with mild to moderate elevations of serum transaminases, most probably due to NAFLD as indicated by liver ultrasonography, in the absence of alcohol abuse history and the exclusion of other liver diseases, 24 mg/d of atorvastatin induced substantial reductions in CVD events (68% *vs* usual care) during the 3-year follow-up period compared with the participants with CHD and normal liver enzymes (39% *vs* usual care); $P = 0.007$[111]. This confirmed the pattern of the higher the CVD risk, the greater the benefit from effective therapy. Moreover, the study results showed that those patients with overt CVD and NAFLD that were at very high risk for recurrent CVD events or CVD death were those who were deprived of statin therapy, up to 10 years ago, because the fear of a transaminase increase with a statin.

The ATTEMPT study was a primary prevention study in patients with MetS without overt CVD or T2DM and its *post hoc* analysis investigated the effect of atorvastatin-based multifactorial intervention on ultrasonography verified NAFLD[115]. There were no CVD events in patients with LDL-C levels < 100 mg/dL (atorvastatin dose 34 mg/dL) for the 42 mo of the duration of the study, while there were 5 non-fatal events occurring in the lower atorvastatin dose (24 mg/d) group (log-rank-$P = 0.024$).

The IDEAL *post hoc* analysis showed a substantially reduced 5-year CVD event rate with atorvastatin 80 mg/d in patients with elevated transaminases levels (probably due to NAFLD) as compared with 20-40 mg of simvastatin, a less effective dose of a less effective hypolipidaemic agent (11.5% for simvastatin and 6.5% for atorvastatin, HR = 0.556; 95%CI: 0.367-0.842; $P = 0.0056$)[116]. This totally confirmed the findings of GREACE and ATTEMPT studies.

Thus, it seems that statin treatment is safe in NAFLD/NASH patients[102-105], may contribute to the normalization of liver function and structure[107-117], and reduces CVD morbidity and mortality in these high CVD risk patients[111,115,116].

CONCLUSION

NAFLD has been considered as an independent CVD risk factor. However, it seems that simple steatosis is not related with higher total, CVD or liver-related mortality compared with the general population. In contrast, increasing values of liver fibrosis scores (in NASH patients) is linked to a progressive increase in total mortality by approximately 70% compared with subjects without fibrosis. The increase in overall mortality was mainly due to a higher CVD mortality. Besides fibrosis, the development of CKD substantially increases total and CVD mortality. NAFLD/NASH is considered to be a risk factor for CKD and CKD contributes to NAFLD pathogenesis within a vicious cycle. Liver and kidney disease progress in parallel substantially reducing life expectancy. NAFLD/NASH increase AS which is independently associated with increased CVD risk across many different patient groups and even in the general population. Early detection of NAFLD/NASH, advanced fibrosis, CKD and increased AS could lead to the treatment of this cluster of CVD risk factors with lifestyle measures and multifactorial drug intervention, mainly based on high intensity statins at moderate to high doses. These seem to be safe, resolve NAFLD/NASH and could contribute to the primary or secondary prevention of CVD[118,119,130,131].

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