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Nonalcoholic fatty liver disease and statins

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ABSTRACT

Objective. Nonalcoholic fatty liver disease (NAFLD) is the most frequent cause of elevated transaminase levels and affects approximately one third of the general population. Patients with NAFLD are at increased risk for cardiovascular events, which represent the leading cause of death in this population. We discuss the safety and efficacy of statins in this population.

Materials/methods. We reviewed the most recent literature on the safety of statins in patients with NAFLD and on their effects on liver histology and cardiovascular events.

Results. It appears that statins can be safely administered to patients with NAFLD, including those with elevated transaminase levels (<3 times the upper limit of normal). Post-hoc analyses of randomized controlled trials also suggest that statins might reduce cardiovascular morbidity in this population. On the other hand, there are few and controversial data on the effects of statins on liver histology in patients with NAFLD.

Conclusions. Statins appear to be safe and might also reduce cardiovascular events in patients with NAFLD. Ongoing and future studies will clarify whether statins might also have a role in the treatment of NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as evidence of hepatic steatosis, either by imaging or by histology, in the absence of secondary causes of hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medications (e.g. methotrexate, corticosteroids, amiodarone) or hereditary disorders (e.g. abetalipoproteinemia) [1]. NAFLD includes nonalcoholic fatty liver (NAFL), characterized by isolated hepatic steatosis without other abnormalities in hepatic histology, and nonalcoholic steatohepatitis (NASH), characterized by the presence of steatosis, inflammation, and ballooning with or without fibrosis [1]. NAFLD represents the commonest chronic liver disease and the leading cause of elevated

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus; MetS, metabolic syndrome; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal; WOSCOPS, West of Scotland Coronary Prevention Study; CARE, Cholesterol and Recurrent Events; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; CHD, coronary heart disease; GREACE, Greek Atorvastatin and Coronary Heart Disease Evaluation; ATTEMPT, Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes; IDEAL, Incremental Decrease in End Points Through Aggressive Lipid Lowering; CT, computed tomography.

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transaminase levels in high-income countries [2,3]. Approximately 34% and 12% of the general population has NAFL and NASH, respectively [4,5].

The pathogenesis of NAFLD involves a first step, where free fatty acids accumulate in the liver, particularly in patients with insulin resistance, abdominal obesity, type 2 diabetes mellitus (T2DM) and/or metabolic syndrome (MetS) [6,7]. In the second step, insulin resistance along with inflammation, oxidative stress, hepatocellular apoptosis and iron deposition result in the progression from NAFL to NASH [6,7]. Accordingly, NAFLD is particularly prevalent in patients with abdominal obesity, T2DM and/or MetS [8–10]. Partly due to the association between NAFLD and these cardiovascular risk factors, NAFLD is associated with increased risk for cardiovascular disease (CVD), which represents the leading cause of death in this population [11–13]. Moreover, cross-sectional studies showed that transaminase levels correlate with insulin resistance and low-density lipoprotein cholesterol (LDL-C) levels [14–16]. Several observational studies also reported that elevated transaminases are associated with increased incidence of T2DM and with higher risk for cardiovascular events [16–20].

There are currently limited options for the management of patients with NAFLD. Diet and exercise represent the fist-line treatment, but it is unclear whether they improve fibrosis and long-term adherence is infrequently achieved [1,21]. Regarding pharmacotherapy, pioglitazone and vitamin E appear to improve liver histology [22], but their effects on cardiovascular events in this population are unknown. Moreover, safety concerns limit the use of both agents. Indeed, pioglitazone increases the risk for weight gain, heart failure, fractures and bladder cancer [23–25], whereas vitamin E appears to be associated with higher risk for prostate cancer and all-cause mortality [26,27].

Given the increased cardiovascular risk of patients with NAFLD, multifactorial intervention targeting all cardiovascular risk factors is essential to prevent CVD in this population [1]. Elevated levels of LDL-C levels are a major modifiable cardiovascular risk factor and statins are the agent of choice for lowering LDL-C levels [28–31]. However, treatment with statins might increase transaminase levels and therefore physicians are frequently reluctant to use these agents in patients with NAFLD [30–33]. Nevertheless, accumulating data suggest that statins are safe in this population, reduce transaminase levels and might also decrease cardiovascular morbidity [34,35]. The aim of the present review is to summarize the existing evidence regarding the safety of statins in patients with NAFLD and to discuss the effects of these agents on cardiovascular disease and liver histology in this population.

