Original article

Safety and efficacy of dyslipidemia treatment in NAFLD patients: a meta-analysis of randomized controlled trials

Mohamed Abdallah[a], Landon Brown[b], John Provenza[b], Raseen Tariq[c], Smitha Gowda[a], Ashwani K. Singal[a,d,*]

[a] Department of Medicine, University of South Dakota Sanford School of Medicine, Sioux Falls, SD, United States
[b] Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States
[c] Department of Medicine, University of Rochester, NY, United States
[d] Division of Transplant Hepatology, Avera Transplant Institute, Sioux Falls, SD, United States

A B S T R A C T

Introduction and Objectives: Practicing physicians often hesitate to use statins and/or other lipid-lowering therapies in NAFLD due to concern for hepatotoxicity. The aim of this study is to examine the safety of lipid lowering therapies in NAFLD patients.
Materials and Methods: Data from randomized control trials (RCT) among NAFLD patients were pooled to examine the effect of lipid-lowering therapies on liver chemistry, lipid profile, and liver histology. Results are reported as the mean difference of the change (pretreatment-posttreatment) between the treatment and control group.
Results: A total of 21 placebo-controlled RCT on 1900 patients (304 receiving statins, 520 other lipid-lowering therapies, and 61 combinations) were treated for 26 weeks [Interquartile range (IQR): 17.5-52 weeks]. Pooled data showed an improved lipid profile without any worsening of ALT, AST, total bilirubin, or alkaline phosphatase at the end of the treatment period. NAFLD activity score improved with other lipid-lowering agents but not with statins. There was no change in individual components of NAFLD activity score or fibrosis stage.
Conclusion: This meta-analysis of randomized controlled trials examining statins and/or other lipid-lowering therapies in NAFLD patients showed no evidence of worsening liver chemistry. Studies with longer use of lipid-lowering therapies are suggested to examine the benefit of liver histology among patients with NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease worldwide [1]. Its spectrum extends from steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma [1]. NASH cirrhosis is currently the second leading etiology for liver transplantation and the fastest growing indication for simultaneous liver-kidney transplantation, hepatocellular carcinoma, and admissions with liver failure [2–5].

NAFLD is currently recognized as the most common cause of elevated liver enzymes [1]. In addition, NAFLD represents the hepatic manifestation of metabolic syndrome and insulin resistance, and includes central obesity, type 2 diabetes mellitus, dyslipidemia and hypertension. Dyslipidemia as a risk factor for the development of NAFLD is frequently observed in these patients, and is characterized by decreased serum high-density lipoprotein (HDL) and increased serum triglycerides (TG) levels [1]. Hence, appropriate treatment of dyslipidemia is important for the management of patients with NAFLD. The mainstay of treatment is 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) reductase inhibitors (i.e., statins) along with lipid-lowering therapies. Improved lipid profile with statins reduces cardiovascular mortality, and statins are recommended to be used for at-risk populations [6]. Statins also provide anti-inflammatory, anti-oxidant, and anti-thrombotic benefits by targeting pathways that are activated in the pathophysiology of NAFLD [7]. Further, the data is accumulating on the benefits of statins on liver fibrosis, HCC risk, liver disease complications, and overall survival [8].

However, the fear of hepatotoxicity with the use of statins and/or triglyceride lowering therapy for dyslipidemia in patients with NAFLD often deters physicians from their use in clinical practice [1, 9]. The objective of this meta-analysis is to examine the effect of using statins or lipid-lowering therapies among NAFLD patients on the risk of hepatotoxicity. We also examined their effects on lipid profile and liver histology.

2. Methods

2.1. Search strategy and study selection for analysis

A comprehensive literature search was conducted in PubMed, EMBASE, PsycINFO, and Cochrane databases through May 2020 for the safety and efficacy of lipid-lowering agents and omega-3 polyunsaturated fatty acid (PUFA) supplementation in patients with NAFLD and is described in the supplementary document. As per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, full-length articles in English reporting on lean NAFLD were identified. Data from selected studies on patients with NAFLD comparing statins and/or lipid-lowering therapy against placebo or other active agents were extracted and pooled in this meta-analysis. Identification of studies for analysis was performed independently by three investigators (M.A., J.P., A.K.S) using inclusion criteria−A) randomized-controlled trials; (b) included adult subjects; c) published in English language; and (d) reported as full papers. The studies were excluded if: (1) without a control group; (2) without data on pre- and post-treatment study outcomes; (3) studies not including lipid-lowering agents; (4) non-randomized studies; or 5) not meeting ≥1 inclusion criteria. We also excluded certain studies despite meeting inclusion and exclusion criteria because they reported results in a format that was not extractable for meta-analysis. Retrieved articles were independently reviewed for their eligibility by the three investigators. Any discrepancy among investigators was resolved by consensus among all the investigators. Given that one of the aims of the study is to evaluate hepatotoxicity of lipid-lowering agents, we included studies that compared the combination of two lipid-lowering agents vs. another agent or a placebo.

2.2. Study quality assessment

Two reviewers (M.A and S.G) independently assessed the methodological quality of studies using the risk of bias by Cochrane for RCTs (Supplementary Fig. 1, 2) [10]. Each study was graded on the study quality as per the following criteria: sequence generation for the randomization of subjects, allocation concealment, participant blinding, outcome assessment blinding, attrition bias, and any other sources of bias. The risk of bias for one of the first three components is defined as a high risk of bias.

2.3. Study outcomes

The primary outcome of this study is the effect of lipid-lowering drugs on liver toxicity evaluated by the change in liver biochemical profile (pre-treatment value − post-treatment value) in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin (TB). Secondary outcomes are the effect of lipid-lowering drugs on a) lipid profile (pre-treatment − post-treatment) in serum levels of total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG) and b) liver histology (pre-treatment − post- treatment) in steatosis grade, lobular inflammation score (LI), ballooning severity, NAFLD activity score (NAS), and fibrosis.

2.4. Data extraction

Data from studies selected for analysis were extracted independently by three authors (J.P., M.A., and S.G.) on A) characteristics (sample size, study population); b) patient demographics (age, gender, and BMI); c) treatment details (type of intervention, comparator group, dose in each group, duration of treatment); c) diabetes mellitus; d) serum liver chemistry before and after treatment (ALT, AST, ALP in IU/l, and total bilirubin in mg/dL); e) serum lipid profile values before and after treatment (TC, LDL, HDL and TG in mg/dL); and f) liver histology before and after treatment (steatosis, lobular inflammation, ballooning, NAS, and fibrosis stage). If studies reported continuous variables with median values, this was converted into mean using standard statistical methods [11]. Similarly, if the unit of variation was reported as standard error of mean, this was converted to standard deviation (SD). For studies reporting laboratory values in molar concentration, these were converted to mass concentration.

2.5. Definitions

NAFLD: Hepatic steatosis in the absence of other causes of liver disease and alcohol use <30 g/d in males and <20 g/d in females [1].

Steatosis grade: on liver histology with% of hepatocytes showing fat as grade 1 (5-33%), grade 2 (34-66%), and grade 3 (≥66%) [12].

