

Beneficial Effect of Ezetimibe on Cholesterol Metabolism Ameliorates Hepatic Steatosis

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To cite this article:

Yichao Zheng, Yifen Wu, Guian Zheng, Yadong Lai, Jiaji Jiang. Beneficial Effect of Ezetimibe on Cholesterol Metabolism Ameliorates Hepatic Steatosis. *European Journal of Clinical and Biomedical Sciences*. Vol. 4, No. 2, 2018, pp. 29-38. doi: 10.11648/j.ejcb.20180402.11

Received: May 5, 2018; Accepted: May 31, 2018; Published: June 14, 2018

Abstract: Background and aim: Cholesterol absorption inhibitor ezetimibe is being used to treat nonalcoholic fatty liver disease (NAFLD) and related metabolic comorbidities. However, its specific efficacy remains unclear. Hence, a meta-analysis was undertaken to clarify the effects of ezetimibe on NAFLD and related metabolic comorbidities. Methods: Electronic databases were searched for clinical trials that investigated the effects of ezetimibe on NAFLD and related metabolic comorbidities. The primary outcome of interest was the effect of ezetimibe on liver enzymes and histology. The secondary outcome of interest was the effect of ezetimibe on lipid metabolism and hepatic insulin resistance. Results: The end-of-treatment (vs. baseline) hepatic steatosis grade and NAFLD activity score (NAS) were significantly improved (steatosis grade: weighted mean difference [WMD]: -0.62, 95% CI: -0.96 to -0.27, $P = 0.0005$; NAS: WMD: -1.00, 95%CI: -1.46 to -0.55, $P < 0.0001$) without significant improvement in hepatic lobular inflammation, ballooning, or fibrosis. In Asian participants, the end-of-treatment alanine aminotransferase was significantly decreased (WMD: -12.11 IU/L, 95%CI: -23.81 to -0.41 IU/L, $P = 0.04$). Treatment with ezetimibe significantly reduced total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) (TC: WMD: -37.96 mg/dL, 95%CI: -59.52 to -16.40 mg/dL, $P = 0.0006$; LDL-C: WMD: -35.55 mg/dL, 95%CI: -57.02 to -14.07 mg/dL, $P = 0.001$) without a significant effect on triglycerides, high-density lipoprotein cholesterol, glycosylated haemoglobin or the homeostasis model of assessment for insulin resistance index. Conclusions: Results of the meta-analysis confirm beneficial effects of ezetimibe on hepatic steatosis and cholesterol metabolism in patients with NAFLD.

Keywords: Ezetimibe, Cholesterol Metabolism, Hepatic Steatosis

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most commonly diagnosed liver diseases, affecting around 25.24% of persons worldwide. [1] The disease can progress all the way to nonalcoholic steatohepatitis (NASH), leading to NASH cirrhosis or even carcinoma in some affected persons. [1-4] Most patients with NAFLD have at least one other metabolic disorder, such as obesity, hyperlipidemia, insulin resistance, or type 2 diabetes mellitus. [5, 6] Moreover, metabolic syndrome has been closely linked to the pathogenesis of NAFLD, predisposing the liver to chronic metabolic insult. [5-7] The currently recommended

treatments for NAFLD include, but are not limited to, lifestyle modifications, lipid-lowering agents, insulin sensitizing agents, and antioxidants, targeting the underlying liver disease as well as the associated metabolic comorbidities. [8-10] At present, no pharmacologic therapies have been approved by regulatory agencies as the first-line treatment specifically for NAFLD. [8, 10] Thus, a study aiming at ultimate development of a first-line medication for this disease and its related metabolic disorders is warranted.

A number of recent clinical trials have been conducted to investigate the role of ezetimibe in the treatment of NAFLD, and some benefits have been shown in terms of improving liver aminotransferase level and liver histology and in

ameliorating dyslipidemia and insulin resistance in patients with NAFLD. [11–20] Most of the studies involving Asian populations have been the uncontrolled pilot studies. A recent, randomized, double-blind, placebo-controlled trial showed no beneficial effects of ezetimibe on patients' liver biochemistry or the histologic changes that accompany NASH. [21] This result, however, must be interpreted in the context of the relatively short-term ezetimibe treatment and selective recruitment of Western patients with NASH. Thus, we conducted a systematic review and meta-analysis to evaluate the effects of ezetimibe on liver biochemistry, liver histology, and NAFLD associated metabolic disorders.

2. Methods

The meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [22]

2.1. Literature Search and Selection

We identified clinical studies to be included in our meta-analysis by systematically searching MEDLINE, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov from their inception to April 10, 2016, with no language restriction. The literature search strategy was as follows: ((ezetimibe) OR (cholesterol absorption inhibitor) OR (Niemann-Pick C1-like 1 inhibitor) OR (NPC1L1 inhibitor)) AND ((nonalcoholic fatty liver disease) OR (nonalcoholic steatohepatitis) OR (nonalcoholic fatty liver) OR (steatohepatitis) OR (steatosis) OR (NAFLD) OR (NASH) OR (NAFL)). References of selected retrieved articles were also manually reviewed. From among all studies we found, we accepted for our analysis all clinical studies in which the effects of ezetimibe on NAFLD were evaluated, regardless of the dosage, follow-up time, and other interventions. We excluded all case reports, commentaries, conference abstracts, review articles, animal studies, and papers from which the data of interest were not reported or could not otherwise be determined.

2.2. Data Extraction and Bias Assessment

Two reviewers independently confirmed the eligibility of the included studies and extracted information regarding the study design, the number and characteristics of the participants, and the interventions. The reviewers also extracted the results of liver biochemistry test, serum lipid and glycosylated haemoglobin (HbA1c) levels, the homeostasis model of assessment of insulin resistance (HOMA-IR) index, and the liver histology findings. Discrepancies between reviewers were resolved by consensus.

