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Original Article

A Class Effect Network Meta-analysis of Lipid Modulation in Non-alcoholic Steatohepatitis for Dyslipidemia

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Abstract

Background and Aims: Pharmaceutical therapy for NASH is associated with lipid modulation, but the consensus on drug treatment is limited and lacks comparative analysis of effectiveness. A network meta-analysis was conducted to compare NASH drug classes in lipid modulation. ***Methods:*** Online databases were searched for randomized controlled trails (RCTs) evaluating NASH treatments in biopsy-proven NASH patients. Treatments were classified into four groups: (1) inflammation, (2) energy, (3) bile acids, and (4) fibrosis based on the mechanism of action. A Bayesian network analysis was conducted with outcome measured by mean difference (MD) with credible intervals (CrI) and surface under the cumulative ranking curve (SUCRA). ***Results:*** Forty-four RCTs were included in the analysis. Bile acid modulating treatments (MD: 0.05, CrI: 0.03–0.07) were the best treatment for improvement in high-density lipid (HDL) cholesterol, followed by treatments modulating energy (MD: 0.03, CrI: 0.02–0.04) and fibrosis (MD: 0.01, CrI: −0.12 to 0.14) compared with placebo. The top three treatments for reduction in triglycerides were treatments modulating energy (MD: −0.46, CrI: −0.49 to −0.43), bile acids (MD: −0.22, CrI: −0.35 to −0.09), and inflammation (MD: −0.08, CrI: −0.13 to −0.03) compared with placebo. SUCRA found treatment modulating fibrosis (MD: −1.27, CrI: −1.76 to −0.79) was the best treatment for reduction in low-density lipid (LDL) cholesterol followed by treatment modulating inflammation (MD: −1.03, CrI: −1.09 to −0.97) and energy (MD: −0.37, CrI: −0.39 to −0.34) compared with placebo, but LDL cholesterol was worsened by treatments modulating bile acids. ***Conclusions:*** Network analysis comparing the class effects of dyslipidemia modulation in NASH found that treatment targets can include optimization of atherogenic dyslipidemia. Future studies are required to evaluate the cardiovascular outcomes.

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Keywords: Lipid modulation; NASH; Dyslipidemia.

Abbreviations: BA, Bile Acid; CrI, Credible Interval; CVD, Cardiovascular Disease; DHA, Docosahexaenoic Acid; DPP4-i, Dipeptidyl Peptidase-4 Inhibitors; EPA, Eicosatetraenoic Acid; FFAs, Free Fatty Acids; GLP1-RA, Glucagon-like Peptide-1 Receptor Agonists; HDL, High-density Lipoprotein; LDL, Low-density Lipoprotein; MACE, Major Adverse Cardiac Events; MD, Mean Difference; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-Alcoholic Steatohepatitis; NAS, NAFLD Activity Score; PUFA, Polyunsaturated Fatty Acid; PPAR-g/a, Proliferator-activated Receptor gamma/alpha; RCTs, Randomized Controlled Trails; SUCRA, Surface Under the Cumulative Ranking Curve; TG, Triglycerides.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) remains the commonest cause of liver disease, contributing to a significant burden on individuals, society, and the economy.[1] The prevalence of non-alcoholic steatohepatitis (NASH), the histological variant associated with a higher risk of developing cirrhosis, is estimated to be between 3–5% and is estimated to increase rapidly, mirroring the global rise in obesity.[2] However, there are no approved pharmacological treatments for NASH,[3] and lifestyle modifications re-

main the cornerstone of therapy for NASH patients.[4] Weight loss, unfortunately, has limited sustainability and effectiveness in subsets of NASH patents such as those who are lean.[5,6] While there are currently multiple drugs that have entered phase III clinical trials, limited efficacy has been demonstrated, with some potentiating coexisting metabolic ailments.[3] Potential NASH treatments undergoing trial currently often target various steps in the pathophysiological process of NASH including lipotoxicity and cell death, inflammation, and fibrosis.[7]

The global prevalence of dyslipidemia and hypertriglyceridemia among NASH patients is estimated to be 72.1% and 83.3% respectively.[8] Dyslipidemia in NASH is characterized by increased low-density lipoprotein (LDL) cholesterol, decreased HDL cholesterol, and increased serum triglycerides.[9,10] Physiological dysfunction in NASH patients increases the likelihood of atherogenesis, thereby subjecting NASH patients to cardiovascular diseases.[11] In addition to the associated liver-related morbidity and mortality, NASH also confers an increased risk of cardiovascular diseases and related deaths in partially by the high prevalence of concurrent dyslipidemia.[12–15] As cardiovascular disease remains the leading cause of mortality in NASH, the efficacy of NASH treatments in modulating dyslipidemia must be considered when choosing a suitable treatment regimen. However, systematic analysis of lipid reduction in NASH trials has yet to be examined. This study aimed to compare the relative effectiveness of NASH drug classes in improving lipid-related biomarkers through a comprehensive network meta-analysis. The article complies with the CONSORT reporting checklist.