Lobular inflammation: graded by number of inflammatory foci per 200X field as grade 1 (<2 foci) grade 2 (2-4 foci), and grade 3 (>4 foci) [12].

Hepatocyte ballooning: graded by number of ballooned hepatocytes as grade 1 (few balloon cells), and grade 2 (many ballooned cells) [12].

NAFLD activity score (NAS): sum of the scores for steatosis, lobular inflammation, and ballooning [12].

NASH−Defined on liver histology with NAS ≥5 [12].

Fibrosis stage−As stage 1 with peri-sinusoidal or portal fibrosis, stage 2 with peri-portal fibrosis, stage 3 as bridging fibrosis, and stage 4 with cirrhosis [12].

2.6. Data analyses

Comprehensive Meta-analysis Software (CMA) was used to pool the data, using random effects model. Pooled effect size represented as Forrest plots is reported as standardized mean difference (SMD) with 95% confidence interval (CI) and considered significant if the 95% CI does not cross '0'. For each study, the SMD is the difference in means between groups divided by standard deviation among the participants in that study.

Heterogeneity between the studies was assessed using the I^2 statistics (I^2 >50% or P <0.05). If the data were heterogeneous, reason/s of heterogeneity were examined using the subgroup and/or sensitivity analyses. Visual inspection of funnel plots Egger's regression test was used to assess the publication bias [13]. P<0.05 was considered significant for all the analyses.

3. Results

3.1. Baseline characteristics

The PRISMA flow diagram and results based on the search strategies and selection criteria described above are outlined in (Fig. 1) [14]. Of the 4818 studies identified in initial literature search, 35 studies met the inclusion criteria. Fourteen studies, however, were excluded (four for the lack of randomization, four other studies for not having data presented in an extractable form for meta-analysis, and six for insufficient data for treatment and/or control). Therefore, twenty-one studies were included in the final meta-analysis. There were 1900 patients (304 received statins, 520 other lipid- lowering
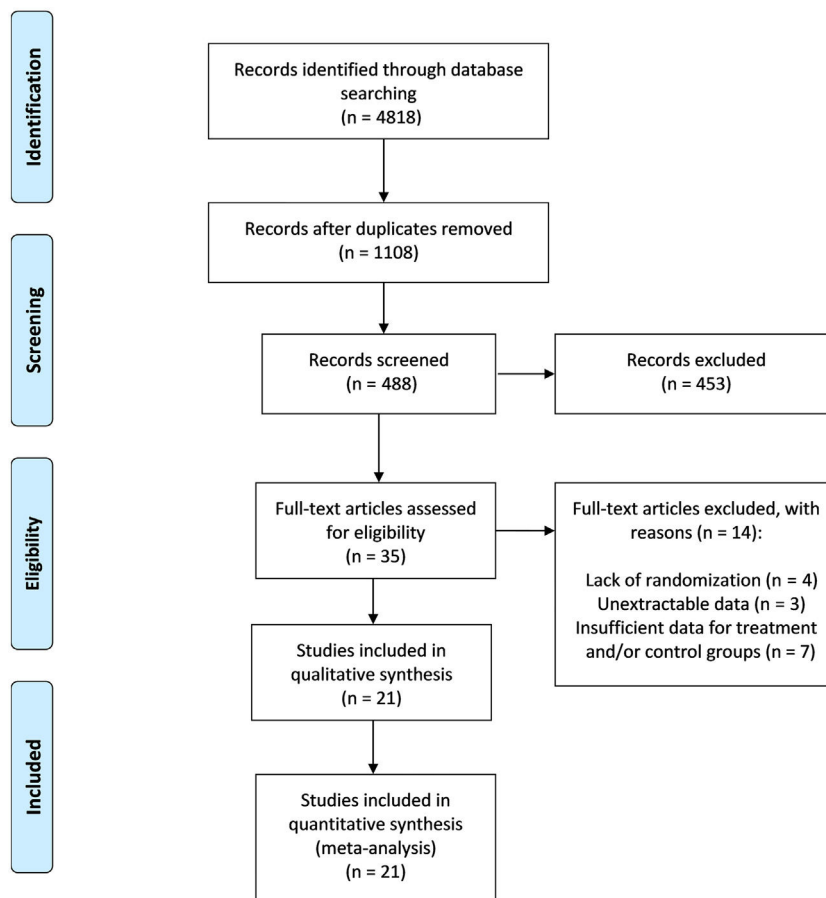
Fig. 1. Effect of treatment on **A)** alanine aminotransferase (ALT), **B)** aspartate aminotransferase (AST), **C)** alkaline phosphatase (ALP), and **D)** total bilirubin (TB).

Table 1

Baseline characteristics of studies included in the analysis.

Author, Year	Total N (Treated)	Mean Age (SD)	% Males	% Diabetes	Mean BMI (SD)	Intervention	Dose	Duration
Argo, 2015 [38]	34 (17)	46.4 (12.1)	35.7	29.4	33.3 (8.0)	N-3 PUFA	3000 mg/day	1 year
Athyros, 2006 [39]	186 (61)‡	59 (13)	66	0	33 (9)	Atorvastatin fen fibrates	20 mg/day 200 mg/day	54 weeks
Athyros, 2010 [32]	437 (227)	60 (14) *	79	50.8	29 (7) *	Various statins ^	Various doses ^	3 years
Basaranoglu, 1999 [40]	46 (23)	41.6 (6.6)	82.6	N/A	28.2 (3.7)	Gemfibrozil	600 mg/day	4 weeks
Chan, 2010 [41]	25 (15)	N/A	60	0	32 (1)	Ezetimibe	10 mg/day	22 weeks
Dasarathy, 2015 [42]	37 (18)	51.5 (6.9)	50	100	34.8 (4.6)	PUFA	EPA 2160 mg+DHA 1440 mg/day	48 weeks
Li, 2015 [43]	78 (39)	52.6 (6.6)	87.2	N/A	28.0 (1.4)	PUFA	1:1 of EHA and DHA	6 months
Loomba, 2015 [44]	50 (25)	49.0 (14.9)	44	28	33.8 (5.2)	Ezetimibe	10mg/day	24weeks
Malaguarnera, 2011 [45]	65 (33)	47.8 (5.9)	60.6	0	26.8 (3.0)	Rosuvastatin	5 mg daily	12 months
Nelson, 2009 [46]	16 (10)	52.6 (8.6)	70	60	37.3	Simvastatin	40 mg/day	12 months
Qin, 2015 [47]	70 (36)	46.0 (10.68)	72	NA	26.4 (3.9)	Omega 3 fatty acid	4 gm/day	3 months
Rana, 2016 [48]	98 (34)	NA	70	NA	27.7 (2)	Rosuvastatin	NA	24 weeks
Rezaei, 2020 [49]	68 (34)	45.5 (8.7)	47.1	0	30.1 (4.1)	Flaxseed oil	20 ml/day	12 weeks
Scoreletti, 2014 [50]	103 (51)	48.6 (11.1)	49	9	34.3 (5.8)	DHA+EPA	4g/day	15-18 months
Shojasaadat, 2019 [51]	114 (38)	41.77(8.92)	51.4	NA	31.5 (3.6)	DHA+EPA	1500mg/day	12 weeks
Sofi, 2010 [52]	11 (6)	55 (30−71)	66.7	NA	29.3 (4.1)	Olive oil enriched with n-3 PUFA	0.83 g/day	12 months
Spadaro, 2008 [53]	40 (18)	50.2 (12.9)	61	N/A	30.1 (4.7)	PUFA	1 g/daily	6 months
Takeshita, 2014 [54]	31 (17)	50.4 (2.9)	64.7	N/A	30.5 (1.2)	Ezetimibe	10 mg/day	6 months
Tobin, 2018 [55]	167 (81)	55.3 (13.3)	44.4	35	32.1 (4.8)	PUFA	3 g/day	24 weeks
Yaghoubi, 2017 [56]	90 (30)	38 (8)	N/A	N/A	27 (3)	Fen fibrate	200 mg /day	12 weeks
Zhu, 2008 [57]	134 (72)	45 (10.9)	71	N/A	26.4 (3.1)	N-3 PUFA	2 g/TID	24 weeks
Summary	1900 (885)	49 (46-52)	62 (36-87)		30 (29-31)			26 (18-52)