The quality of each of the randomized controlled trials (RCTs) identified in the search was evaluated by means of the Cochrane risk of bias tool (<http://handbook.cochrane.org>). Quality of the nonrandomized studies identified was evaluated by means of the Newcastle-Ottawa scale (NOS). [23] Studies with a total score of 7–9 were deemed high-quality studies,

those with a total score of 4–6 were deemed medium-quality studies, and those with a total score of 0–3 were deemed low quality studies.

2.3. Outcome Measures

The primary outcome measure for patients being treated with ezetimibe was change in the liver histology. A well-recognized scoring system, developed by Brunt *et al.*, [24] was used to assess the degree of hepatocyte ballooning (with a possible score of 0–2), liver steatosis (0–3), lobular inflammation (0–3), and fibrosis (0–4). The NAFLD activity score (NAS) was calculated as the unweighted sum of the scores for steatosis, lobular inflammation, and ballooning. [25] When Brunt score or NAS was not reported, changes in alanine aminotransferase (ALT) concentrations were evaluated instead. The secondary outcome measures were changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, total cholesterol, HbA1c, and the HOMA-IR index. The subgroup analyses were performed on the basis of patients ethnicity, treatment duration and study design if data is available.

2.4. Statistical Analysis

For continuous variables of interest, mean \pm SD values were obtained. If the mean \pm SD values could not be extracted directly from the study report, we requested these values from the authors. If the authors did not reply to our query, we estimated the mean \pm SD study-specific values according to the method of Tong *et al.* [26] A random effects model was used for pooled data, with the results presented as the mean difference (with 95% confidence intervals) and I^2 as an index of heterogeneity. The heterogeneity of trials was considered mild if I^2 was $< 30\%$, moderate if I^2 was $\geq 30\%$ and $\leq 50\%$, and substantial if I^2 was $> 50\%$. Funnel plots were used to check for possible publication bias. If the funnel plots were asymmetric, Egger's test was performed. All statistical analyses were performed with Review Manager 5.3, by which mean differences can be calculated automatically from the mean \pm SD values. $P < 0.05$ was considered statistically significant.

3. Results

We initially identified 545 studies in our search of literature. We then screened the titles and abstracts and excluded redundancy. i.e., 192 studies that had been identified previously in another database, 305 non-pertinent studies, 18 animal studies, 1 case report, 5 conference abstracts, and 13 commentaries and reviews. After a detailed review of the full report, one study was excluded because the data had been included in another report [20], and another study was excluded because data important to our analysis were not available [7]. In addition, one study published in Ukraine was excluded because the data were incomplete in the abstract and we were unable to obtain the full text. [27] Thus a total of eight studies were included in our meta-analysis (Figure 1).

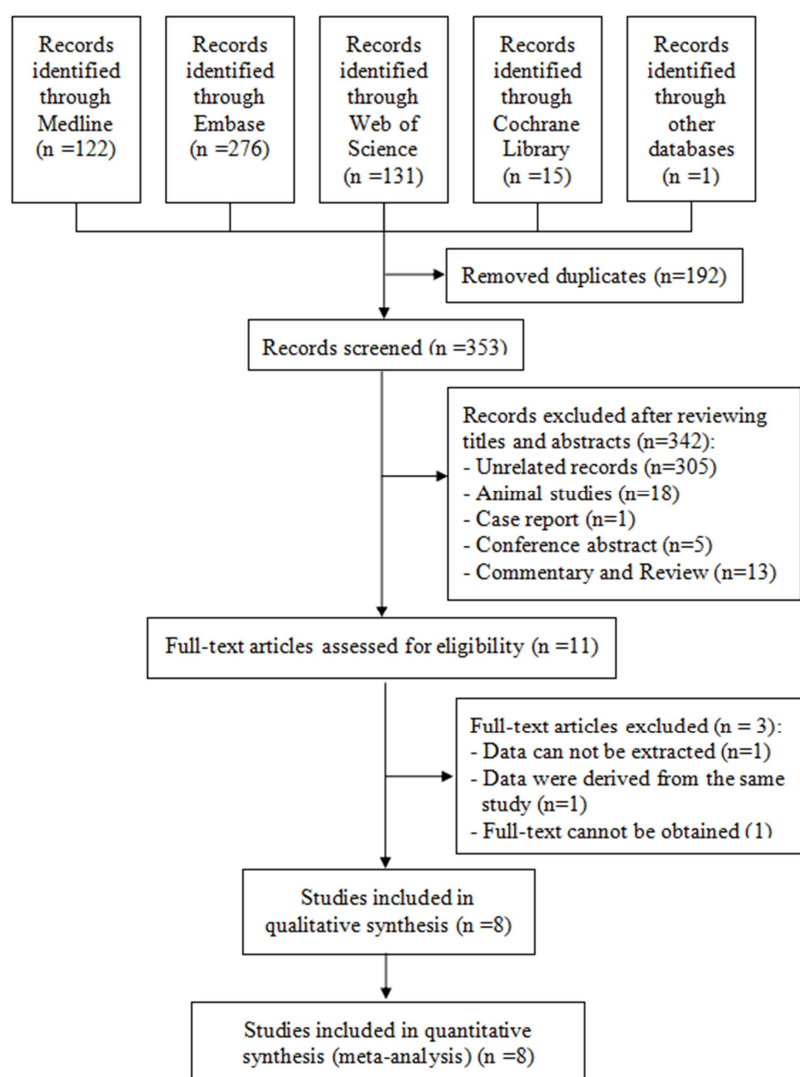


Figure 1. Flow diagram of the search strategy and selection of studies for the analysis.