2. Safety of Statins in Patients with NAFLD

Several observational studies suggested that statins are safe in patients with elevated transaminase levels. In these studies, patients had no evidence of hepatitis B or C or alcohol abuse and therefore the most likely cause of elevated transaminase levels was NAFLD [2,3]. In an early report, patients with elevated transaminase levels were given atorvastatin or simvastatin at a median dose of 10 and 20 mg/day, respectively (n = 342), or were not treated with a statin (n = 2,245) [36]. The incidence of further elevation in transaminase levels was similar in the two groups [36]. 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 transaminase levels at baseline than in those with normal transaminase levels (n = 1,437) [36]. However, the incidence of severe elevation in transaminase levels (>10 times the ULN or >10 times the baseline transaminase levels) did not differ between the two groups [36]. Another observational study (n = 3,399) in patients with elevated transaminase levels who were treated with lovastatin reported similar findings [37].

Randomized controlled studies also showed that statins are safe in patients with elevated transaminase levels presumably due to NAFLD. In a pooled analysis of the West of Scotland Coronary Prevention Study (WOSCOPS), Cholesterol and Recurrent Events (CARE) trial and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (n = 19,592 patients with coronary heart disease (CHD) or without established CVD), the incidence of further elevation in transaminase levels was similar in patients with elevated transaminase levels (<3 times the ULN) who were treated with pravastatin 40 mg/day (n = 317) and in those who were given placebo (n = 262) [38]. In a post-hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study (n = 1,600 patients with CHD), 437 patients had elevated transaminase levels (<3 times the ULN) at baseline [34]. Treatment with atorvastatin (mean dose 24 mg/day) resulted in normalization of transaminase levels whereas patients who were not given a statin showed further rises in transaminase levels [34]. In a post-hoc analysis of the Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT) study (n = 1,123 patients with MetS), 326 patients had elevated transaminase levels (<3 times the ULN) at baseline [10]. Treatment with atorvastatin aiming at LDL-C levels <130 or <100 mg/dl (mean dose 24 and 34 mg/day, respectively) resulted in normalization in of transaminase levels in 89% and 94% of the patients, respectively [10]. More recently, a post-hoc analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study (n = 8,888 patients with CHD) reported similar findings in patients treated with higher doses of statins [35]. At baseline, 1,081 patients had elevated transaminase levels (<2 times the ULN) and treatment with either simvastatin 20–40 mg/day or atorvastatin 80 mg/day reduced transaminase levels [35].

Several small studies also showed that statins are safe in patients with NAFLD. In a subgroup analysis of the Dallas Heart Study, patients with hepatic steatosis (diagnosed with magnetic resonance spectroscopy) who were taking statins (n = 54) had similar alanine transaminase (ALT) levels with patients with steatosis who were not on statins (n = 584) [39]. A number of small uncontrolled studies showed that treatment with statins reduces transaminase levels in patients with NAFLD (Table 1) [40–49]. Three larger randomized controlled studies also reported similar findings [50–52]. In the first, 186 patients with NAFLD and MetS but without T2DM

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Table 1 – Studies evaluating statins in patients with nonalcoholic fatty liver disease using non-invasive methods (hepatic inflammation and fibrosis was not evaluated in any of these studies).

Ref.	n	Statin	Dose (mg/day)	Follow-up (months)	Evaluation method	Change in transaminase levels	Change in steatosis
[26]	27	Atorvastatin	10	6	CT	Reduction ($p < 0.02$)	Improvement ($p = 0.0001$)
[28]	28	Atorvastatin	20	6	US	Reduction ($p < 0.001$)	Improvement (p NR)
[29]	23	Rosuvastatin	10	8	None	Reduction ($p < 0.001$)	Not evaluated
[30]	25	Atorvastatin	10-80	12	US	Reduction (p NR)	No change
[32]	26	Simvastatin	20	6	None	Reduction ($p < 0.0001$)	Not evaluated
[36]	186	Atorvastatin or fenofibrate or both	20 or 160	12	US	Similar reduction with atorvastatin and combination and smaller reduction with fenofibrate ($p < 0.05$ for all changes)	Improvement (p NR)
[37]	209	Pravastatin or placebo	80	9	None	Pravastatin: reduction (p NR) Placebo: increase (p NR)	Not evaluated
[38]	189	Pitavastatin or atorvastatin	2-4 or 10-20	3	CT	Similar reduction with pitavastatin and atorvastatin ($p = 0.047$ and $p = 0.025$, respectively)	Similar improvement with both statins ($p = 0.014$ and $p = 0.021$, respectively)