*Results for patients on statin therapy.

^ Statin drug (median statin dose per day in mg [range]): Atorvastatin 25 (10−80), Simvastatin 22 (10−40), Pravastatin 29 (20−40), Fluvastatin 40 (40−40).

‡ [atorvastatin (n=63), fen fibrate (n=62), combination of atorvastatin and fen fibrate (n=61)].

Table 2
Liver chemistry profile [values given as mean (SD), IU/liter except for TB in mg/dL] before and after treatment.

Author, Year	ALT pre-treatment	ALT post-treatment	AST pre-treatment	AST post-treatment	ALP pre-treatment	ALP post-treatment	TB pre-treatment	TB post-treatment
Argo, 2015	72.8 (30.9)	56.7 (28.3)	N/A	N/A	N/A	N/A	N/A	N/A
Athyros, 2006	51 (24)	30 (7)	38 (13)	24 (6)	N/A	N/A	N/A	N/A
Athryos, 2010 ^	57 (8)	37 (6)	49 (7)	26 (4)	N/A	N/A	N/A	N/A
Basaranoglu, 1999	72 (37.0)	49.7 (28.2)	49.1 (20.4)	38.9 (20.2)	N/A	N/A	N/A	N/A
Chan, 2010	29 (2)	30 (3)	N/A	N/A	N/A	N/A	N/A	N/A
Dasarathy, 2015	60.1 (27.6)	56.9 (30.9	47.7 (22.8)	41.7 (17.4)	N/A	N/A	1.1 (0.3)	1.1 (0.3)
Li, 2015	89.2 (12.4)	67.8 (5.3)	82 (9.6)	60.3 (6.8)	N/A	N/A	N/A	N/A
Loomba, 2015	47 (29)	48 (43)	33 (23)	33 (36)	74 (34)	89 (45)	0.4 (0.4)	0.4 (0.3)
Malaguarnera, 2011	184 (49.2)	57.8 (21.4)	145 (46.8)	38.5 (30.2)	N/A	N/A	N/A	N/A
Nelson, 2009	70.4 (29.6)	49.5 (15.6)	43.3 (14.8)	36.5 (11.5)	86.1 (30.9)	89.7 (23.2)	N/A	N/A
Qin, 2015*	31.5 (25, 51.2)	25.5 (21.2, 30)	28 (23.2, 34.7)	27 (21, 30.7)	NA	NA	NA	NA
Rana, 2016	51.9 (17.5)	59.9 (30.6)	44.6 (17.8)	52.9 (27.3)	NA	NA	NA	NA
Rezaei, 2020	27.6 (20.8)	23 (15.8)	16.6 (9.2)	14.4 (7.9)	N/A	N/A	N/A	N/A
Scoreletti, 2014	54.0 (43)	44.0 (34)	38.0 (24)	30.0 (27)	NA	NA	NA	NA
Shojasaadat, 2019	34.8 (24.2)	35.3 (21.1)	28.2 (11.9)	27.1 (9.7)	NA	NA	NA	NA
Sofi, 2010	87 (16.9)	56.3 (14.4)	48.8 (7.6)	29.2 (3.4)	NA	NA	NA	NA
Spadaro, 2008	56.6 (24.1)	39.5 (14)	31.5 (13.2)	28 (8.8)	N/A	N/A	N/A	N/A
Takeshita, 2014	53.2 (8.6)	49.3 (6.5)	41.8 (6.7)	33.7 (4.1)	N/A	N/A	N/A	N/A
Tobin, 2018	37.5 (39)	38.1 (37.7)	27.1 (20.3)	28.7 (24.6)	85.5 (45.3)	83.2 (40.3)	0.5 (0.3)	0.5 (0.2)
Yaghoubi, 2017	78 (11)	53 (26)	70 (30)	41 (17)	N/A	N/A	N/A	N/A
Zhu, 2008	62.8 (35.9)	39.3 (18.9)	38.1 (21)	30.5 (12.7)	N/A	N/A	N/A	N/A

^ Results for patients on statin therapy.
*Median, interquartile range (IQR).

agents and 61 with combination therapy). The mean age of patients treated with single agent or a combination of two lipid-lowering agents was 49.3 (95% CI: 46.4-52.2) years, with 61.6% males (range: 35.7-87.2%). The mean body mass index was 30 (95% CI: 29-31) Kg/m^2. The median duration of treatment was 26 weeks [25-75% Interquartile range (IQR): 17.5-52 weeks] (Table 1). Among eleven studies with available information, 28.4% (range: 0-100) of patients were included with diabetes mellitus as comorbidity. Most importantly, 18 out of the included 21 studies (85.7%) had an elevated ALT at baseline.

3.2. Risk of bias within studies

Of 21 RCTs, all studies reported on random sequence generation (Supplementary Figs. 1 and 2). Four RCTs did not report on concealment of allocation. Ten studies did not blind the study personnel or participants, and thirteen studies did not blind the outcome assessor/s. Four RCTs did not report on the attrition rate, and one study failed to provide information on selective reporting of the outcomes. The

overall risk of bias was estimated to be low in twelve out of the twenty-one studies included in the meta-analysis.

3.3. Primary outcome—Change in liver chemistry

Data on ALT, AST, ALP, and serum total bilirubin values before and after treatment for intervention and control arms (Table 2) were pooled for SMD (95% CI) on change (pre-treatment − post-treatment).

Change in serum ALT levels was similar after intervention versus the control arm on pooled data from 21 studies, with mean difference (95% CI) of 0.35 (-0.19-0.88, P = 0.21). The data were heterogeneous with I^2 = 96, P<0.001 (Fig. 2A). There was no publication bias, Egger's regression test P = 0.21.

