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Ezetimibe decreased nonalcoholic fatty liver disease activity score but not hepatic steatosis

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Background/Aims: A number of clinical trials reported varying effects of cholesterol lowering agents in nonalcoholic fatty liver disease (NAFLD) patients. We, therefore, assessed the changes in hepatic steatosis and NAFLD activity score (NAS) after treatment with cholesterol lowering agents in NAFLD patients by meta-analysis.

Methods: The Cochrane Library, the MEDLINE, and the Embase databases were searched until May 2015, without any language restrictions, for randomized controlled trials (RCTs) and nonrandomized studies (NRSs). Additional references were obtained from review of bibliography of relevant articles. The quality of evidence was assessed using the grading of recommendations assessment, development and evaluation guidelines.

Results: Three RCTs (n = 98) and two NRSs (n = 101) met our study inclusion criteria (adult, NAFLD, liver biopsy). Liver biopsy was performed in all five studies, but only the three studies reported NAS. Ezetimibe significantly decreased NAS (standardized mean difference [SMD], −0.30; 95% confidence interval [CI], −0.57 to −0.03) but not hepatic steatosis in RCT (SMD, −0.1; 95% CI, −0.53 to 0.32), while the effect was significant for both NAS and intrahepatic content in NRSs (SMD, −3.0; 95% CI, −6.9 to 0.91).

Conclusions: Ezetimibe decreased NAS without improving hepatic steatosis.

Keywords: Meta-analysis; Non-alcoholic fatty liver disease; Hydroxymethylglutaryl-CoA reductase inhibitors; Ezetimibe

INTRODUCTION

Metabolic syndrome is a major risk factor for nonalcoholic fatty liver disease (NAFLD), with approximately half of all NAFLD patients also having hypercholesterolemia [1]. Current treatment for NAFLD consists largely of lifestyle modifications and treatment of comorbid conditions such as hyperlipidemia. Experimental studies in mice have shown that ezetimibe and statins not only reduce hepatic inflammation but also fibrosis [2]. Several studies also suggested that hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors may improve liver function tests and histology of NAFLD patients [3,4].

Results from both randomized control trials (RCTs) and non-RCT studies (NRSs) on the effects of cholesterol lowering agents have been difficult to interpret due to the variations in study designs, diagnostic criteria and types of cholesterol lowering agents used. For instance, a sub-study of the St. Francis heart study of 455 subjects showed that, 20 mg of atorvastatin combination with vitamins effectively reduced the odds of developing

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hepatic steatosis by 71% in healthy individuals as well as those with NAFLD [5]. Another study by Park et al. [6] which included 45 subjects showed ezetimibe as a promising agent for the treatment of NAFLD; however, this study did not have a control arm. In addition, most existing investigations were case control studies [7], and there are currently only four RCTs examining this important issue [4,8,9].

A recent Cochrane systematic review in 2013 identified only two RCTs with a total 205 participants, and neither study evaluated the histological response to statin therapy [7]. The authors concluded that there were insufficient evidence to either support or refute the use of statins in patients with NAFLD.

In the present study, we investigated the efficacy of cholesterol lowering agents in biopsy-proven NAFLD patients. Primary outcome was changes in hepatic steatosis, while the secondary outcomes were improvements in NAFLD activity score (NAS) as assessed by liver biopsy.

METHODS

Data source and literature source

Two investigators independently searched MEDLINE (January 1, 1946 to May 30, 2015), Embase (January 1, 1947 to May 30, 2015) and the Cochrane Central Register of Controlled Trials (CENTRAL; January 1, 1966 to May 30, 2015) without language or publication year restriction.

The following keywords, MeSH and free text were searched through MEDLINE: NAFLD, statin, and ezetimibe (Supplementary Table 1). Bibliographies of potentially relevant articles were manually reviewed to identify additional relevant studies. The identified articles were assessed individually for inclusion (Supplementary Table 2).

Study selection

The studies were initially abstracted if they included the following keywords: NAFLD, statin, cholesterol lowering agent, ezetimibe. For inclusion, the studies were independently selected by two stages of screening using the Population Intervention Comparison Outcome framework [10]. Since the study objective was the histological effect with the lipid lowering agents, only those studies with liver biopsy results for diagnosis of NAFLD and post-treatment were included [11,12]. The required intervention included HMG-CoA reductase inhibitors or ezetimibe which can be administered at any dose for at least 6 months. The control group received no lipid lowering intervention or placebo, and there were no change of weight in all studies. The primary endpoint was improvement in hepatic steatosis while the secondary endpoint was improvement of NAS and safety.

Data extraction

Using a pre-defined data extraction form, two reviewers (H.Y.L. and D.W.J.) independently extracted data from each study. Any disagreement was independently reviewed by a third reviewer (H.J.K.). The following variables were extracted from the selected studies: (1) hepatic steatosis as evaluated by liver biopsy and/or quantitative fat measurement by magnetic resonance imaging (MRI); (2) NAS measurement before and after therapeutic intervention. All outcomes were assessed by differences between treated and control groups. The results were expressed as mean and standard deviations.

Assessment of study methodological quality

Two reviewers (H.Y.J. and D.W.J.) independently assessed the methodological qualities of included studies. The study quality was evaluated using the risk of bias by Cochrane for RCTs (Supplementary Fig. 1) and Newcastle Ottawa scale for NRSs (Supplementary Table 2) [13]. Any unresolved disagreements between reviewers were resolved by the third author (H.J.K.). Publication bias was not assessable due to the small numbers of studies.

Statistical analysis

We analyzed continuous data using standardized mean difference to combine trials that measure the same outcome but utilized different methods. The primary outcome was change of hepatic steatosis by liver biopsy (and MRI quantification in one study). The histological grading in NAFLD, inflammation, and fibrosis was based on scoring systems by either Brunt et al. [14] or Kleiner [15]. Secondary outcome were changes in NAS.

To assess for heterogeneity, we estimated the proportion of between-study inconsistency due to true differences between studies (rather than differences due

to random error or chance) using the I^2 statistic, with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. Outcomes were analyzed using random effects model and standardized mean difference (SMD) to assess changes in measurements made by different scales. All analyses were performed using RevMan version 5.2 (http://community.cochrane.org/). This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Revise and Meta-Analyses (PRISMA) statement.

RESULTS

Identification of studies

Fig. 1 shows the details of literature research and selection process of the meta-analysis. The initial search strategy identified 857 articles. Of these, 667 publications were excluded after reviewing the title and abstract which indicated that they did not fulfill the selection criteria (Supplementary Table 3). For the remaining 39 articles [4,6-11,13-44], we performed full manuscript review and identified five relevant studies (three RCTs and two NRSs) to include in this meta-analysis.