3.1. Characteristics of the Included Studies

The eight studies included in our analysis, along with the basic study details, are shown in Table 1. Two of the eight studies were RCTs [11, 21], five were prospective cohort study [12-14, 16, 17] and one was retrospective controlled study [15]. The risk of bias was rated low for a study of Loomba [21] and rated unclear for a study of Takeshita [11] (data not showed). The quality of a study of Abel was deemed high with NOS score of seven [15] while the remaining studies

were rated as medium-quality with NOS score ranged from five-six [12-14, 16, 17]. The included studies involved a total of 339 patients with NAFLD, and 274 of these patients were taking 10 mg of ezetimibe daily. Statin therapy was used concomitantly to patients in one study, and lifestyle modification was prescribed concomitantly to patients in four studies and singly to patients in one. Mean duration of the ezetimibe treatment was 11 months (range, 6–24 months).

Table 1. Studies included in the meta-analysis and basic study details.

| Authors | Year | Study design | Patients (n) | Intervention | Dosage (mg/day) |
|------------------------------|------|--------------------------------|--------------|-----------------------|-----------------|
| Abel <i>et al.</i> [15] | 2009 | Retrospective controlled study | 19 | Ezetimibe+simvastatin | 10 |
| | | | 26 | Simvastatin | NA |
| Enjoji <i>et al.</i> [16] | 2010 | Prospective cohort study | 8 | Ezetimibe | 10 |
| Yoneda <i>et al.</i> [14] | 2010 | Prospective cohort study | 10 | Ezetimibe+Lifestyle | 10 |
| Park <i>et al.</i> [12] | 2011 | Prospective cohort study | 45 | Ezetimibe+Dietary | 10 |
| Shiwa <i>et al.</i> [17] | 2011 | Prospective cohort study | 129 | Ezetimibe+Lifestyle | 10 |
| Oza <i>et al.</i> [13] | 2014 | Prospective cohort study | 21 | Ezetimibe+Lifestyle | 10 |
| Takeshita <i>et al.</i> [11] | 2014 | RCT | 17 | Ezetimibe+Lifestyle | 10 |
| | | | 14 | Lifestyle | NA |
| Loomba <i>et al.</i> [21] | 2015 | RCT | 25 | Ezetimibe | 10 |
| | | | 25 | Placebo | NA |

Table 1. Continue.

| Authors | Primary disease | Concomitant disease | Population | Duration of ezetimibe use |
|------------------------------|-----------------|--|------------|---------------------------|
| Abel <i>et al.</i> [15] | NAFLD | Type 2 diabetes and metabolic syndrome | Western | 6 months |
| | NAFLD | | Western | 6 months |
| Enjoji <i>et al.</i> [16] | NAFLD | NA | Asian | 12 months |
| Yoneda <i>et al.</i> [14] | NASH | Dyslipidemia | Asian | 6 months |
| Park <i>et al.</i> [12] | NAFLD | NA | Asian | 24 months |
| Shiwa <i>et al.</i> [17] | NAFLD | Dyslipidemia | Asian | 167.9±133.5 days |
| Oza <i>et al.</i> [13] | NAFLD | Dyslipidemia | Asian | 12 months |
| Takeshita <i>et al.</i> [11] | NAFLD | NA | Asian | 6 months |
| | NAFLD | NA | Asian | 6 months |
| Loomba <i>et al.</i> [21] | NASH | NA | Western | 24 weeks |
| | NASH | NA | Western | 24 weeks |

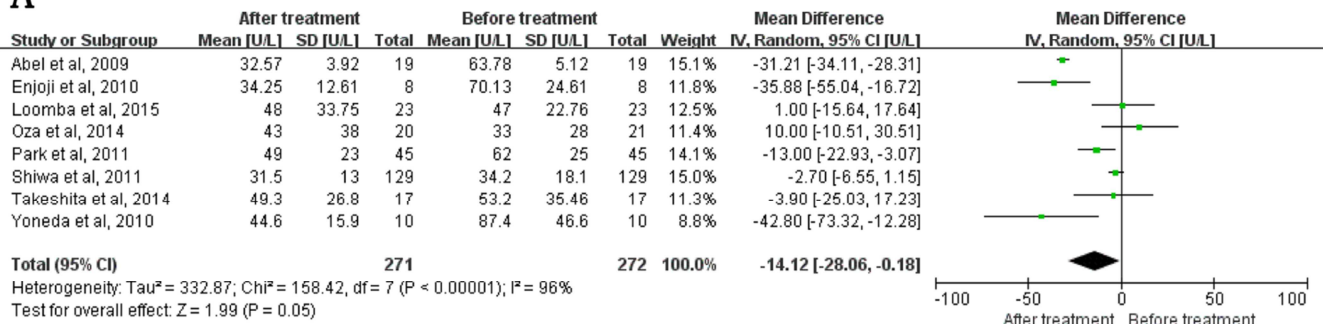
RCT, randomized controlled trial; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