CT: computed tomography; US: ultrasound; NR, not reported.

were randomized to atorvastatin 20 mg/day, fenofibrate 160 mg/day or their combination [50]. Atorvastatin reduced transaminase levels more than fenofibrate and as much as combination treatment [50]. In the second [n = 326 patients with chronic liver disease (n = 209 with NAFLD)], treatment with pravastatin 80 mg/day for 9 months reduced transaminase levels whereas patients treated with placebo showed an increase in transaminase levels [51]. In a more recent study (n = 189), atorvastatin 10–20 mg/day was as effective as pitavastatin 2–4 mg/day in reducing transaminase levels [52]. In a smaller placebo-controlled study in patients with NAFLD (n = 16), treatment with simvastatin 40 mg/day for 12 months had no effect on transaminase levels [53].

Based on these reassuring data, current guidelines state that statins are safe to use in patients with NAFLD [1,54]. However, statins are contraindicated in patients with transaminase levels >3 times the ULN and should be discontinued if transaminase levels rise to >3 times the ULN during treatment [30]. On the other hand, the safety of statins is reflected on the recent US guidelines for the management of

Table 2 – Studies evaluating statins in patients with nonalcoholic fatty liver disease using liver biopsy alone or in combination with non-invasive methods.

Ref.	n	Statin	Dose (mg/day)	Follow-up (months)	Evaluation method	Change in transaminase levels	Change in steatosis	Change in inflammation in biopsy	Change in fibrosis in biopsy
[27]	5	Pravastatin	40	6	Biopsy	Reduction (p NR)	Improvement (p NR)	Improvement (p NR)	No change
[31]	10	Atorvastatin	10	9	Biopsy	Reduction ($p = 0.0071$)	Improvement (p NR)	No change	No change
[33]	43	Atorvastatin	10	12	Biopsy and CT	Reduction (<0.001)	Improvement in both biopsy and CT ($p < 0.001$ and p NR, respectively)	Improvement ($p < 0.05$)	No change
[34]	20	Pitavastatin	2	12	Biopsy and CT	Reduction ($p < 0.01$)	No change in biopsy Improvement in CT (p NR)	No change	No change
[35]	6	Rosuvastatin	10	12	Biopsy and US	Reduction ($p < 0.001$)	Improvement in both biopsy and US (p NR)	Improvement (p NR)	Improvement (p NR)
[39]	16	Simvastatin or placebo	40	12	Biopsy	No change with either treatment	No change with either treatment	No change with either treatment	No change with either treatment
[46]	19	Rosuvastatin	2.5	24	Biopsy and CT	No change	No change in biopsy Improvement in CT (p NR)	No change	No change

CT: computed tomography; US: ultrasound; NR, not reported.

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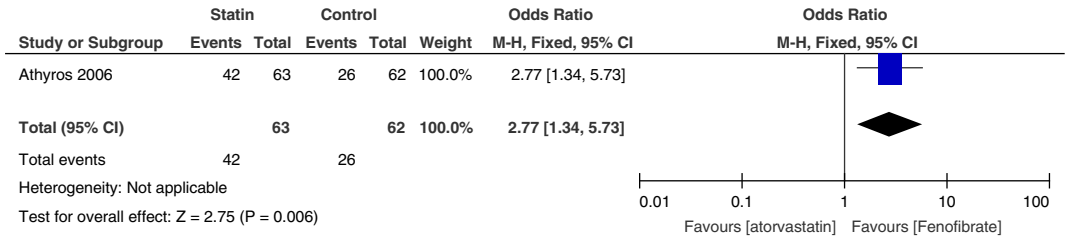

Fig. 1 – Forest plot of comparison of the effect of atorvastatin on nonalcoholic fatty liver disease (biochemical + ultrasonographic diagnosis).

dyslipidemia, according to which transaminase levels should not be measured during treatment with statins unless symptoms suggesting hepatotoxicity arise [31].