Study characteristics and patient populations

Table 1 describes characteristics of the five included studies. The five studies comprised a total of 199 participants who received either statins (n = 47) or ezetimibe (n = 42) in the treatment group, and placebo (n = 97) or ursodeoxycholic acid (UDCA) (n = 13) in the control group. Ezetimibe was administered for 6 months and statins was administered from 6 months to 6 years [8,9]. Two studies were conducted in the USA, and one each in Japan, Sweden, and Romania. The study by Nelson et al. [4], Ekstedt et al. [28] and Georgescu and Georgescu [30] used statins, while the study by Loomba et al. [8] and Takeshita et al. [9] used ezetimibe as the lipid lowering agent. By inclusion criteria, liver biopsy was performed in all five studies, but magnetic resonance spectroscopy was also used in one study [8]. The control subjects received placebo except for those in the study by Georgescu and Georgescu [30] which used UDCA. In terms of race/ethnicity, three studies [4,28,30] included mostly or all Caucasian, while two studies [8,9] included mostly or all Asians. In both studies that used ezetimibe for 6 months, the baseline cholesterol level was within normal range (180 to 190 mg/dL). However, in the study by Georgescu and Georgescu [30] in which statin was used, the baseline cholesterol levels were high with mean level ranging 318 to 326 mg/dL. Loomba et al. [8] studied Caucasian subjects (baseline BMI, 33 to 34 kg/m^2), while Takeshita et al. [9] studied East Asian subjects with lower BMI (baseline BMI, 28 to 31 kg/m^2).

Quality of the studies

Among the three RCTs, the quality of two studies [8,9] was satisfactory, but one study [4] did not have random allocation sequence, optimal allocation concealment, and detailed data description. However, treated and control

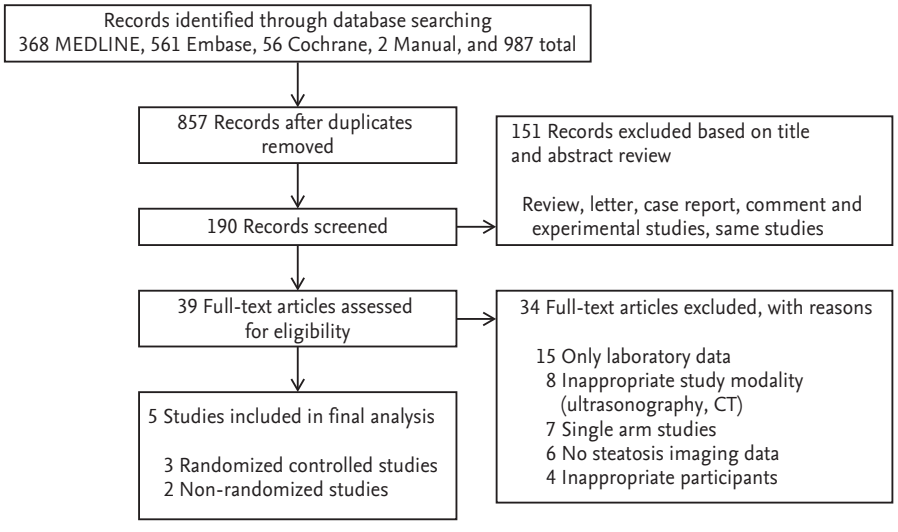

Figure 1. Preferred Reporting Items for Systematic Revise and Meta-Analyses (PRISMA) diagram of the literature search. CT, computed tomography.

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Table 1. Study characteristics

Variable	Nelson et al. (2009) [4]	Takeshita et al. (2014) [9]	Loomba et al. (2015) [8]	Georgescu et al. (2007) [30]	Ekstedt et al. (2007) [28]
Study design	RCT	RCT	RCT	Open label	Retroactive-prospective
Country	USA	Japan	USA	Romania	Sweden
Percentage with NASH	100	NR	100	100	65
Intervention	Simvastatin 40 mg	Ezetimibe 10 mg	Ezetimibe 10 mg	Atorvastatin 10 mg	Any statin
Treatment duration, mon	12	6	6	18.7	73.2
No. with repeat biopsy[a]	10	16	17	10	17
Mean duration between biopsy	Baseline (within 6 mon) and 12 mon	Baseline and 6 mon	Baseline (within 6 mon) and 6 mon	Baseline (within 2 wk) and last visit	13.8 ± 1.2 yr from first biopsy
Race/ethnicity	White, Hispanic, African	Asian	Caucasian	Caucasian	White
Sample size	16	32	50	23	68
Male sex	11	20	19	NR	48
Mean age, yr	53	52.5	49.2	55	47.1
Cholesterol, mg/dL	208–231	170–199	170–182	318–326	230–264
BMI, kg/m^2, range	34–37	28–31	33–34	35	27–30
Percentage of diabetes	28	NR	12	NR	80
Improvement in histology, mean ± SD					
Steatosis (grade or %)					
Before	25.0% ± 14.7%	1.56 ± 0.18	2.00 ± 1.00	2.60 ± 0.27	20.4% ± 7.5%
After	23.8% ± 21.2%	1.31 ± 0.15	1.00 ± 1.00	1.40 ± 0.17	11.1% ± 8.9%[b]
p value	0.8847	0.3000	0.2500	0.0001	0.001
Lobular inflammation					
Before	NR	NR	1.41 ± 0.49	1.80 ± 0.20	0 ± 0
After	NR	NR	1.65 ± 0.59	1.50 ± 0.17	0.12 ± 0.32
Ballooning					
Before	NR	0.69 ± 0.20	1.29 ± 0.57	1.10 ± 0.13	0.12 ± 0.32
After	NR	0.41 ± 0.15	1.00 ± 0.77	0.80 ± 0.10	0.41 ± 0.60
Fibrosis					
Before	1.25 ± 0.70	NR	1.35 ± 1.23	1.50 ± 0.17	0.88 ± 0.83
After	1.50 ± 0.90	NR	1.29 ± 1.28	1.30 ± 0.13	1.35 ± 1.33
Mean NAS					
Before	NR	3.71 ± 0.50	5.2 ± 2.00	6.70 ± 1.337	NR
After	NR	3.06 ± 0.45	4.0 ± 2.00[c]	5.00 ± 1.563[d]	NR
p value	NR	0.1850	0.2910	0.0176	NR

RCT, randomized controlled trials; NASH, nonalcoholic steatohepatitis; NR, not reported; BMI, body mass index; NSC, no statistical significant change.

[a]Exclude patients who complete the study but did not have repeat liver biopsy.

[b]$p = 0.01$.

[c]5% or 33% had a 2+ point improvement in nonalcoholic fatty liver diseases activity score.

[d]Mean differences –2.0 with $p < 0.0001$.