Mean serum AST levels from baseline value were also similar between treatment and control arm on pooled data from 19 studies, with mean difference (95% CI) of 0.58 (-0.05-1.2, P<0.07). The data were heterogeneous with I^2 = 96, P<0.001 (Fig. 2B). There was no publication bias, P = 0.66.
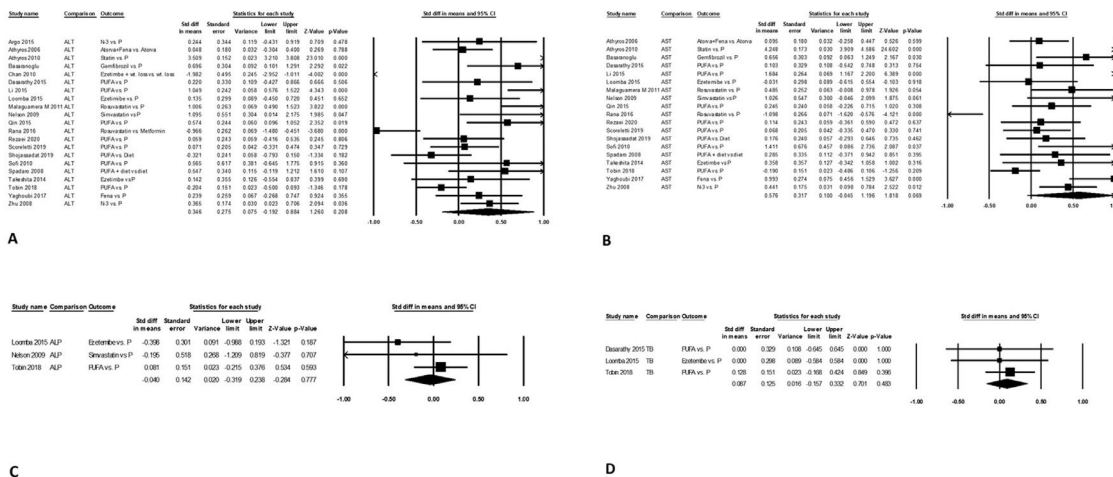

Fig. 2. Effect of treatment on **A)** serum total cholesterol (TC), **B)** low-density lipoprotein (LDL), **C)** high-density lipoprotein (HDL), and **D)** triglycerides (TG).

Table 3
Lipid profile [values given as mean (SD), mg/dL] before and after treatment.

Author, Year	TC pre-treatment	TC post-treatment	LDL pre-treatment	LDL post-treatment	TG pre-treatment	TG post-treatment	HDL pre-treatment	HDL post-treatment
Argo, 2015	191.5 (41)	193.9 (45.8)	122.6 (32.6)	124.1 (36.3)	155 (77.1)	132.2 (45.4)	N/A	N/A
Athyros, 2006	239.8 (38.7)	158.6 (27.1)	158.6 (42.5)	92.8 (15.5)	212.6 (115.2)	106.3 (35.4)	N/A	N/A
Athyros, 2010^	245.9 (27)	162.4 (7.7)	170.2 (19.3)	96.7 (7.7)	194.9 (53.1)	132.9 (26.6)	37.1 (7.7)	39.8 (7.7)
Basaranoglu, 1999	N/A	N/A	N/A	N/A	229 (141)	153 (90)	N/A	N/A
Chan, 2010	224.3 (11.6)	189.5 (11.6)	147 (11.6)	119.9 (7.7)	177.2 (17.8)	132.9 (8.9)	42.5 (3.9)	42.5 (3.9)
Dasarathy, 2015	177.9 (40.2)	182.5 (55.5)	N/A	N/A	175.2 (91.6)	211.5 (160.8)	40.6 (7.1)	43.2 (8.9)
Li, 2015	216.6 (15.5)	181.8 (11.6)	150.8 (11.6)	119.9 (23.2)	230.3 (26.6)	159.4 (26.6)	N/A	N/A
Loomba, 2015	182.0 (26.0)	152.0 (46.0)	99.0 (37.0)	76.0 (30)	152.0 (63)	125.0 (70)	NA	NA
Malaguarnera, 2011	201.1 (27.1)	177.9 (30.9)	100.5 (30.9)	77.3 (30.9)	194.9 (70.9)	177.2 (35.4)	42.5 (7.7)	42.5 (30.9)
Nelson, 2009	230.5 (72.5)	209.1 (114.7)	138.5	102.7	388.7 (507.9)	490 (890.5)	N/A	N/A
Qin, 2015	206.1 (45.6)	187.2 (40.6)	126.5 (25.5)	114.8 (25.9)	187.8 (91.2)	135.5 (75.3)	49.1 (7.3)	51 (8.5)
Rana, 2016	205.1 (29.3)	146.8 (19)	113.2 (38.3)	59.4 (12.5)	260.7 (21.4)	138.1 (14.2)	37.9 (5.1)	40.4 (4.6)
Rezaei, 2020	185.6 (42.5)	179 (46.4)	111.4 (34.8)	104 (34.8)	168.3 (141.7)	150.6 (115.2)	39.8 (6.6)	40.6 (7.3)
Scoreletti, 2014	189.5 (42.5)	181.7 (42.5)	116 (34.8)	108.3 (34.8)	159.4 (106.3)	132.9 (106.3)	38.7 (7.7)	42.5 (11.6)
Shojasaadat, 2019	188.4 (22.7)	201.3 (23.6)	104.4 (18.6)	107.9 (22.8)	158.6 (62.8)	165.9 (80.8)	45. (6.4)	45.1 (5.8)
Sofi, 2010	213.8 (27.9)	213 (23.1)	131.6 (24.6)	133.6 (32.3)	164.5 (85.5)	132.8 (63.7)	44.3 (5.5)	60.3 (9.3)
Spadaro, 2008	194.4 (26.8)	189.4 (15.9)	N/A	N/A	147.4 (41.1)	110 (39.1)	43.5 (14.7)	46.8 (12.9)
Takeshita, 2014	198.8 (7.7)	179.8 (6.6)	N/A	N/A	126.7 (9.7)	129.3 (11.5)	52.6 (3.1)	52.6 (2.3)
Tobin, 2018	N/A	N/A	N/A	N/A	192 (125.1)	157.8 (84.2)	N/A	N/A
Yaghoubi, 2017	186 (29)	179 (17)	N/A	N/A	143 (37)	101 (20)	N/A	N/A
Zhu, 2008	243.6 (32.1)	196.4 (29.4)	126.1 (38.7)	3.12 (32.5)	349 (238.3)	184.2 (91.2)	39.1 (9.3)	48.3 (9.3)

^ Results for patients on statin therapy * Percentage of patient improvement or stability after 6 months (95% CI) ** Median and interquartile range (IQR).

Change in serum ALP levels after intervention compared to control arm was similar on pooled data from three studies, with mean difference (95% CI) of -0.04 (-0.32 - 0.24, P = 0.78). The data were homogeneous with $I^2 = 6$, P = 0.34 without publication bias, P = 0.46 (Fig. 2C).

Change in mean serum bilirubin levels after intervention compared to control arm was similar on pooled data from three studies, with mean difference (95% CI) of 0.09 (-0.16 - 0.33, P = 0.48). The data were homogeneous with $I^2 = 0$, P = 0.89 without publication bias, P = 0.077 (Fig. 2D).