Even though statins appear to be safe in terms of liver toxicity in patients with NAFLD, other safety issues should also be considered. Recently, statin treatment has been associated with increased risk for T2DM [55,56]. Several mechanisms have been proposed to explain this association, including reduced insulin secretion, reduced translocation of glucose transporter 4 and impaired insulin signal transduction [57]. The risk of new-onset T2DM during treatment with statins is greater in obese patients and in those with prediabetes [58,59], who also frequently have NAFLD [8–10]. Accordingly, the risk of T2DM might be higher in patients with NAFLD treated with statins. However, there are no studies that evaluated the incidence of T2DM during treatment with statins in patients with NAFLD. On the other hand, it should be emphasized that the risk of diabetes during treatment with statins is outweighed by the reduction in cardiovascular events [55,56]. Another concern during statin treatment is the risk of myalgia with or without creatine kinase (CK) elevations. Even though CK elevations are infrequent, myalgia may affect 7–29% of patients treated with statins in registries and observational studies [60]. Again, there are no studies that evaluated the incidence of CK increase or myopathy in patients with NAFLD treated with statins. Interestingly, the addition of exercise training to statin treatment does not appear to affect CK and ALT levels compared with statin treatment alone [61]. This is of particular importance, since exercise training has well-established benefits on cardiovascular events [62] and might also improve liver histology in patients with NAFLD [63].

3. Effects of Statins on Cardiovascular Morbidity in Patients with NAFLD

Recently, post-hoc analyses of 3 randomized controlled trials suggested that statins reduce cardiovascular events in patients with elevated transaminase levels, presumably due to NAFLD. In a post-hoc analysis of the GREACE trial, treatment with atorvastatin for 3 years reduced cardiovascular events by 39% in patients with normal transaminase levels [34]. On the other hand, atorvastatin reduced cardiovascular events by 68% in patients with CHD and elevated transaminase levels ($p = 0.0074$ compared with the cardiovascular risk reduction in patients with normal transaminase levels) [34]. In a post-hoc analysis of the ATTEMPT study, treatment with atorvastatin for 42 months aiming at LDL-C levels <100 mg/dl in patients with MetS and elevated transaminase levels reduced cardiovascular events more than treatment with atorvastatin aiming at LDL-C levels <130 mg/dl ($p = 0.024$) [10]. Finally, in a post-hoc analysis of the IDEAL trial, treatment with atorvastatin 80 mg/day reduced cardiovascular events more than simvastatin 20–40 mg/day only in patients with CHD and elevated transaminase levels and not in those with normal transaminase levels (p for heterogeneity = 0.0277) [35]. Even though these preliminary data suggest that statins reduce cardiovascular morbidity in patients with NAFLD, the presence of NAFLD does not differentiate the management of dyslipidemia according to both the European and US guidelines [30,31].

In patients who cannot achieve LDL-C targets despite treatment with the maximal tolerated dose of a potent statin, options include adding ezetimibe of a bile-acid binding resin.

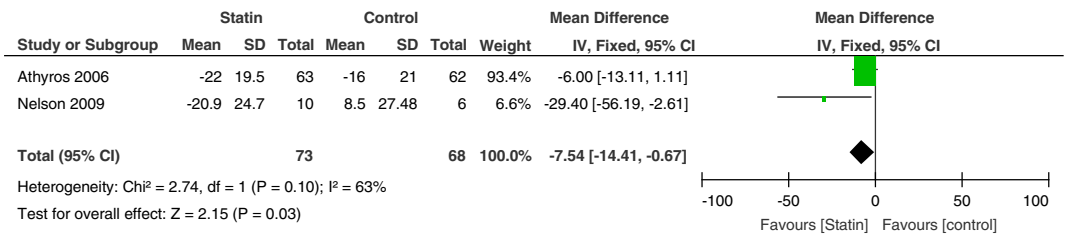

Fig. 2 – Forest plot of comparison of the effect of statins on alanine transaminase levels in nonalcoholic fatty liver disease.