3.2. Effect of Ezetimibe on Aminotransferases

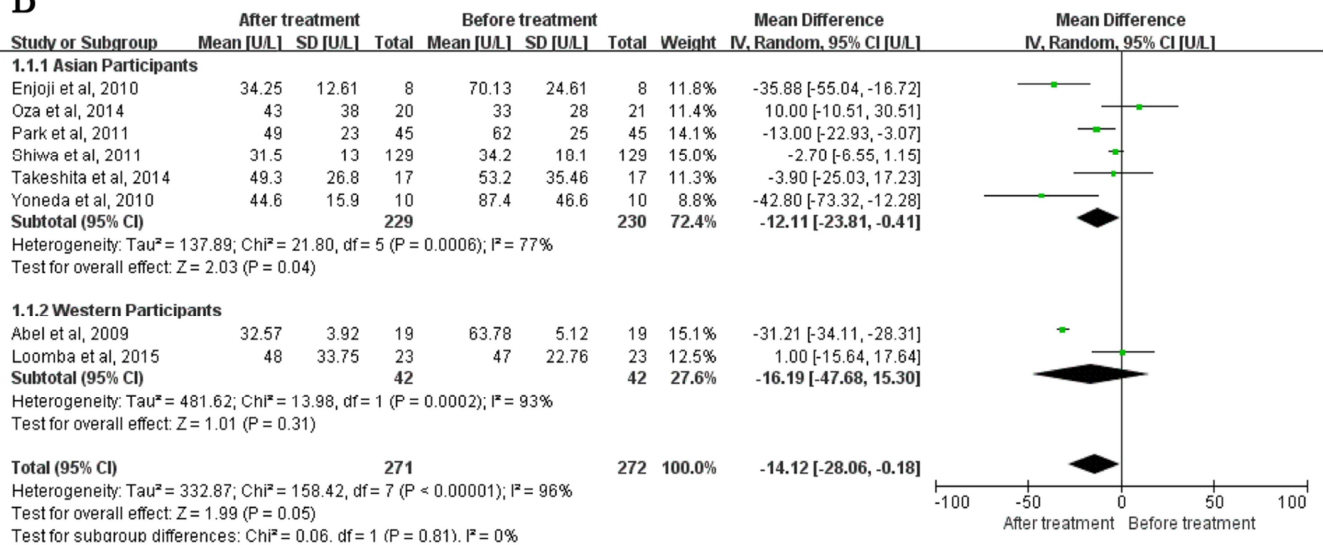
The end-of-treatment ALT concentration, in comparison to the baseline ALT concentration, was moderately reduced (weighted mean difference [WMD]: -14.12 IU/L, 95%CI: -28.06 to -0.18 IU/L, $P = 0.05$, $I^2 = 96\%$, Figure 2A). When values were compared on the basis of ethnicity, the end-of-treatment ALT concentration was significantly reduced in Asian participants (WMD: -12.11 IU/L, 95%CI: -23.81 to -0.41 IU/L, $P = 0.04$, $I^2 = 77\%$), but there was not a significant reduction in Western participants (WMD: -16.19 IU/L,

95%CI: -47.68 to 15.30 IU/L, $P = 0.31$, $I^2 = 93\%$) (Figure 2B). When values were compared on the basis of the duration of treatment, the end-of-treatment ALT concentration was moderately reduced in patients treated with ezetimibe for 6-months (WMD: -16.20 IU/L, 95%CI: -33.38 to 0.98 IU/L, $P = 0.06$, $I^2 = 86\%$) and significantly reduced in patients treated for 12 months (WMD: -23.39 IU/L, 95%CI: -44.62 to -2.16 IU/L, $P = 0.03$, $I^2 = 74\%$) (Figure 2C). The funnel plots for ALT analysis were symmetrical (Figure 3).

A



B



C

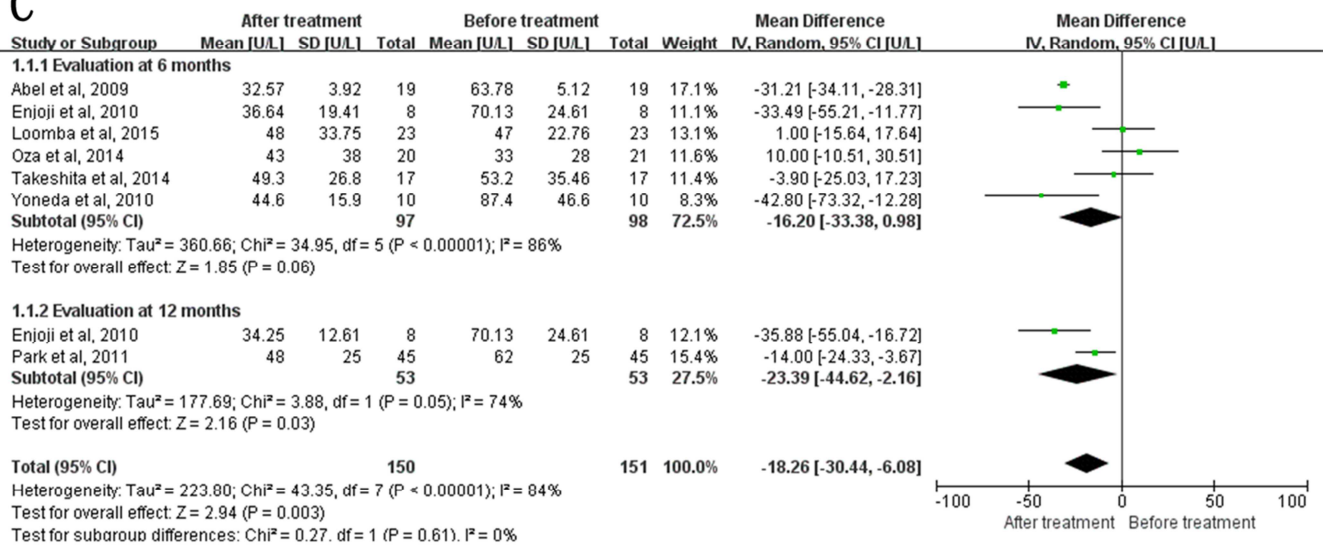


Figure 2. Meta-analysis of the effect of ezetimibe on ALT. (A) Meta-analysis of the effect of ezetimibe on ALT without stratification; (B) Stratification based on the ethnicity of participants; (C) Stratification based on the duration of treatment. ALT: alanine aminotransferase.