3.4. Secondary outcomes

3.4.1. Change in lipid profile

Data on TC, LDL, HDL, and TG values before and after treatment for the intervention as well for the control arm were extracted (Table 3). Data were pooled in the statistical software for MD (95% CI) on the change (pre-treatment − post-treatment) in the two arms.

Mean (95% CI) serum TC level was lower by 0.58 (0.03-1.31), P = 0.039 after intervention compared to control arm on pooled data from 18 studies. The data were heterogeneous with $I^2 = 95$, P<0.001 (Fig. 3A). There was no publication bias, P = 0.068.

Mean (95% CI) serum LDL level was lower by 0.83 (0.20-1.5, P = 0.01), after intervention compared to control arm on pooled data from 16 studies. The data were heterogeneous with $I^2 = 95$, P<0.001 (Fig. 3B). There was no publication bias, P = 0.90.

Mean (95% CI) serum HDL level changed by -0.04 (-0.39 - 0.32), P = 0.84 (Fig. 3C) after intervention compared to control arm on pooled data from eight studies. The data were homogeneous with $I^2 = 67$, P = 0.003, with a publication bias on Egger's test, P = 0.049.

Mean (95% CI) serum TG level was lower by 0.46 (0.05-0.88), P<0.03 after intervention compared to control arm on pooled data from 21 studies. The data were heterogeneous with $I^2 = 93$, P<0.001 (Fig. 3D). There was no publication bias, P = 0.67.
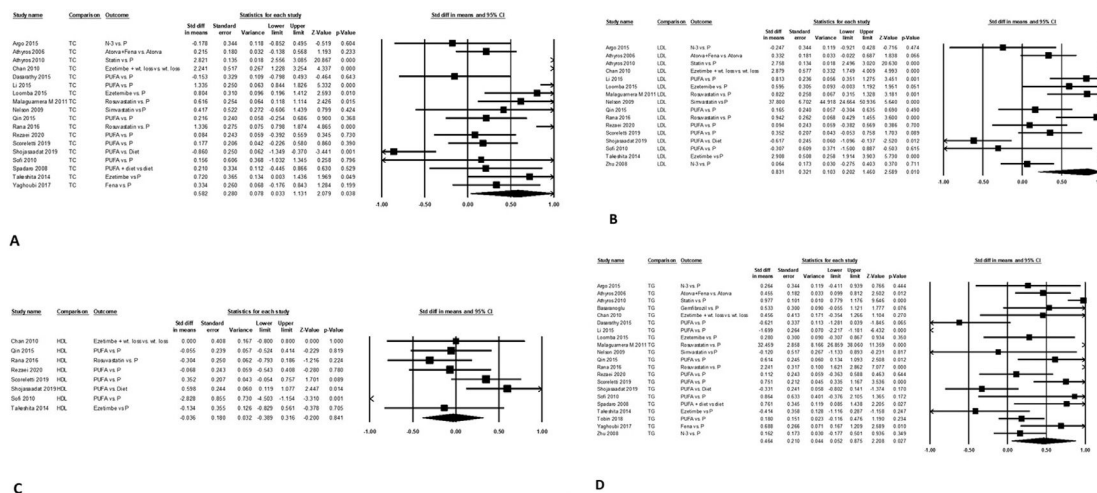

Fig. 3. Effect of treatment on **A)** steatosis grade, **B)** lobular inflammation score (LI), **C)** hepatocyte ballooning score, **D)** Non-alcoholic fatty liver disease (NAFLD) activity score (NAS), and **E)** fibrosis stage.
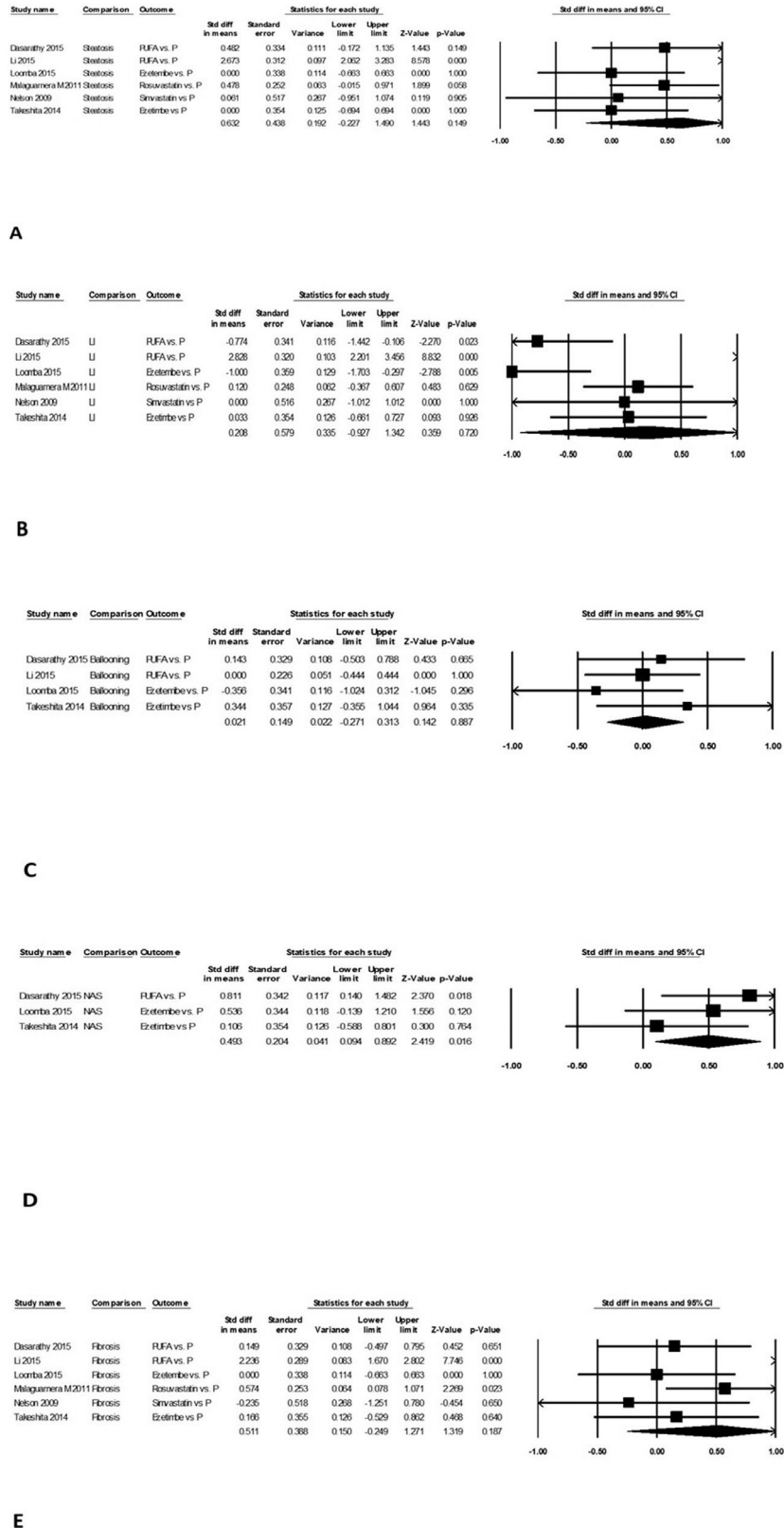
Fig. 4. Effect of treatment on A) steatosis grade, B) lobular inflammation score (LI), C) hepatocyte ballooning score, D) Non-alcoholic fatty liver disease (NAFLD) activity score (NAS), and E) fibrosis stage.