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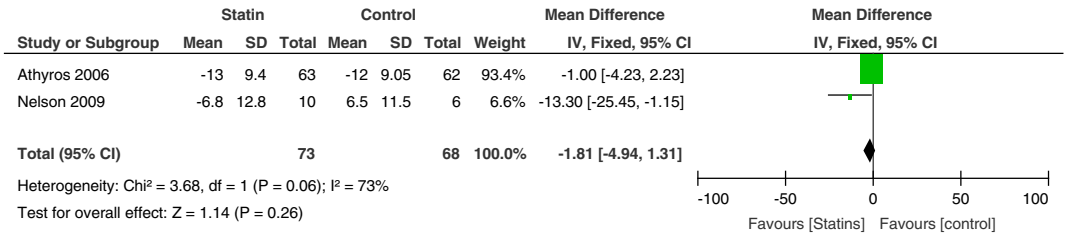

Fig. 3 – Forest plot of comparison of the effect of statins on aspartate transaminase levels in nonalcoholic fatty liver disease.

There are no studies that evaluated the effects of these agents on cardiovascular events in patients with NAFLD. Small uncontrolled studies suggested that ezetimibe reduces transaminase levels and improves steatosis in this population [64,65]. However, in a more recent study, ezetimibe combined with diet had similar effects on transaminase levels and steatosis compared with diet alone [66]. On the other hand, colesevelam, a bile-acid binding resin, increased steatosis in a randomized, placebo-controlled study [67]. Clearly, more data are needed to clarify the role of ezetimibe and bile-acid binding resins in the management of NAFLD.

4. Effects of Statins on Liver Histology in Patients with NAFLD

Given the involvement of oxidative stress, subclinical inflammation and increased apoptosis in the pathogenesis of NAFLD, statins might improve liver histology in these patients through their pleiotropic effects [68–71]. Indeed, animal studies reported that statins prevent the progression of hepatic inflammation and fibrosis by exerting antiinflammatory, antiapoptotic and antioxidant effects, by reducing stress-activated c-Jun N-terminal kinase (JNK) activation, by decreasing the hepatic expression of transforming growth factor-β and connective tissue growth factor, by improving peroxisomal β-oxidation, by up-regulating the expression of endothelial nitric oxide synthase (NOS) and down-regulating the expression of inducible NOS, and by inhibiting the activation of hepatic stellate cells [72–74].

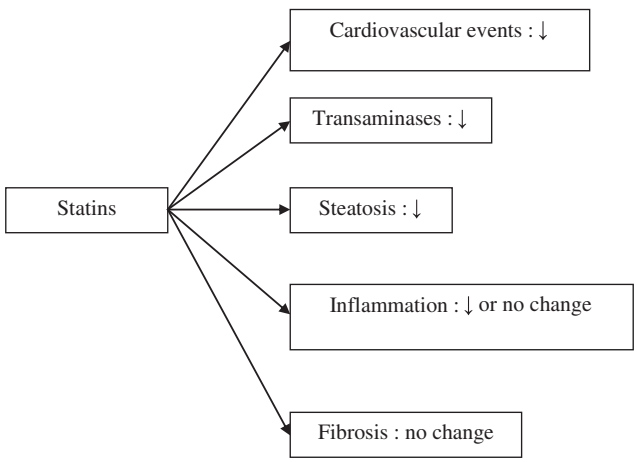

Fig. 4 – Effects of statins on cardiovascular events and on the liver in patients with nonalcoholic fatty liver disease.

In humans, few small uncontrolled studies used ultrasound or computed tomography (CT) to evaluate the effects of statins on liver steatosis and most showed an improvement [40,42,47]. In a larger randomized study, atorvastatin was more effective than fenofibrate and as effective as atorvastatin combined with fenofibrate in reducing liver echogenicity [50]. In another randomized study, atorvastatin 10–20 mg/day was as effective as pitavastatin 2–4 mg/day in reducing hepatic steatosis in CT [52].