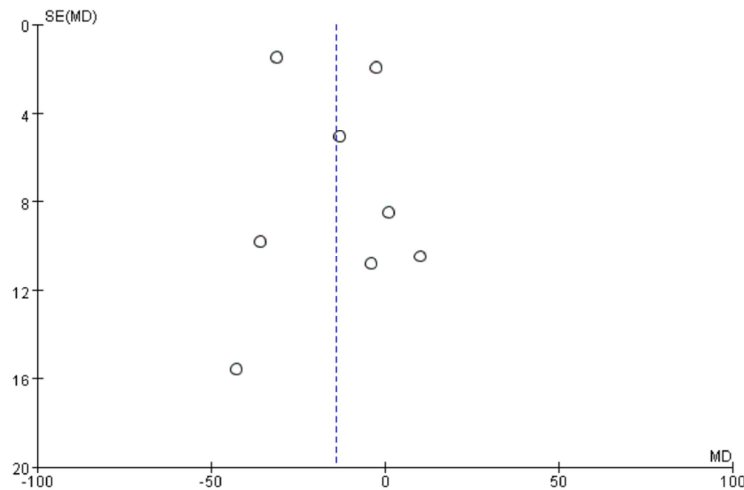


Figure 3. Funnel plot for the meta-analysis of the effect of ezetimibe on ALT.

3.3. Effect of Ezetimibe on Liver Histology

The end-of-treatment hepatic steatosis grade and NAS score were significantly improved in comparison to the baseline values (steatosis grade: WMD: -0.62 , 95%CI: -0.96 to -0.27 , $P = 0.0005$, $I^2 = 59\%$, Figure 4; NAS: WMD: -1.00 , 95%CI: -1.46 to -0.55 , $P < 0.0001$, $I^2 = 9\%$, Figure 5). No significant histologic improvements were seen in terms of lobular inflammation, ballooning, or fibrosis following treatment with ezetimibe (lobular inflammation grade: WMD: 0.11 , 95%CI: -0.41 to 0.63 , $P = 0.69$, $I^2 = 80\%$; ballooning score: WMD: -0.14 , 95%CI: -0.33 to 0.05 , $P = 0.15$, $I^2 = 0\%$; fibrosis stage: WMD: -0.05 , 95%CI: -0.37 to 0.26 , $P = 0.75$, $I^2 = 0\%$).

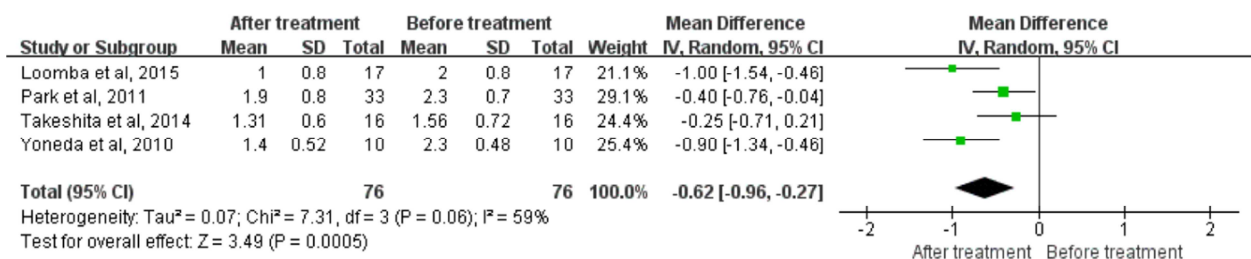
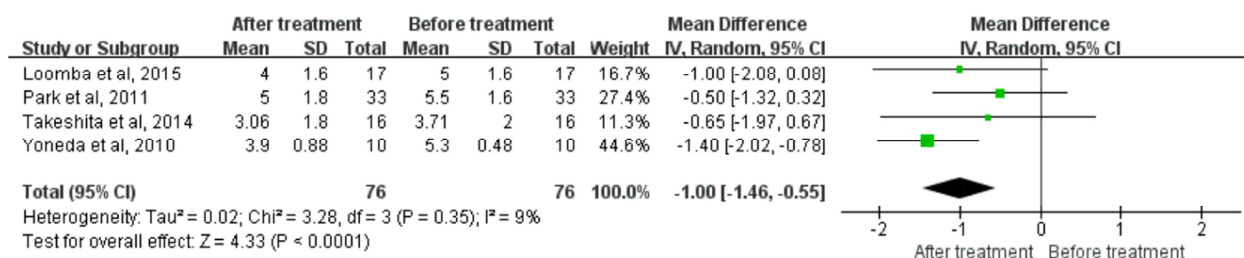


Figure 4. Meta-analysis of the effect of ezetimibe on hepatic steatosis.



NAS: nonalcoholic fatty liver disease activity score.

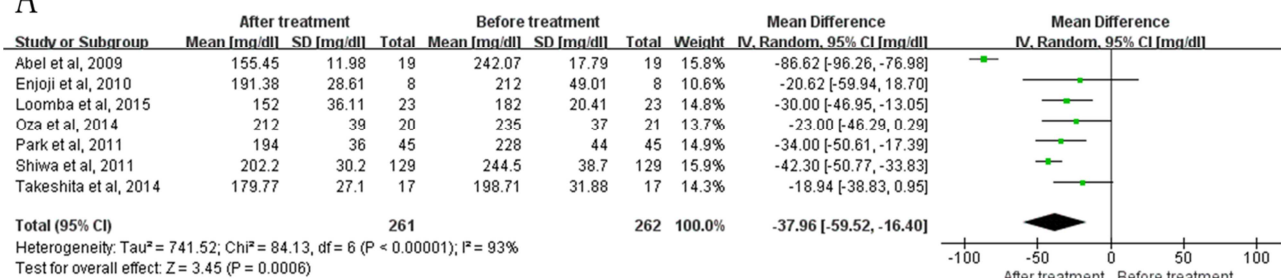
Figure 5. Meta-analysis of the effect of ezetimibe on the NAS.