3.4.2. Change in liver histology

Data on steatosis grade, lobular inflammation score, hepatocyte ballooning score, NAS and fibrosis before and after treatment for the intervention as well for the control arm were extracted (Supplementary Table 1). Data were pooled in the statistical software for MD (95% CI) on the change (pre-treatment − post-treatment) in the two arms.

Change in steatosis grade was similar after intervention compared to control arm on pooled data from six studies, with mean difference (95% CI) of 0.63 (-0.23-1.49, P = 0.15). The data were heterogeneous with I^2 = 90, P<0.001 (Fig. 4A). There was no publication bias, P = 0.69.

Change in lobular inflammation score was similar after intervention compared to control arm on pooled data from six studies, with mean difference (95% CI) of 0.21 (-0.93-1.34, P = 0.80). The data were heterogeneous with I2 = 94, P<0.001 (Fig. 4B). There was no publication bias, P = 0.79.

Change in hepatocyte ballooning severity was similar after intervention compared to control arm on pooled data from four studies, with mean difference (95% CI) of 0.02 (-0.27-0.31, P = 0.89). The data were homogeneous with I^2 = 0, P = 0.53 (Fig. 4C). There was no publication bias, P = 0.87.

Mean (95% CI) NAS was lower by 0.49 (0.09-0.89), P<0.02 (Fig. 4D) after intervention compared to control arm on pooled data from three studies. The data were homogeneous with I^2 = 3, P = 0.36. There was no publication bias, P = 0.16.

Mean (95% CI) fibrosis stage was lower by 0.51 (-0.25 - 1.27), P = 0.19 (Fig. 4E) after intervention compared to control arm on pooled data from six studies. The data were heterogeneous with I^2 = 88, P<0.001. There was no publication bias, P = 0.36.

3.5. Subgroup analyses

Results were similar when pooled data were analyzed only for 12 studies with low risk of study bias (Supplementary Table 2). Similarly, results did not change on separately pooling 10 studies using lipid-lowering therapies and five using statins. The study using combination of statins and lipid-lowering drugs was counted in the subgroup of statins. Both subgroups improved LDL levels (mg/dL) by 1.8 on 8 non-statin studies and 1.64 in 5 studies using statins. Similarly, TG levels (mg/dL) decreased by 1.1 in 10 non-statin studies and 2.6 in 5 studies using statins. However, the decrease TC levels (mg/dL) decreased by 1.1 in 9 studies using non-statin based medications, but there was no change in 5 studies using statins (Supplementary Table 3). Although no publication bias was detected, heterogeneity between studies was noted in both subgroups for most analyses.

4. Discussion

The main finding of this meta-analysis is that drugs used for dyslipidemia among patients with NAFLD are not associated with worsening of liver enzymes, including patients with elevated liver chemistry at baseline. Further, lipid-lowering therapies are associated with improvement in lipid profile, especially LDL levels and TG. Although there was improvement in NAFLD activity score, there was no benefit on its components or on fibrosis.

Asymptomatic ALT elevation with statins is dose−related, and occurs in less than 3% within the first 12 weeks of therapy, which improves spontaneously in the majority of patients [15]. In another meta−analysis (n = 49,275), statin use versus placebo was not associated with liver enzymes elevation of > 3 times upper limit normal (1.1% vs. 1.1%, OR 1.3, 95% CI: 0.99−1.62) [16]. Further, the incidence of acute liver failure with statins has been shown to be similar to that of the general population (1:130,000 vs. 1:114,000) [17]. Our NAFLD focused analysis also showed no increased risk of elevation of liver enzymes with use of statins or lipid-lowering drugs. Our study findings strengthen the recently published American Gastroenterology Association Clinical Practice Update based on an expert review advocating that statins and other lipid lowering therapies are safe and effective in NAFLD patients and should not be avoided because of fears of hepatotoxicity [18]. Although drug induced hepatotoxicity are linked to fibrates, compelling evidence for fibrate-induced hepatotoxicity is not available [19]. In a meta-analysis of twenty-six studies on 9494 individuals, the use of fibrates combined with statins was associated with increased risk of hepatotoxicity [20]. However, in the current meta-analysis, use of fibrates and omega-3 fatty acids among NAFLD patients did not increase this risk.

The benefit of statins or lipid-lowering therapies on histological improvement of NASH remains controversial. For example, use of eicosapentanoic acid among patients with NASH or NAFLD did not show any benefit on the liver histology [21, 22]. In another study on 100 subjects, use of statins protected from steatosis, NASH, and fibrosis stage F2-4. This effect was dose dependent and was stronger in subjects not carrying the *PNPLA3* at-risk variant [23]. Also, resolution of NASH was shown in 19 out of 20 patients after treatment with rosuvastatin in some reports [24]. Our subgroup analysis, however, did not show improvement of NAS or any of its components with statin or non-statin therapy. This finding is similar to the recently published American Gastroenterology Association Clinical Practice Update based on expert review concluding that no firm recommendation could be derived on the benefit of lipid-lowering therapies on liver histology [18]. The lack of benefit could be due to short period of treatment and observation of about 26 weeks in this pooled data. In a recent report, the observation period on the benefit of statins to reduce the risk of hepatocellular carcinoma was 4-19 years [25]. Studies with long-term treatment are needed to establish the role of these drugs among patients with NASH on improvement of liver disease.

Dyslipidemia among NAFLD patients confers increased risk of cardiovascular disease, the most common cause of death in these patients [26−28]. The association of effective treatment of dyslipidemia on the cardiovascular outcomes is variable with benefit in many studies [29−33], however, no benefit was shown in a recently reported analysis of subjects enrolled in the National Health and Nutrition Examination Survey [34]. In addition, statins use has been shown to protect from NASH and fibrosis among at-risk individuals with improvement in liver histology in NASH patients. Statins also reduce portal pressure, liver disease severity and decompensation, hepatocellular carcinoma risk, and patient mortality in patients with cirrhosis [23, 24, 35, 36].

Pooled data from 21 RCT with large sample size and satisfactory follow up duration is a strength of our study. However, our study is limited by heterogeneous data due to variations across studies on active ingredient, dose, treatment regimen, duration of treatment, and follow up period. Despite heterogeneous data, this pooled data confirms safety of treatment of dyslipidemia among NAFLD patients, with no increased risk for liver enzyme elevations and hepatotoxicity. Although, there are previous studies highlighting safety of drugs for dyslipidemia in NAFLD patients including a recently published practice guidance document by the American Gastroenterological Association, our meta-analysis of all randomized controlled studies on different lipid-lowering therapies has not been performed earlier and provides a high level of evidence to further reassure physicians and providers on the safety of these drugs for treatment of dyslipidemia in NAFLD patients. With effective improvement of lipid profile and reduced risk for cardiovascular event, and added potential benefit on liver disease, the findings of this meta-analysis on safety on treatment of dyslipidemia in NAFLD patients will be reassuring to the practicing physicians. However, it is recommended to obtain baseline liver chemistry profile before initiating the treatment, and practice repeated testing on follow up during treatment of dyslipidemia among patients with NAFLD [37].