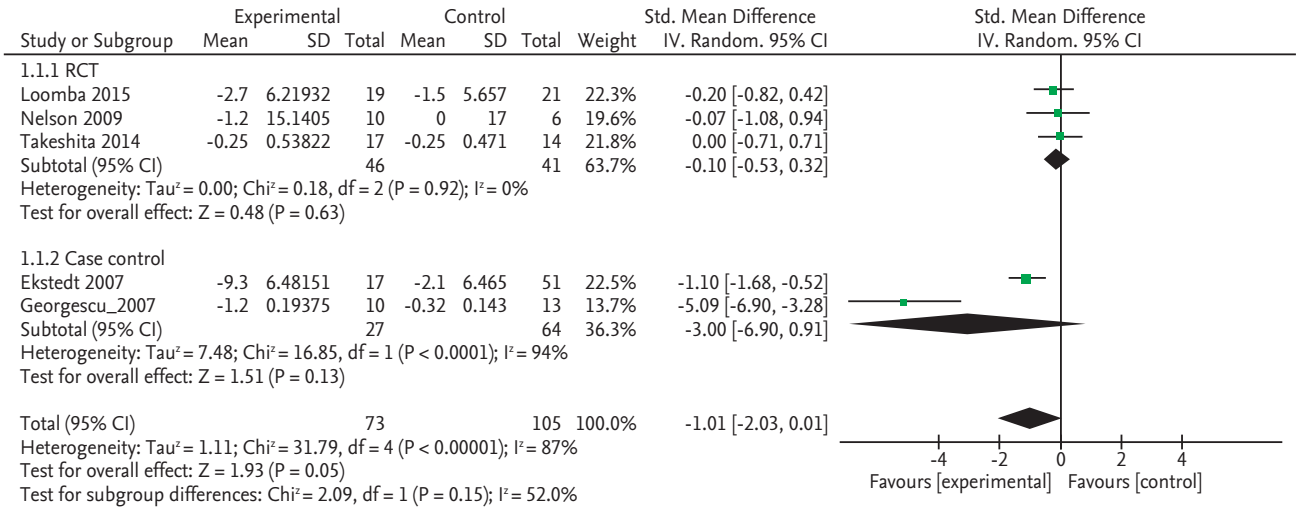

Figure 2. Forest plot for improving rate of intrahepatic fat. RCT, randomized controlled trials; SD, standard deviation; IV, interval variable; CI, confidence interval.

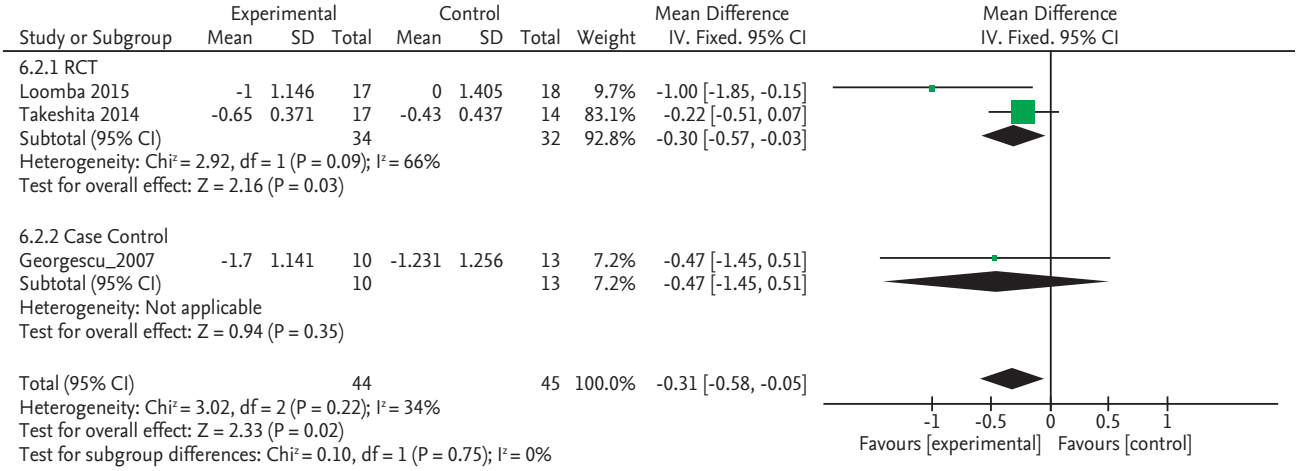

Figure 3. Forest plot for improving rate of nonalcoholic fatty liver diseases activity score in randomized controlled trials (RCT). SD, standard deviation; IV, interval variable; CI, confidence interval.

groups in all three RCTs were well-matched based on baseline characteristics with well-defined treatment response. In the two NRSs, subjects in the two groups were not well-matched since they were not randomized. The level of evidence and grade of recommendation for each outcome are summarized in Supplementary Table 2.

Hepatic steatosis

Cholesterol lowering agents did not significantly decreased the hepatic steatosis in NAFLD patients in the three RCTs (SMD, –0.10; 95% confidence interval [CI], –0.53 to 0.32) or in two NRSs (SMD, –3.00; 95% CI, –6.90 to 0.91) (Fig. 2).

Nonalcoholic fatty liver diseases activity score

Only two RCTs and one NRS reported the NAS data. Meta-analyzed result of the two RCT studies demonstrated a significant improvement of NAS (SMD, –0.30; 95% CI, –0.57 to –0.03). As shown in Fig. 3, pooled estimate of all three studies with available data also showed significant improvement. However, the mean reduction of NAS was modest: –1.0 in in Loomba et al. [8] and –0.65 in Takeshita et al. [9] but slightly higher in the case control study by Georgescu and Georgescu (mean, –1.7) [30].

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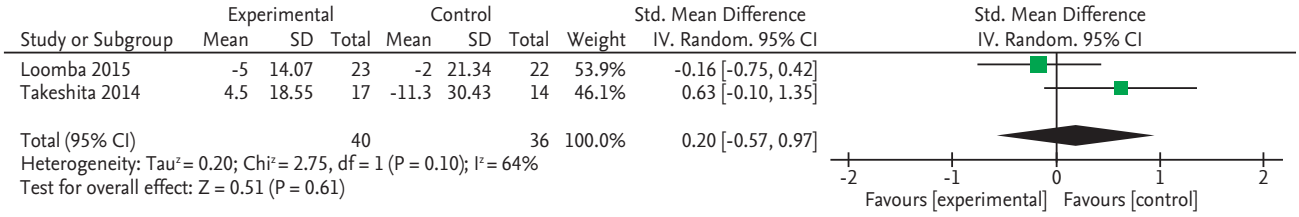

Figure 4. Forest plot for decrease of serum fasting glucose. Std., standardized; SD, standard deviation; IV, interval variable; CI, confidence interval.