3.4. Effect of Ezetimibe on Serum Lipids

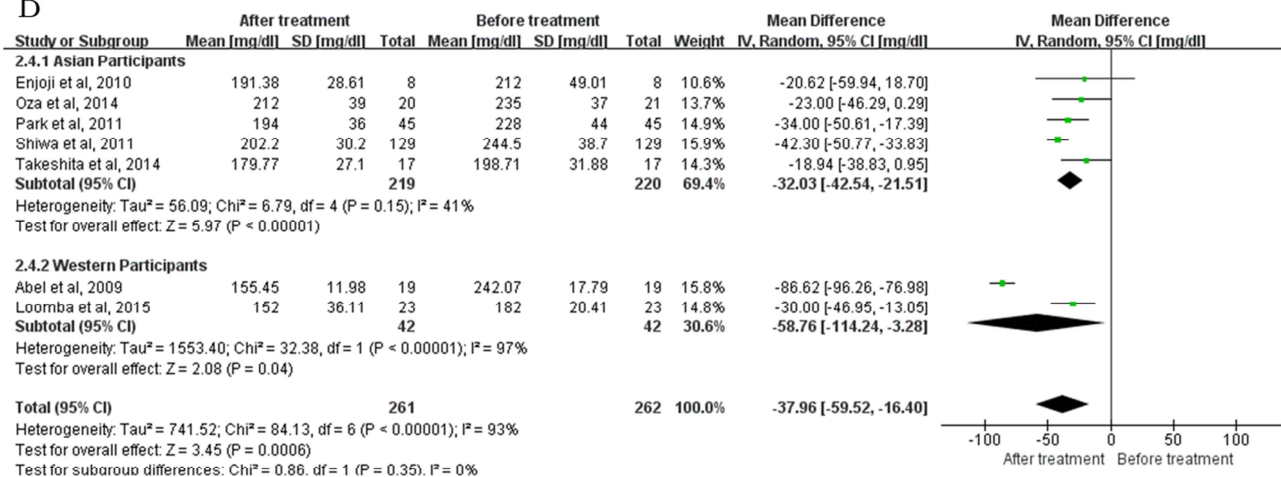
The end-of-treatment total cholesterol level, in comparison to the baseline level, was significantly reduced in patients who were given ezetimibe (WMD: -37.96 mg/dL, 95%CI: -59.52 to -16.40 mg/dL, $P = 0.0006$, $I^2 = 93\%$, Figure 6A). The heterogeneity of studies was diminished after excluding the study of Abel *et al.* (WMD: -32.46 mg/dL, 95%CI: -40.96 to -23.96 mg/dL, $P < 0.00001$, $I^2 = 31\%$). The beneficial effect of ezetimibe on total cholesterol was seen in both Asian (WMD:

-32.03 mg/dL, 95%CI: -42.54 to -21.51 mg/dL, $P < 0.00001$; $I^2 = 41\%$) and Western participants (WMD: -58.76 mg/dL, 95%CI: -114.24 to -3.28 mg/dL, $P = 0.04$, $I^2 = 97\%$, Figure 6B). Meta-analysis of the RCTs revealed that treatment with ezetimibe, vs. the control condition, significantly reduced the total cholesterol level (WMD: -28.52 mg/dL, 95%CI: -43.11 to -13.93 mg/dL, $P = 0.0001$, $I^2 = 0\%$, Figure 6C). The funnel plot for total cholesterol analysis was asymmetrical, but Egger's test indicated little likelihood of publication bias ($P = 0.205$).

A



B



C

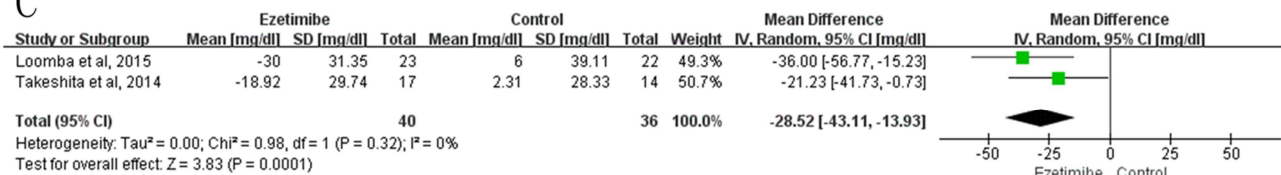
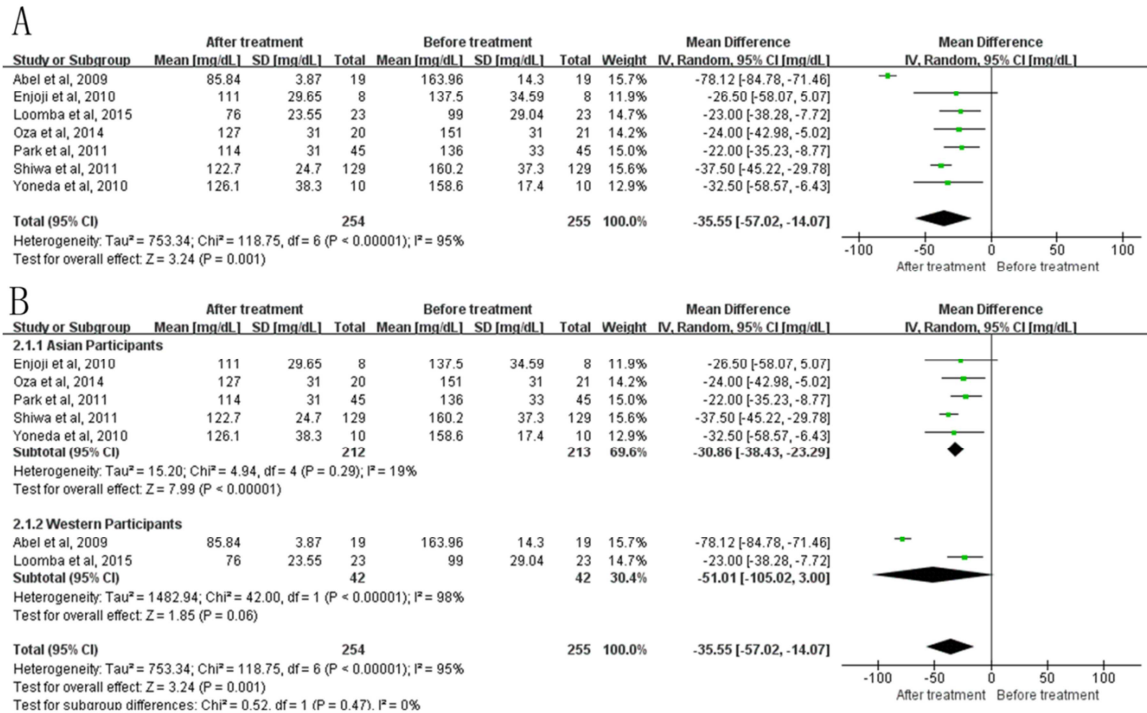