5. Conclusion

This meta-analysis of randomized controlled trials examining statins and/or other lipid-lowering therapies in NAFLD patients showed no evidence for worsening of liver chemistry. Studies with longer use of lipid-lowering therapies are suggested to examine benefit on liver histology among patients with NAFLD.

Funding

Author Contributions

MA drafted the article and interpreted the data; LB conceived the idea and extracted the study data; JP extracted the study data; RT contributed to drafting the article; SG extracted the study data; AKS conceived the study design, performed analyses, provided study supervision, and drafted the article. All the authors approved the final version of the manuscript.

Conflicts of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.aohep.2022.100738.

References

[1] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease—Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67 (1):328–57. https://doi.org/10.1002/hep.29367.

[2] Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148(3):547–55. https://doi.org/10.1053/j.gastro.2014.11.039.

[3] Singal AK, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. Transplantation 2014. https://doi.org/10.1097/TP.0000000000000048.

[4] Axley P, Ahmed Z, Arora S, Haas A, Kuo YF, Kamath PS, et al. NASH is the most rapidly growing etiology for acute-on-chronic liver failure-related hospitalization and disease burden in the United States—A population-based study. Liver Transpl 2019;25(5):695–705. https://doi.org/10.1002/lt.25443.

[5] Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol 2019;17(4):748–55 e3. https://doi.org/10.1016/j.cgh.2018.05.057.

[6] Adhyaru BB, Jacobson TA. New cholesterol guidelines for the management of atherosclerotic cardiovascular disease risk—A comparison of the 2013 American College of Cardiology/American Heart Association Cholesterol Guidelines with the 2014 National Lipid Association recommendations for patient-centered management of dyslipidemia. Endocrinol Metab Clin N Am 2016;45(1):17–37. https://doi.org/10.1016/j.ecl.2015.09.002.

[7] Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis—Molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des 2012;18(11):1519–30 <Go to ISI>:// WOS:000304821900009.

[8] Bosch J, Gracia-Sancho J, Abraldes JG. Cirrhosis as new indication for statins. Gut 2020. https://doi.org/10.1136/gutjnl-2019-318237.

[9] Chalasani N. Statins and hepatotoxicity—Focus on patients with fatty liver. Hepatology 2005;41(4):690–5. https://doi.org/10.1002/hep.20671.

[10] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.

[11] McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res 2020:962280219889080. https://doi.org/10.1177/0962280219889080.

[12] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology (Baltimore, Md) 2005;41(6):1313–21. https://doi.org/10.1002/hep.20701.

[13] Deeks JJ AD, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. 2nd ed. London: BMJ Books; 2005.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses—The PRISMA statement. PLoS Med 2009;6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097.

[15] Chang CY, Schiano TD. Review article—Drug hepatotoxicity. Aliment Pharmacol Ther 2007;25(10):1135–51. https://doi.org/10.1111/j.1365-2036.2007.03307.x.

[16] de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity—A meta-analysis. Pharmacotherapy 2004;24(5):584–91. https://doi.org/10.1592/phco.24.6.584.34738.

[17] Onofrei MD, Butler KL, Fuke DC, Miller HB. Safety of statin therapy in patients with preexisting liver disease. Pharmacotherapy 2008;28(4):522–9. https://doi.org/10.1592/phco.28.4.522.

[18] Speliotes EK, Balakrishnan M, Friedman LS, Corey KE. Treatment of dyslipidemia in common liver diseases. Clin Gastroenterol Hepatol 2018;16(8):1189–96. https://doi.org/10.1016/j.cgh.2018.04.023.

[19] Hedrington MS, Davis SN. Peroxisome proliferator-activated receptor alpha-mediated drug toxicity in the liver. Expert Opin Drug Metab Toxicol 2018;14 (7):671–7. https://doi.org/10.1080/17425255.2018.1483337.

[20] Geng Q, Ren JY, Li SF, Chen H. [A meta-analysis on the safety of combination therapy with fenofibrate and statins]. Zhonghua Xin Xue Guan Bing Za Zhi 2013;41 (12):1063–8.

[21] Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M, Group E-AS. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology 2014;147(2):377–84 e1. https://doi.org/10.1053/j.gastro.2014.04.046.

[22] Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease—Results from the Welcome* study. Hepatology (Baltimore, Md) 2014;60 (4):1211–21. https://doi.org/10.1002/hep.27289.

[23] Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, et al. Statin use and non-alcoholic steatohepatitis in at risk individuals. J Hepatol 2015;63 (3):705–12. https://doi.org/10.1016/j.jhep.2015.05.006.

[24] Kargiotis K, Athyros VG, Giouleme O, Katsiki N, Katsiki E, Anagnostis P, et al. Resolution of non-alcoholic steatohepatitis by rosuvastatin monotherapy in patients with metabolic syndrome. World J Gastroenterol 2015;21(25):7860–8. https://doi.org/10.3748/wjg.v21.i25.7860.

[25] Islam MM, Poly TN, Walther BA, Yang HC, Jack Li YC. Statin use and the risk of hepatocellular carcinoma—A meta-analysis of observational studies. Cancers (Basel) 2020;12(3). https://doi.org/10.3390/cancers12030671.

[26] Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149(2):389–97 e10. https://doi.org/10.1053/j.gastro.2015.04.043.

[27] Tariq R, Axley P, Singal AK. Extra-hepatic manifestations of nonalcoholic fatty liver disease—A review. J Clin Exp Hepatol 2020;10(1):81–7. https://doi.org/10.1016/j.jceh.2019.07.008.

[28] Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis—Natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. Ann Med 2011;43(8):617–49. https://doi.org/10.3109/07853890.2010.518623.

[29] Graham I, Cooney MT, Bradley D, Dudina A, Reiner Z. Dyslipidemias in the prevention of cardiovascular disease—Risks and causality. Curr Cardiol Rep 2012;14 (6):709–20. https://doi.org/10.1007/s11886-012-0313-7.

[30] Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia—An update. Metabolism 2016;65(8):1109–23. https://doi.org/10.1016/j.metabol.2016.05.003.

[31] Corey KE, Misdraji J, Gelrud L, Zheng H, Chung RT, Krauss RM. Nonalcoholic steatohepatitis is associated with an atherogenic lipoprotein subfraction profile. Lipids Health Disease 2014;13:100. https://doi.org/10.1186/1476-511x-13-100.

[32] Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study—A post-hoc analysis. Lancet 2010;376 (9756):1916–22. https://doi.org/10.1016/S0140-6736(10)61272-X.

[33] Tikkanen MJ, Fayyad R, Faergeman O, Olsson AG, Wun CC, Laskey R, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. Int J Cardiol 2013;168(4):3846–52. https://doi.org/10.1016/j.ijcard.2013.06.024.