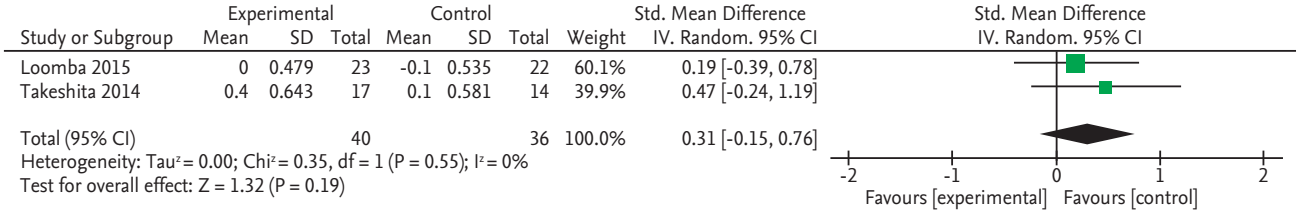

Figure 5. Forest plot for decrease of serum glycated hemoglobin. Std., standardized; SD, standard deviation; IV, interval variable; CI, confidence interval.

Safety

There was no significant change in serum fasting glucose levels in the two RCTs (SMD, 0.20; 95% CI, –0.57 to 0.97) (Fig. 4) [8,9]. Data on glycated hemoglobin (HbA1c) changes were also only reported in these two RCTs and there was no significant change (SMD, 0.31; 95% CI, –0.15 to 0.76) (Fig. 5) [8,9].

DISCUSSION

Our meta-analysis showed that ezetimibe decreased NAS (SMD, –0.30; 95% CI, –0.57 to –0.03) without observable improvement in hepatic steatosis. A recent systematic review suggested that statin therapy may improve serum aminotransferase and ultrasound findings [7]. The fundamental differences between our meta-analysis and the previous systemic review were the quantitative methods used for assessment of hepatic steatosis. Our meta-analysis is based only on biopsy, and in one study also MRI-estimated proton density fat fraction (MRI-PDFF) to quantify hepatic fat contents. Contrary to the previous systemic review which included sonography studies for hepatic steatosis assessment, we excluded studies using the sonographic method because it is subjective and poorly quantifiable [11]. Computed tomography (CT) scan is also a less sensitive method to diagnose fatty liver [12], and is therefore a subjective method to estimate quantitative changes in intrahepatic fat content. Thus, we excluded sonographic and CT-based studies in our meta-analysis [32]. Recent data showed that MRI-PDFF has become the primary imaging modality to assess intrahepatic fat content due to their high correlation with liver histology [45], and its clinical use has also been approved by the Food and Drug Administration (FDA) in the USA MRI-PDFF has emerged as a reference standard to measure hepatic steatosis in the radiation zone and is used as the primary modality for endpoint measurement in several clinical trials [45].

Of the RCTs only the two studies which used ezetimibe included NAS data. These two studies showed an improvement in NAS. The study by Loomba et al. [8] used both MRI-PDFF and liver biopsy. In fact, the primary end point of the study was changes in hepatic steatosis as measured by MRI-PDFF, with paired liver biopsy performed in 77.8% of study subjects [8]. We analyzed this study as their biopsy results were well-matched with similar baseline NAS in both groups (5 points each) as well as similar proportion lost at follow-up in both groups (32% vs. 28%, respectively). Moreover, baseline characteristics were also similar in both groups with regards to cholesterol levels, sex and age distribution. These two studies showed a trend of improvement in alanine aminotransferase (ALT) but there was no signif-

icant improvement when all four studies with information on ALT were included in the meta-analysis (Supplementary Fig. 2).

Several recent studies have suggested that long-term use of statins could increase the risk of diabetes mellitus and raise serum glucose levels [46]. In this meta-analysis, we did not find any significant increase in fasting serum glucose or HbA1c levels following statin use for 6 months. Takeshita et al. [9] reported a significant increase in HbA1c following the treatment; however, there was no significant increase in HbA1c observed when improvement rate was analyzed. Moreover, statin administration was also not associated with liver toxicity (Supplementary Fig. 2).

This meta-analysis had several limitations. First, the number of included studies was small. As such, we had to pool two cholesterol lowering agents (statin and ezetimibe) together in our analysis. Even though both have lipid-lowering effects, their mechanism of action is different. Second, there is considerable heterogeneity in design and endpoints among the available studies. For example, only three of the five studies were RCTs. Third, there were considerable heterogeneity in the two NRSs. The study by Ekstedt et al. [28] found a greater improvement in hepatic steatosis but the mean baseline cholesterol level was higher in the ezetimibe intervention group than the control at, 264 mg/dL vs. 230 mg/dL (p = 0.04), respectively. In the study by Georgescu and Georgescu [30] the improvement of hepatic steatosis was also observed in the control group who were however treated with UDCA administration.

In summary, the current meta-analysis found that lipid lowering agents can improve NAS in subjects with NAFLD but effects in hepatic steatosis were not observed. Given the small number of available RCTs, as well as a small number of study subjects in interventional studies overall, further large scale RCTs are needed to effectively evaluate the effects of cholesterol-lowering agents in improving intrahepatic fat in NAFLD patients with high baseline cholesterol levels.

KEY MESSAGE

1. Ezetimibe decreased nonalcoholic fatty liver disease (NAFLD) activity score without improving hepatic steatosis.
2. Cholesterol lowering agents did not significantly decreased the hepatic steatosis in NAFLD patients.
3. There was no significant increase in glycated hemoglobin levels following statin use for 6 months.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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Supplementary Table 1. Search strategy