Figure 6. Meta-analysis of the effect of ezetimibe on total cholesterol. (A) Meta-analysis of the effect of ezetimibe on total cholesterol without stratification; (B) Stratification based on the ethnicity of participants; (C) Stratification based on the study design.

The end-of-treatment LDL-C level, in comparison to the baseline level, was significantly reduced in patients given ezetimibe (WMD: -35.55 mg/dL, 95%CI: -57.02 to -14.07 mg/dL, $P = 0.001$, $I^2 = 95\%$, Figure 7A). Heterogeneity of the studies was again diminished by omitting the study of Abel *et al.* (WMD: -29.63 mg/dL, 95%CI: -36.48 to -22.77 mg/dL, $P < 0.00001$, $I^2 = 19\%$). Subgroups analysis showed that

treatment with ezetimibe moderately reduced LDL-C in Western participants (WMD: -51.01 mg/dL, 95%CI: -105.02 to 3.00 mg/dL, $P = 0.06$, $I^2 = 98\%$) and significantly decreased LDL-C in Asian participants (WMD: -30.86 mg/dL, 95%CI: -38.43 to -23.29 mg/dL, $P < 0.00001$, $I^2 = 19\%$, Figure 7B). The funnel plots for total cholesterol analysis appeared symmetrical (Figure 8).



LDL-C: low-density lipoprotein cholesterol.

Figure 7. (A) Meta-analysis of the effect of ezetimibe on LDL-C without stratification; (B) Stratification based on the ethnicity of participants.

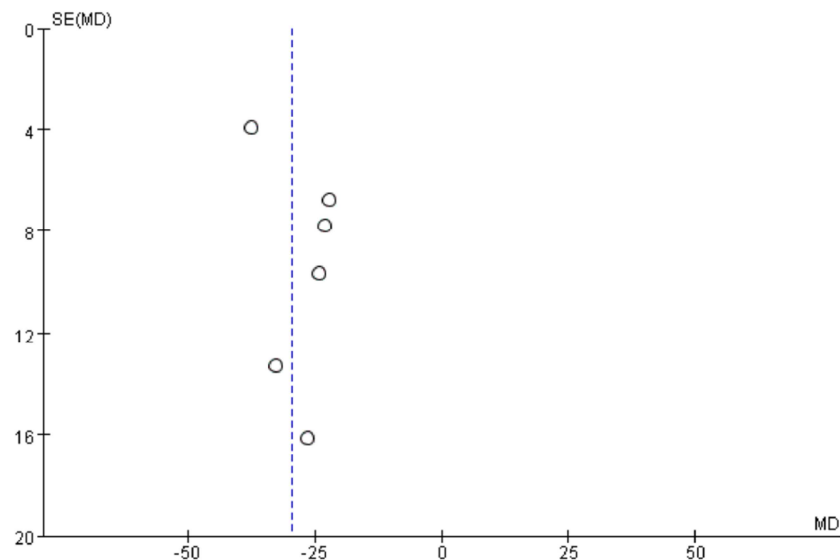


Figure 8. Funnel plot for meta-analysis of LDL-C.

Compared to the baseline triglyceride level, there was no evidence of significant reduction in end-of-treatment triglyceride level (WMD: -27.41 mg/dL, 95%CI: -63.29 to

8.46 mg/dL, $P = 0.13$, $I^2 = 91\%$). In addition, no significant difference was observed between the baseline and end-of-treatment HDL-C level (WMD: 1.94 mg/dL, 95%CI:

−1.62 to 5.51 mg/dL, $P = 0.29$, $I^2 = 60\%$).

3.5. Effect of Ezetimibe on Glucose Metabolism

End-of-treatment HbA1c, in comparison to baseline HbA1c, did not decrease significantly (WMD: 0.09%, 95%CI: −0.05 to 0.23%, $P = 0.21$, $I^2 = 0\%$). Neither was there a significant change between the baseline and end-of-treatment HOMA-IR index (WMD: −0.18, 95%CI: −0.42 to 0.05, $P = 0.12$, $I^2 = 0\%$).