[34] Shahab O, Biswas R, Paik J, Bush H, Golabi P, Younossi ZM. Among patients with NAFLD, treatment of dyslipidemia does not reduce cardiovascular mortality. Hepatol Commun 2018;2(10):1227–34. https://doi.org/10.1002/hep4.1241.

[35] Pose E, Napoleone L, Amin A, Campion D, Jimenez C, Piano S, et al. Safety of two different doses of simvastatin plus rifaximin in decompensated cirrhosis (LIVER-HOPE-SAFETY)—A randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Gastroenterol Hepatol 2020;5(1):31–41. https://doi.org/10.1016/S2468-1253(19)30320-6.

[36] Pose E, Trebicka J, Mookerjee RP, Angeli P, Gines P. Statins—Old drugs as new therapy for liver diseases? J Hepatol 2019;70(1):194–202. https://doi.org/10.1016/j.jhep.2018.07.019.

[37] Bays H, Cohen DE, Chalasani N, Harrison SA. The National Lipid Association's Statin Safety Task F. An assessment by the statin liver safety task force−2014 update. J Clin Lipidol 2014;8(3 Suppl):S47–57. https://doi.org/10.1016/j.jacl.2014.02.011.

[38] Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH−A double-blind, randomized, placebo-controlled trial. J Hepatol 2015;62(1):190–7. https://doi.org/10.1016/j.jhep.2014.08.036.

[39] Athyros VG, Mikhailidis DP, Didangelos TP, Giouleme OI, Liberopoulos EN, Karagiannis A, et al. Effect of multifactorial treatment on non-alcoholic fatty liver disease in metabolic syndrome−A randomised study. Curr Med Res Opin 2006;22 (5):873–83. https://doi.org/10.1185/030079906X104696.

[40] Basaranoglu M, Acbay O, Sonsuz A. A controlled trial of gemfibrozil in the treatment of patients with nonalcoholic steatohepatitis. J Hepatol 1999;31(2):384. https://doi.org/10.1016/s0168-8278(99)80243-8.

[41] Chan DC, Watts GF, Gan SK, Ooi EM, Barrett PH. Effect of ezetimibe on hepatic fat, inflammatory markers, and apolipoprotein B-100 kinetics in insulin-resistant obese subjects on a weight loss diet. Diabetes Care 2010;33(5):1134–9. https://doi.org/10.2337/dc09-1765.

[42] Dasarathy S, Dasarathy J, Khiyami A, Yerian L, Hawkins C, Sargent R, et al. Double-blind randomized placebo-controlled clinical trial of omega 3 fatty acids for the treatment of diabetic patients with nonalcoholic steatohepatitis. J Clin Gastroenterol 2015;49(2):137–44. https://doi.org/10.1097/mcg.0000000000000099.

[43] Li YH, Yang LH, Sha KH, Liu TG, Zhang LG, Liu XX. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. World J Gastroenterol 2015;21(22):7008–13. https://doi.org/10.3748/wjg.v21.i22.7008.

[44] Loomba R, Sirlin CB, Ang B, Bettencourt R, Jain R, Salotti J, et al. Ezetimibe for the treatment of nonalcoholic steatohepatitis−Assessment by novel magnetic resonance imaging and magnetic resonance elastography in a randomized trial (MOZART trial). Hepatology (Baltimore, Md) 2015;61(4):1239–50. https://doi.org/10.1002/hep.27647.

[45] Malaguarnera M, Vacante M, Russo C, Gargante MP, Giordano M, Bertino G, et al. Rosuvastatin reduces nonalcoholic fatty liver disease in patients with chronic hepatitis C treated with α-interferon and ribavirin−Rosuvastatin reduces NAFLD in HCV patients. Hepat Mon 2011;11(2):92–8.

[46] Nelson A, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis−A randomized placebo-controlled trial. J Clin Gastroenterol 2009;43(10):990–4. https://doi.org/10.1097/MCG.0b013e31819c392e.

[47] Qin Y, Zhou Y, Chen SH, Zhao XL, Ran L, Zeng XL, et al. Fish oil supplements lower serum lipids and glucose in correlation with a reduction in plasma fibroblast growth factor 21 and prostaglandin E2 in nonalcoholic fatty liver disease associated with hyperlipidemia−A randomized clinical trial. PLoS One 2015;10 (7):e0133496. https://doi.org/10.1371/journal.pone.0133496.

[48] Rana H, Yadav SS, Reddy HD, Singhal S, Singh DK, Usman K. Comparative effect of insulin sensitizers and statin on metabolic profile and ultrasonographical score in non alcoholic fatty liver disease. J Clin Diagn Res 2016;10(8):OC19–23. https://doi.org/10.7860/JCDR/2016/19887.8336.

[49] Rezaei S, Sasani MR, Akhlaghi M, Kohanmoo A. Flaxseed oil in the context of a weight loss program ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease−A randomized double-blind controlled trial. Br J Nutr 2020:1–24. https://doi.org/10.1017/s0007114520000318.

[50] Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease−Results from the Welcome* study. Hepatology (Baltimore, Md) 2014;60 (4):1211–21. https://doi.org/10.1002/hep.27289.

[51] Shojasaadat F, Ayremlou P, Hashemi A, Mehdizadeh A, Zarrin R. A randomized controlled trial comparing effects of a low-energy diet with n-3 polyunsaturated fatty acid supplementation in patients with non-alcoholic fatty liver disease. J Res Med Sci 2019;24:21. https://doi.org/10.4103/jrms.JRMS_282_18.

[52] Sofi F, Giangrandi I, Cesari F, Corsani I, Abbate R, Gensini GF, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients−A preliminary study. Int J Food Sci Nutr 2010;61(8):792–802. https://doi.org/10.3109/09637486.2010.487480.

[53] Spadaro L, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, et al. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. Dig Liver Dis 2008;40(3):194–9. https://doi.org/10.1016/j.dld.2007.10.003.

[54] Takeshita Y, Takamura T, Honda M, Kita Y, Zen Y, Kato K, et al. The effects of ezetimibe on non-alcoholic fatty liver disease and glucose metabolism−A randomised controlled trial. Diabetologia 2014;57(5):878–90. https://doi.org/10.1007/s00125-013-3149-9.

[55] Tobin D, Brevik-Andersen M, Qin Y, Innes JK, Calder PC. Evaluation of a high concentrate omega-3 for correcting the omega-3 fatty acid nutritional deficiency in non-alcoholic fatty liver disease (CONDIN). Nutrients 2018;10(8). https://doi.org/10.3390/nu10081126.

[56] Yaghoubi M, Jafari S, Sajedi B, Gohari S, Akbarieh S, Heydari AH, et al. Comparison of fenofibrate and pioglitazone effects on patients with nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2017;29(12):1385–8. https://doi.org/10.1097/MEG.0000000000000981.

[57] Zhu FS, Liu S, Chen XM, Huang ZG, Zhang DW. Effects of n-3 polyunsaturated fatty acids from seal oils on nonalcoholic fatty liver disease associated with hyperlipidemia. World J Gastroenterol 2008;14(41):6395–400 https://www.ncbi.nlm.nih.gov/pubmed/19009658.