Database	Time span	Search strategy
Medline	1946–2015.05	1. ezetimibe[tiab] OR ezetimib[tiab] 1835 2. "ezetimibe" [Supplementary Concept] 1320 3. 1 OR 2 2085 4. ("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors" [Pharmacological Action] 30544 5. Statins[tiab] OR Statin[tiab] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[tiab] OR "HMG-CoA Reductase Inhibitors"[tiab] OR "HMG-CoA Reductase Inhibitor"[tiab] OR "HMG-CoA Inhibitors"[tiab] OR "HMG-CoA Inhibitor"[tiab] OR atorvastatin[tiab] OR BMY 21950[tiab] OR cerivastatin[tiab] OR crilvastatin[tiab] OR fermodulin[tiab] OR fluvastatin[tiab] OR Lovastatin[tiab] OR Meglutol[tiab] OR mevastatin[tiab] OR "phosphoadenosinediphosphoribose "[tiab] OR pitavastatin[tiab] OR Pravastatin[tiab] OR red yeast rice[tiab] OR rosuvastatin[tiab] OR Simvastatin[tiab] 37958 6. 4 OR 5 43462 7. 3 OR 6 44027 8. steatohepatitis[tiab] OR Steatohepatitides[tiab] OR "fatty liver"[tiab] OR "hepatic fat"[tiab] 17500 9. (("Fatty Liver"[Mesh:NoExp]) OR "Non-alcoholic Fatty Liver Disease"[Mesh]) OR ("Liver/metabolism"[Mesh] OR "Liver/pathology"[Mesh]) 280089 10. 8 OR 9 285684 11. 7 AND 10 1464 12. (groups[tiab] OR trial[tiab] OR randomly[tiab] OR "drug therapy"[subheading] OR placebo[tiab] OR randomized[tiab] OR "controlled clinical trial"[ptyp] OR "randomized controlled trial"[ptyp]) NOT (animals[Mesh Term] NOT (humans[Mesh Term] AND animals[Mesh Term])) 3081519 13. 11 AND 12 368
Embase	1974–2015.05	1. ezetimibe:ab,ti OR ezetimib:ab,ti 2933 2. 'ezetimibe'/exp 6237 3. 1 OR 2 6652 4. 'hydroxymethylglutaryl coenzyme A reductase inhibitor'/exp 101806 5. Statins:ab,ti OR Statin:ab,ti OR 'Hydroxymethylglutaryl-CoA Reductase Inhibitors':ab,ti OR 'HMG-CoA Reductase Inhibitors':ab,ti OR 'HMG-CoA Reductase Inhibitor':ab,ti OR 'HMG-CoA Inhibitors':ab,ti OR 'HMG-CoA Inhibitor':ab,ti OR atorvastatin:ab,ti OR cerivastatin:ab,ti OR crilvastatin:ab,ti OR fermodulin:ab,ti OR fluvastatin:ab,ti OR Lovastatin:ab,ti OR Meglutol:ab,ti OR mevastatin:ab,ti OR 'phosphoadenosinediphosphoribose':ab,ti OR pitavastatin:ab,ti OR Pravastatin:ab,ti OR redyeastrice:ab,ti OR rosuvastatin:ab,ti OR Simvastatin:ab,ti 56766 6. 4 OR 5 108937 7. 3 OR 6 109970 8. steatohepatitis:ab,ti OR Steatohepatitides:ab,ti OR 'fatty liver':ab,ti OR 'hepatic fat':ab,ti 26638 9. 'fatty liver'/de OR 'nonalcoholic fatty liver'/exp 39529 10. 8 OR 9 43645 11. 7 AND 10 1417 12. 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR 'cross over' OR 'cross-over' OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* 1766501 13. 11 AND 12 417 14. 11 AND ('conference abstract'/it OR 'conference review'/it) 180 15. 13 OR 14 561

(Continued)

Supplementary Table 1. Continued

Database	Time span	Search strategy
Cochrane	2015.05	1. ezetimibe or ezetimib:ti,ab,kw 622 2. MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees 2843 3. MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees and with qualifier(s): [Pharmacology - PD] 363 4. Statins or Statin or "Hydroxymethylglutaryl-CoA Reductase Inhibitors" or "HMG-CoA Reductase Inhibitors" or "HMG-CoA Reductase Inhibitor" or "HMG-CoA Inhibitors" or "HMG-CoA Inhibitor" or atorvastatin or BMY 21950 or cerivastatin or crilvastatin or fermodulin or fluvastatin or Lovastatin or Meglutol or mevastatin or "phosphoadenosinediphosphoribose" or pitavastatin or Pravastatin or red yeast rice or rosuvastatin or Simvastatin:ti,ab,kw 9064 5. 1 - 4 / OR 9151 6. steatohepatitis or Steatohepatitides or "fatty liver" or "hepatic fat":ti,ab,kw 869 7. MeSH descriptor: [Fatty Liver] this term only 306 8. MeSH descriptor: [Non-alcoholic Fatty Liver Disease] explode all trees 17 9. MeSH descriptor: [Liver] explode all trees and with qualifier(s): [Metabolism - ME] 765 10. MeSH descriptor: [Liver] explode all trees and with qualifier(s): [Pathology - PA] 684 11. 6 - 10 / OR 2147 12. 5 AND 11 58 13. 12 / Trial 56
KoreaMed	2015.05	1. ezetimibe[ALL] OR ezetimib[ALL] 2. Statins[ALL] OR Statin[ALL] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[ALL] OR "HMG-CoA Reductase Inhibitors"[ALL] OR "HMG-CoA Reductase Inhibitor"[ALL] OR "HMG-CoA Inhibitors"[ALL] OR "HMG-CoA Inhibitor"[ALL] OR atorvastatin[ALL] OR BMY 21950[ALL] OR cerivastatin[ALL] OR crilvastatin[ALL] OR fermodulin[ALL] OR fluvastatin[ALL] OR Lovastatin[ALL] OR Meglutol[ALL] OR mevastatin[ALL] OR "phosphoadenosinediphosphoribose" [ALL] OR pitavastatin[ALL] OR Pravastatin[ALL] OR red yeast rice[ALL] OR rosuvastatin[ALL] OR Simvastatin[ALL] 3. 1 OR 2 103 4. steatohepatitis[ALL] OR Steatohepatitides[ALL] OR "fatty liver"[ALL] OR "hepatic fat"[ALL] 5. 3 AND 4 2

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Supplementary Table 2. Ottawa quality assessment scale Cohort studies

Bias		Ekstedt et al. (2007) [28]	Georgescu et al. (2007) [30]
Selection	(1) Representativeness of the exposed cohort	★	★
	(2) Selection of the non-exposed cohort	★	★
	(3) Ascertainment of exposure	★	★
	(4) Demonstration that outcome of interest was not present at start of study		★
Comparability outcome	Comparability of cohorts on the basis of the design or analysis		
	(1) Assessment of outcome	★	★
	(2) Was follow-up long enough for outcomes to occur	★	★
	(3) Adequacy of follow up of cohort	★	★

Supplementary Table 3. Characteristics of excluded studies (ordered by study ID)