4. Discussion

The role of cholesterol overload in liver injury, the dysregulated lipid metabolism, and the hepatic insulin resistance in patients with NAFLD have led to the recent development of ezetimibe for the treatment of NAFLD and the associated metabolic comorbidities. [8, 9, 28-30] Although various studies in animal models of NAFLD have confirmed the efficacy of ezetimibe in improving liver steatosis, inflammation, and even fibrosis, [31–35] clinical trials have yielded conflicting results, and this might partly explain the heterogeneity of the studies included in our meta-analysis. The significance of our meta-analysis is that we were able to resolve the uncertainty arising from the previous studies.

The meta-analysis we undertook confirmed the significant improvement in hepatic steatosis and NAS scores seen previously in patients given ezetimibe. The anti-steatosis effect of ezetimibe is thought to be based on its dual role in inhibiting intestinal absorption of cholesterol and suppressing delivery of cholesterol to the liver. [18, 19, 29] Recent studies have shown that ezetimibe efficiently reduces the absorption of dietary and biliary cholesterol in the proximal jejunum and inhibits the transport of serum cholesterol to liver by binding to Niemann-Pick C1-like 1 (NPC1L1) sterol transporter in the enterocyte brush border membrane and hepatocyte canalicular membrane. [36, 37] In humans, NPC1L1 protein is expressed predominantly in the liver and to a lesser extent in the intestine. [19] Thus, the heretofore demonstrated anti-steatosis activity of ezetimibe plus the results of the present meta-analysis underscore the promise of ezetimibe for ameliorating hepatic steatosis. Although the MOZART trial showed no significant improvement in the hepatic steatosis grade in patients given ezetimibe over that in control patients [21], we speculated that the lack of a difference might be due to the relatively short-term treatment carried out in the study. In the study conducted by Park *et al.*, 24-month treatment with ezetimibe significantly improved the hepatic steatosis grade in a cohort of patients with NAFLD. [12] Therefore, further studies, ideally large scale RCTs, are needed to confirm the effectiveness of long-term ezetimibe treatment in improving hepatic steatosis. Despite the potential beneficial effects of ezetimibe on hepatic steatosis uncovered in our meta-analysis, we failed to see any significant improvement in lobular inflammation, hepatocyte ballooning, or liver fibrosis with ezetimibe treatment. Thus, we believe the improvement in NAS scores in patients given ezetimibe was due largely to the reduction in steatosis grade.

In the meta-analysis of the effects of ezetimibe on liver enzymes, we found some improvement in ALT in patients given ezetimibe. Interestingly, we found that the beneficial effect of ezetimibe on ALT was greater in Asian patients than in Western patients. In consistent with previous analysis, the beneficial effects of ezetimibe on liver biochemistry improvement was more prominent if the duration of ezetimibe treatment was extended.

We also evaluated the effects of ezetimibe on NAFLD associated metabolic disorders. Like other researchers, [11-21] we found, regardless of the ethnicity of the patients recruited into the cohort studies and study design, that treatment with ezetimibe is sufficient for decreasing the serum total cholesterol and LDL-C levels in patients with NAFLD. Ezetimibe reduces the total cholesterol and LDL-C level by selectively targeting NPC1L1, which mediates intestinal absorption of luminal cholesterol and counterbalances hepatobiliary excretion of cholesterol. [38-40] However, our meta-analysis showed no beneficial effects of ezetimibe on serum triglyceride and HDL-C levels. There have been a few pilot studies that have shown some beneficial effects of ezetimibe on serum triglyceride and HDL-C levels in patients with NAFLD, [12, 14, 17] but this therapeutic benefit was not confirmed in recent RCTs. [11, 21] It is possible that the significant reduction in serum triglycerides and improved HDL-C level observed in the previous cohort studies were due to concomitant interventions rather than to the ezetimibe alone. The interactions between ezetimibe and NPC1L1 may be unrelated to triglyceride and HDL-C metabolism. [29] In our analysis of the effects of ezetimibe on glucose metabolism, as assessed by the serum HbA1c level and HOMA-IR index, we found no significant improvement in HbA1c or HOMA-IR in patients with NAFLD treated with ezetimibe. This result is consistent with that of previous clinical studies in which the effects of ezetimibe on hepatic insulin sensitivity was investigated in patients with NAFLD. [13-16, 21] Thus, the beneficial effects of ezetimibe on serum cholesterol reduction and hepatic steatosis amelioration concluded in present meta-analysis were largely due to its inhibition of cholesterol absorption, not the concomitant effects of the lifestyle modification that was thought to improve glucose and triglyceride metabolism.

We also acknowledge a few limitations of our meta-analysis. First, the number of included studies was relatively small. Only four studies evaluated liver histology and only two studies were RCTs. Second, there was considerable heterogeneity in the study design and endpoints among the available studies. Stratification of studies based on study design, patient ethnicity and treatment duration diminished the heterogeneity. Third, most of studies included in the present meta-analysis recruited a heterogeneous patients that may encompasses a spectrum of liver diseases ranging from NAFL to NASH and even NASH cirrhosis. It is interesting to know if the therapeutic effects of ezetimibe is influenced by different stages of NAFLD. However, subgroup analysis based on the severity of liver disease is impossible because the detail information regarding the severity of liver

disease was not reported in most studies. Hence further studies that investigated the role of ezetimibe in treatment of different stages of NAFLD are warranted.

5. Conclusion

In conclusion, the present meta-analysis found that the ezetimibe is effective in attenuating the aminotransferases, hepatic steatosis and serum cholesterol level in patients with NAFLD. However, given the small number of available RCTs and a small number of study subjects in interventional studies overall, large scale RCT are necessary to provide further evidence of the utility of ezetimibe in treating different stages of NAFLD.

Acknowledgements

The authors who have taken part in this study declared that they do not have anything to declare regarding funding from industry or conflict of interest with respect to this manuscript. This work was supported by Youth Research Grant of Fujian Provincial Health and Family Planning Commission (Grant 2017-1-86).

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