There are also limited data on the effects of statins on liver histology. In an early retrospective study in 68 patients with NAFLD, those who were treated with statins (n = 17) showed an improvement in steatosis and no change in inflammation or fibrosis during a follow-up of 13.8 years [75]. In contrast, patients who did not receive a statin showed progression in fibrosis and no change in steatosis or inflammation [75]. Several small (n = 5–43) and uncontrolled studies prospectively evaluated the effects of statins on liver histology in patients with NAFLD (Tables 1 and 2). Most showed that treatment with statins reduces hepatic steatosis [41,45,47,49] but in some there was no change [48,76]. In some studies, an improvement in inflammation was also observed [41,47,49] but not in others [45,48,76]. However, fibrosis was not reduced in any study [41,45,47,48,76] except in a small preliminary report in 6 patients treated with rosuvastatin for 6 months [49]. In contrast, in the only placebo-controlled study with repeat biopsy in patients with NAFLD (n = 16), treatment with simvastatin 40 mg/day for 12 months had no effect on liver histology [53]. In addition to the small number of patients included in statin studies in patients with NAFLD, these conflicting data might also reflect variability in statin response between patients. Indeed, LDL-C reduction varies during treatment with the same dose of the same statin. A large number of single nucleotide polymorphisms that affect response to statins have been identified, which explain partly this variability [77–79]. Given the limited and conflicting data on the effect of statins in liver histology in patients with NAFLD, current guidelines state that statins should not be used to treat NAFLD [1]. On the other hand, observational studies suggest that treatment with statins is associated with lower risk for hepatocellular cancer (HCC) [80–82]. This beneficial effect of statins might be due to their antiproliferative, immunomodulatory and antiangiogenic effects or due to the prevention of cirrhosis in patients with NAFLD and might be of clinical importance given the rising incidence of HCC in this population [83,84].

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Finally, we performed a meta-analysis of the two randomized controlled studies that evaluated statins in patients with NAFLD, one comparing atorvastatin with fenofibrate and the other comparing simvastatin with placebo [50,53]. Another randomized study was not included, because two statins were compared [52]. Quality of randomized controlled trials was assessed by the Cochrane Collaboration's risk of bias tool. The risk of bias of each randomized trial was assessed using the following domains: sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, and selective reporting [85]. Results from randomized controlled trials were pulled together and meta-analyzed. Dichotomous variables are presented as odds ratios (OR) with 95% confidence interval (CI), and continuous variables as mean differences with 95% CI. The fixed-effect model was used, and the analysis was performed at the 0.05 significance level. Heterogeneity was assessed using the I^2 statistic, with values greater than 50% representing substantial heterogeneity [86]. Sensitivity analysis and subgroup analysis were not performed due to lack of adequate number of studies. For all analyses we used RevMan 5.3 (Nordic Cochrane Center, Copenhagen, Denmark).

NAFLD patients on atorvastatin had higher rate of combined biochemical and ultrasonographic improvement compared to fenofibrate (OR 2.77; 95% CI 1.34 to 5.73) (Fig. 1). At the end of the studies, compared with controls, ALT levels decreased [−7.54 (95% CI −14.4 to −0.67, I^2 = 0.63%)] (Fig. 2) whereas aspartate transaminase levels did not change [−1.81 (95% CI −4.94 to 1.31, I^2 = 0.73%)] (Fig. 3). Both studies were assessed as having high risk of bias. The study by Nelson et al. is a double-blind study but they did not clearly report the methods of sequence generation and allocation concealment. Two patients were lost to follow-up and only 10 patients had repeat liver biopsies but authors did not explicitly report the reasons for withdrawal (attrition bias) [53]. The study by Athyros et al. is not blinded (open label study) but with adequate method of sequence generation. However, the method of allocation concealment is unclear [50]. Both studies suffer from selective reporting with important for analysis outcome data missing [50,53].

5. Conclusions

Statins appear to be safe in patients with elevated transaminase levels due to NAFLD. Post-hoc analyses of randomized controlled trials also suggest that statins might reduce cardiovascular morbidity in this population. On the other hand, the effects of statins on liver histology in patients with NAFLD are controversial (Fig. 4). Ongoing and future studies will clarify whether statins might also have a role in the treatment of NAFLD.

Author Contributions

KT drafted the paper. VGA and AK revised the draft critically for important intellectual content. PP performed the meta-analysis of the studies that evaluated the effects of statins on nonalcoholic fatty liver disease.

Conflict of Interest

None.

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