Study	Journal	Reason for exclusion
Abdelmalek (2010)	Am J Gastroenterol 105:S116	Only an abstract of the study was available
Abel (2009)	Med Sci Monit 15(12):Ms6-11	Inappropriate primary end point (only laboratory data)
Abel (2009)	Orv Hetil 150(21):989-993	Inappropriate primary end point (only laboratory data)
Adams (2004)	Indian J Gastroenterol 23(4):127-128	Review
Adams (2006)	Postgrad Med J 82(967):315-322	Inappropriate intervention
Adams (2015)	Nat Rev Gastroenterol Hepatol 12(3):126-127	Review
Aggarwal (2009)	Hepatology 50:789A	Inappropriate primary end point (no steatosis data)
Ahmed (2006)	Med Hypotheses 66(2):440-441	Review
Ahmed (2006)	Scand J Gastroenterol 41(5):631	Review
Ahmed (2009)	Diabetes ObesMetab 11(3):188-195	Review
Ahmed (2010)	Expert Opin Drug Saf 9(4):511-514	Inappropriate participants
Ahmed (2010)	Drug Discov Today 15(15-16):590-595	Review
Antonopoulos (2006)	Atherosclerosis 184(1):233-234	Review
Arendt (2011)	Am J Gastroenterol 106:78-80	Inappropriate primary end point (no steatosis data)
Athyros (2006)	Curr Med Res Opin 22:873-883	Inappropriate study modality (ultrasonography)
Athyros (2011)	Ann Med 43(3):167-171	Review
Athyros (2013)	Expert Opin Investig Drugs 22(9):1089-1093	Review
Averna (2015)	Atheroscler Suppl 17(C):27-34	Review
Bayard (2006)	Am Fam Physician 73(11):1961-1969	Review
Bays (2014)	J Clin Lipidol 8(3 Suppl):S47-57	Review
Beaton (2012)	Can J Gastroenterol 26(6):353-357	Review
Blais (2015)	Gastroenterology 148(4):S982.	Inappropriate study design (single arm study)
Bril (2013)	Diabetes 62, A164 DOI:10.2337/db13-388-679	Inappropriate primary end point (no steatosis data)
Budoff (2009)	J Am Coll Cardiol 53(10):A276	only an abstract of the study was available
Bugianesi (2004)	Clin Gastroenterol 18(6 SPEC.ISS.):1105-1116	Review
Buscher (2004)	Dtsch Med Wochenschr 129(SUPPL. 2):S60-S62	Review
Calamita (2007)	Expert Opin Ther Targets 11(9):1231-1249	Review
Cao (2012)	Zhonghua Gan Zang Bing Za Zhi 20(4):304-309	Inappropriate study design (rat model)
Carnelutti (2012)	Dig Liver Dis 44:S25-S26	Inappropriate primary end point (no steatosis data)
Chalasani (2005)	Hepatology 41(4):690-695	Review
Chan (2007)	J Gastroenterol Hepatol (Australia) 22(6):801-808	Review
Chan (2009)	Atheroscler Suppl 10(2)	Same study (Chan 2010)
Chan (2010)	Diabetes Care 33:1134-1139 DOI:10.2337/dc09-1765	Inappropriate participants (patients with central obesity)
Chang (2013)	FASEB J 27	Inappropriate study design (rat model)
Chuthan (2013)	Minerva Gastroenterol Dietol 59(1):69-87	Review
Congdon (2006)	J Fam Pract 55(10):905-906	Review
Conjeevaram (2009)	Hepatology (Baltimore, MD) 50:774a	Inappropriate intervention (fenofibrate)
de Alwis (2008)	J Hepatol 48(SUPPL. 1):S104-S112	Review
de Alwis (2010)	Curr Pharm Des 16(17):1958-1962	Review
De Keyser (2013)	Pharmacoepidemiol Drug Saf 22:373	Inappropriate study design (single arm study)
Del Ben (2014)	World J Gastroenterol (26):8341-8350	Review
Delgado (2008)	Eur J Intern Med 19(2):75-82	Review

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Supplementary Table 3. Continued

Study	Journal	Reason for exclusion
Della Corte (2011)	Expert Opin Pharmacother 12(12):1901-1911	Review
Dima (2012)	Rom J Intern Med 50(1):19-25	Review
Drapkina (2011)	Endocr Pract 17(6):21A-22A	Inappropriate primary end point (only laboratory data)
Drapkina (2011)	Diab Vasc Dis Res 8(1):56-57	Inappropriate primary end point (only laboratory data)
Drapkina (2012)	J Hepatol 56:S507	Inappropriate primary end point (only laboratory data)
Duvnjak (2007)	World J Gastroenterol 13(34):4539-4550	Review
Duvnjak (2009)	J Physiol Pharmacol 60 Suppl 7:57-66	Review
Elsheikh (2014)	Gastroenterology 146(5):S-710	Inappropriate primary end point (only laboratory data)
Enjoji (2010)	Lipids Health Dis 9:29	Inappropriate study modality (ultrasonography)
Eslami (2013)	Cochrane Database Syst Rev 12:Cd008623	Review
Farrell (2014)	Clin Gastroenterol Hepatol 12(1):152-155	Review
Federico (2006)	Dig Liver Dis 38(11):789-801	Review
Filippatos (2010)	World J Hepatol 2(4):139-142	Review
Foster (2010)	Gastroenterology 138(5):S803	Same study (Foster 2011)
Foster (2011)	Am J Gastroenterol 106:71-77	Only an abstract of the study was available
Gitto (2015)	Gastroenterol Res Pract 2015	Review
Gomez(2006)	Aliment Pharmacol Ther 23(11):1643-1647	Inappropriate study modality (ultrasonography)
Gossard (2011)	Drugs Today (Barc) 47(12):915-922	Review
Hardwick (2011)	Drug Metab Rev 43:78	Inappropriate study design (rat model)
Harrison (2003)	Drugs 63(22):2379-2394	Review
Harrison (2004)	Clin Liver Dis 8(3):715-728	Review
Harrison (2014)	Hepatology 60:630A	Review
Hatzitolios (2004)	Indian J Gastroenterol 23(4):131-134	Inappropriate study modality (ultrasonography)
Hughes (2006)	Med Hypotheses 67(6):1463-1464	Review
Hyogo (2008)	Metabolism 57:1711-1718	Same study (hyogo 2012)
Hyogo (2012)	Dig Liver Dis 44(6):492-496	Inappropriate study design (single arm study)
Ioannou (2015)	J Lipid Res 56(2):277-285	Inappropriate study design (rat model)
Ivanova (2013)	Eur J PrevCardiol 20(1):S76	Inappropriate study modality (ultrasonography)
Kalaitzakis (2014)	Minerva Gastroenterol Dietol 60(1):15-24	Review
Karagiannis (2014)	Curr Vasc Pharmacol 12:505-511	Inappropriate primary end point (no steatosis data)
Kashi (2008)	Semin Liver Dis 28(4):396-406	Review
Khedmat (2011)	Hepat Mon 11(2):74-85	Review
Kim (2012)	Gastroenterology 142(5):S545	Inappropriate study design (rat model)
Kimura (2010)	J Gastroenterol 45(7):750-757	Inappropriate study design (single arm study)
Koehler (2012)	Hepatology 56:595A-596A	Inappropriate primary end point (only laboratory data)
Kopec (2011)	Nutr Clin Pract 26(5):565-576	Review
Korneeva (2010)	J Hepatol 52:S146	Same study (Korneeva 2012)
Korneeva (2012)	Cardiovasc Res 93:S79-S80	Inappropriate study modality (ultrasonography)
Krawczyk (2010)	Best Pract Res Clin Gastroenterol 24(5):695-708	Review
Lam (2009)	Ann Hepatol 8(SUPPL. 1):S51-S59	Review
Lam (2010)	Therap Adv Gastroenterol 3(2):121-137	Review
Le (2012)	J Clin Exp Hepatol 2(2):156-173	Review

Supplementary Table 3. Continued

Study	Journal	Reason for exclusion
Leerapun (2011)	Hepatol Int 5(1):8-9	Review
Lewis (2010)	Dig Dis Sci 55(3):560-578	Review
Liangpunsakul (2003)	Curr Treat Options Gastroenterol 6(6):455-463	Review
Liberopoulos (2006)	Aliment Pharmacol Ther 24(4):698-699	Review
Lomonaco (2013)	Drugs 73(1):1-14	Review
Loomba (2014)	Hepatology (Baltimore, MD) 60:226a DOI:10.1002/hep.27457	Same study (Loomba 2015)
Lowyck (2007)	Acta Gastroenterol Belg 70(4):381-388	Review
Machado (2014)	Expert Rev Gastroenterol Hepatol 8(5):487-500	Review
Malinowski (2013)	Pharmacotherapy 33(2):223-242	Review
Marchesini (2011)	Expert Opin Emerg Drugs 16:121-136	Review
Maroni (2010)	J Hypertens 28:e547	Inappropriate primary end point (only laboratory data)
Maroni (2011)	Am J Med Sci 342(5):383-387	Inappropriate primary end point (only laboratory data)
Marzocchi (2003)	Gastroenterol Int 16(1-2):9-16	Review
Mathur (2012)	J Am Coll Surg 215(3):S25	Inappropriate study design (rat model)
Mazzella (2014)	Clin Liver Dis 18(1):73-89	Review
Mazzella (2015)	Gastroenterology 149(2):274-278	Review
McAvoy (2006)	Br J Diab Vasc Dis 6(6):251-260	Review
Mehta (2010)	Ther Adv Endocrinol Metab 1(3):101-115	Review
Mendez (2007)	Liver Int 27(9):1157-1165	Review
Miao (2014)	Am J Gastroenterol 109:S186	Only an abstract of the study was available
Mihaila (2009)	Hepatogastroenterology 56(93):1117-1121	Inappropriate primary end point (only laboratory data)
Mihaila (2012)	Arch Balkan Med Union 47(3):249-254	Review
Mishra (2007)	Curr Drug Discov Technol 4(2):133-140	Review
Moreno (2005)	Med Clin (Barc) 125(3):108-116	Review
Moscatiello (2008)	Mini Rev Med Chem 8(8):767-775	Review
Moseley (2008)	J Clin Gastroenterol 42(4):332-335	Review
Mouzaki (2012)	Ann Gastroenterol 25(3):207-217	Review
Musso (2010)	Hepatology 52(1):79-104	Review
Musso (2010)	Obes Rev 11(6):430-445	Review
Musso (20103	Curr Pharm Des 19(29):5297-5313	Review
Musso (2011)	Curr Opin Lipidol 22(6):489-496	Review
Musso (2014)	Diabetologia 57(5):850-855	Review
Nguyen (2012)	J Gastroenterol Hepatol (Australia) 27(SUP-PL.2):58-64	Review
Nikhil (2012)	Natl Med J India 25(2):94-95	Same study (Foster 2011)
Nobili (2012)	J Gastroenterol 47(1):29-36	Review
Nseir (2012)	Dig Dis Sci 57(7):1773-1781	Review
Nseir (2013)	Curr Atheroscler Rep 15:305	Review
Oben (2008)	CPD Bull Clin Biochem 9(2):47-53	Review
Oni (2013)	J Am Coll Cardiol 61(10):E1427	Inappropriate primary end point (only laboratory data)
Onofrei (2008)	Pharmacotherapy 28(4):522-529	Review

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Supplementary Table 3. Continued

Study	Journal	Reason for exclusion
Paragh (2009)	Orv Hetil 150(26):1205-1212	Review
Park (2010)	Clin Chim Acta 411(21-22):1735-1740	Same study (Park 2011)
Park (2011)	J Gastroenterol 46(1):101-107	Inappropriate study design (single arm study)
Park (2013)	Diabetes Metab J 37(4):240-248	Review
Pastori (2015)	Dig Liver Dis 47(1):4-11	Review
Patel (2009)	Gastroenterology 136(5):A847	Inappropriate primary end point (no steatosis data)
Perlemuter (2007)	Nat Clin Pract Endocrinol Metab 3(6):458-469	Review
Pireau (2013)	Acta Clinica Belgica 68(6):463	Inappropriate primary end point (only laboratory data)
Portincasa (2007)	J Gastrointestin Liver Dis 16(2):167-169	Review
Pramfalk (2011)	Curr Opin Lipidol 22(3):225-230	Review
Preiss (2008)	Clin Sci 115(5-6):141-150	Review
Quercioli (2009)	Cardiovasc Hematol Disord Drug Targets 9(4):261-270	Review
Rallidis (2004)	Atherosclerosis 174(1):193-196	Inappropriate study design (single arm study)
Ratziu (2007)	Gastroenterol Clin Biol 31(3):333-340	Review
Reihner (1991)	Fortschr Med 109(8):189-194	Inappropriate participants (patients with cholecystectomy)
Renno (2012)	Lab Invest 92:465A-466A	Inappropriate study design (rat model)
Riche (2014)	Ann Pharmacother 48(1):137-141	Inappropriate study design (case study)
Riley (2008)	Int J ClinPract 62(3):374-381	Inappropriate primary end point (only laboratory data)
Rizzo (2014)	Expert Opin Pharmacother 15(8):1065-1068	Review
Rizzo (2014)	Curr Vasc Pharmacol 12(5):741-744	Review
Rudovich (2010)	J Hepatol 52(6):952-953	Inappropriate study design (single arm study)
Samy (2011)	Arab J Gastroenterol 12:80-85 DOI:10.1016/j.ajg.2011.04.008	Inappropriate primary end point (only laboratory data)
Schattenberg (2011)	Curr Opin Lipidol 22(6):479-488	Review
Schneier (2015)	Expert Rev Gastroenterol Hepatol 9(5):671-683	Review
Schreuder (2008)	World J Gastroenterol 14(16):2474-2486	Review
Schwenger (2014)	World J Gastroenterol 20(7):1712-1723	Review
Seng (2008)	Curr Opin Lipidol 19(6):592-599	Review
Shiwa (2011)	Nihon Shokakibyo Gakkai Zasshi 108(8):1383-1392	Inappropriate study modality (ultrasonography)
Siebler (2006)	World J Gastroenterol 12(14):2161-2167	Review
Skrypnyk (2014)	Lik Sprava (5-6):113-121	Inappropriate participants (patients with heart attack)
Sochman (2006)	Cas Lek Cesk 145(6):443-446; discussion 447-448	Review
Takahashi (2015)	World J Gastroenterol 21(13):3777-3785	Review
Takaki (2014)	Int J Mol Sci 15(5):7352-7379	Review
Takeshita (2011)	J Hepatol 54:S346	Same study (Takeshita 2014)
Takeshita (2011)	Hepatology (Baltimore, MD) 54:1117a	Same study (Takeshita 2014)
Tandra (2009)	Curr Treat Options Cardiovasc Med 11(4):272-278	Review
Targher (2010)	Dig Liver Dis 42(5):331-340	Review
Targher (2013)	Semin Thromb Hemost 39(2):214-228	Review

Supplementary Table 3. Continued

Study	Journal	Reason for exclusion
Tilg (2005)	Nat Clin Pract Gastroenterol Hepatol 2(3):148-155	Review
Tolman (2007)	Ther Clin Risk Manag 3(6):1153-1163	Review
Torres (2007)	Curr Treat Options Gastroenterol 10(6):425-434	Review
Torres (2008)	Gastroenterology 134(6):1682-1698	Review
Torres (2012)	Clin Gastroenterol Hepatol 10(8):837-858	Review
Toth (2010)	Clin Lipidol 5(5):655-684	Review
Trovato (2014)	EPMA J 5(1)	Review
Tzefos (2011)	J Clin Lipidol 5(6):450-459	Review
Tziomalos (2014)	World J Hepatol 6(10):738-744	Review
Ushio (2012)	Diabetes 61:A458	Inappropriate study design (rat model)
Vuppalanchi (2009)	Hepatology 49(1):306-317	Review
Wierzbicki (2012)	Curr Opin Lipidol 23(4):345-352	Review
Wilkins (2013)	Am Fam Physician 88(1):35-42	Review
Xiao (2013)	Hepatobiliary Pancreat Dis Int 12(2):125-135	Review
Yamagishi (2006)	Med Hypotheses 66(4):844-846	Review
Yamagishi (2013)	Dig Liver Dis 45(1):82	Same study (Hyogo 2012)
Yoneda (2010)	Hepatol Res 40(6):566-573	Review
Yoneda (2011)	Hepatol Res 41(11):1025-1026	Review
Yoneda (2011)	J Gastroenterol 46(3):415-416; author reply 417	Review
Yoshida (2011)	Curr Vasc Pharmacol 9(1):121-123	Review
Younossi (2014)	Aliment Pharmacol Ther 39(1):3-14	Review
Zvenigorodskaja (2009)	Am J Hypertens 22:10	Inappropriate primary end point (only laboratory data)

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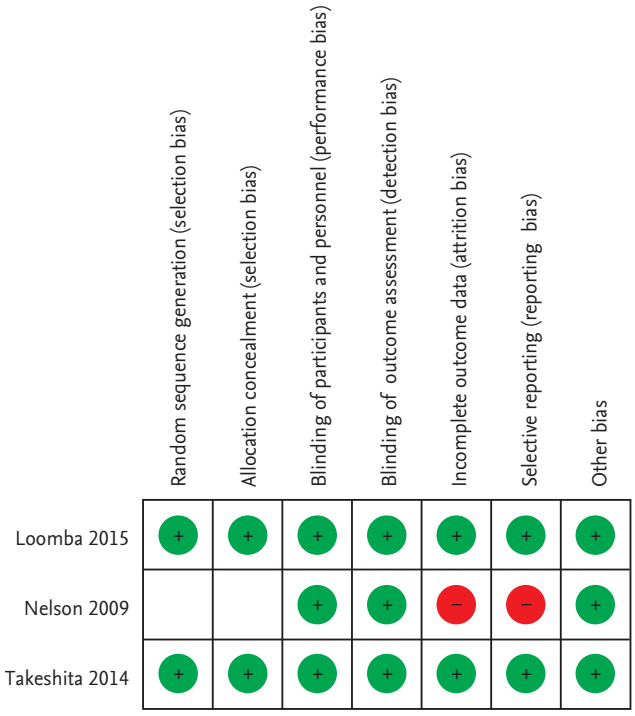
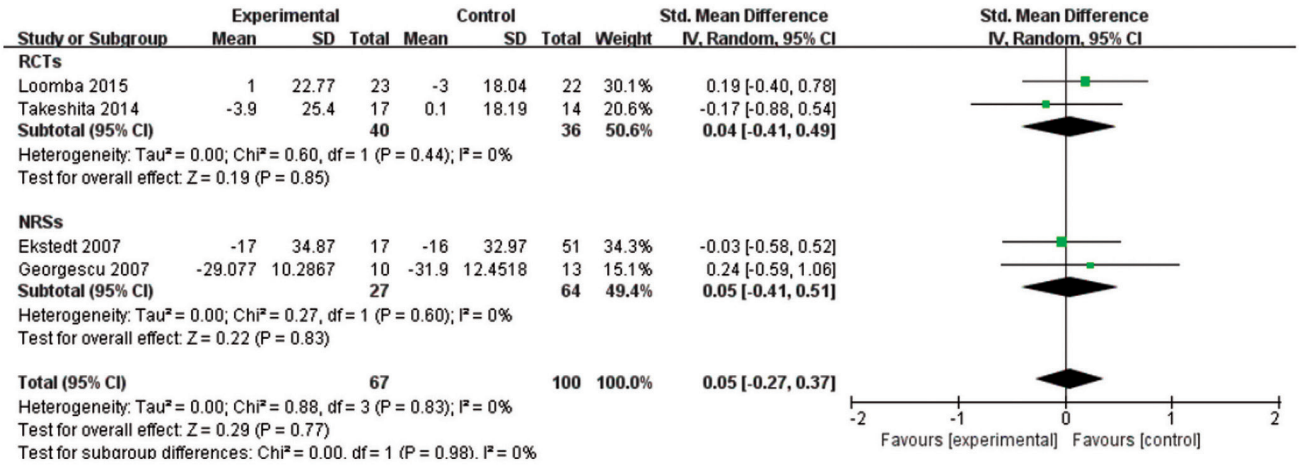


Supplementary Figure 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



Supplementary Figure 2. Forest plot for decrease of serum alanine aminotransferase (ALT). SD, standard deviation; IV, interval variable; CI, confidence interval; Std., standardized; RCT, randomized controlled trial; NRS, nonrandomized study.

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