Methods

Search strategy

The network meta-analysis was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extended statement for network analysis.[16,17] A comprehensive search for NASH randomized controlled trials (RCTs) was conducted in the Ovid Medline database, Embase, and CENTRAL with assistance from a medical librarian on October 1, 2021. A search filter by the Cochrane Collaboration was used to identify RCT. Articles were included from inception without the use of a date filter. An example of the search strategy can be found in the Supplementary File 1. References were managed using Endnote X9 for duplicate removal. The references of the included articles were also manually screened to perform a comprehensive search (Fig. 1).

Eligibility and selection criteria

Three authors (JX, CHN, YHC) independently screened abstracts and evaluated the full text for inclusion based on the eligibility criteria. Discrepancies were resolved by consensus and in consultation with a senior author (MDM). The eligibility criteria for inclusion in this network meta-analysis limited publications to (1) RCTs by study design, (2) studies that evaluated treatments in patients with a biopsy-proven diagnosis of NASH and (3) those that reported sufficient data on outcomes of interest including but not limited to reduction in LDL levels, improvements in HDL cholesterol levels, and reduction in triglyceride levels. Trials evaluating a combination of drugs in the same treatment arm were excluded. Systematic reviews, meta-analyses, conference abstracts, case series, correspondence, and editorials were excluded. Only English articles were considered for inclusion. The focus of this meta-analysis was primarily on adult populations; pediatric studies were excluded. In addition, duplicate studies reporting results from a common database were also excluded. When articles did not present continuous variables in mean and standard deviations, estimation of mean and standard deviations from median and range was carried out using the widely adopted formula previously described by Wan *et al*.[18] In the case of trials from the same institutional database analyzing the same cohort of participants across multiple publications, the most recent publication was included.

Classification of treatments

The classification of treatments was conducted as previously described in our previous network analysis.[19] Briefly, NASH treatments of the included articles were classified into four major groups, (1) inflammation, (2) energy, (3) bile acids, and (4) fibrosis based on the mechanism of action. Treatments were classified according to these groups based on the pathophysiology of disease and mechanism of action of drugs, which could in turn give rise to insights regarding disease pathways. This was done with expert consensus and with reference to previously published treatment classifications.[19,20] When treatment modulated more than one pathway, it was classified by the pathway that it modulates the most. The exception were drugs modulating bile acid pathways, as there are enough drugs to be included as a separate group in this analysis.

Risk of bias assessment

The risk of bias assessment was assessed using the Cochrane Risk of Bias 2.0.[21] Included articles were examined on seven domains including random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. Disagreements were resolved by consensus or appeal to a third author.

Statistical analysis

Statistical analysis was performed with RStudio (R version 4.0.3). The analysis was conducted in a Bayesian network model from a generalized liner model using BUGSnet and JAGS software. The unit of measure in the network meta-analysis was mean difference (MD) for continuous events with an identity-link. Bayes iterations parameters were set to 1,000 burn-ins, 1,000 adaptations, and 10,000 iterations for the Markov Chain Monte Carlo algorithm.[22] Model fit was examined by visual inspection of the trace and density plot. Surface under the curve cumulative ranking probabilities (SUCRA) analysis was considered as the endpoint of treatment outcomes. The SURCRA analysis ranks each treatment group from 0–1 with a higher number relating to an increase probability of a successful event. Both fixed and random effects models were performed, and evaluation of model fitting was based on the Deviance Information Criterion (DIC). Consistency, which assesses statistical agreement between indirect and direct evidence required for validation of the transitivity assumption was examined through DIC and unrelated mean effects model.[22] The current analysis was conducted in a fixed effects and consistency model. The outputs of the meta-analysis were presented as MDs with the corresponding credible intervals (Crl). Publication

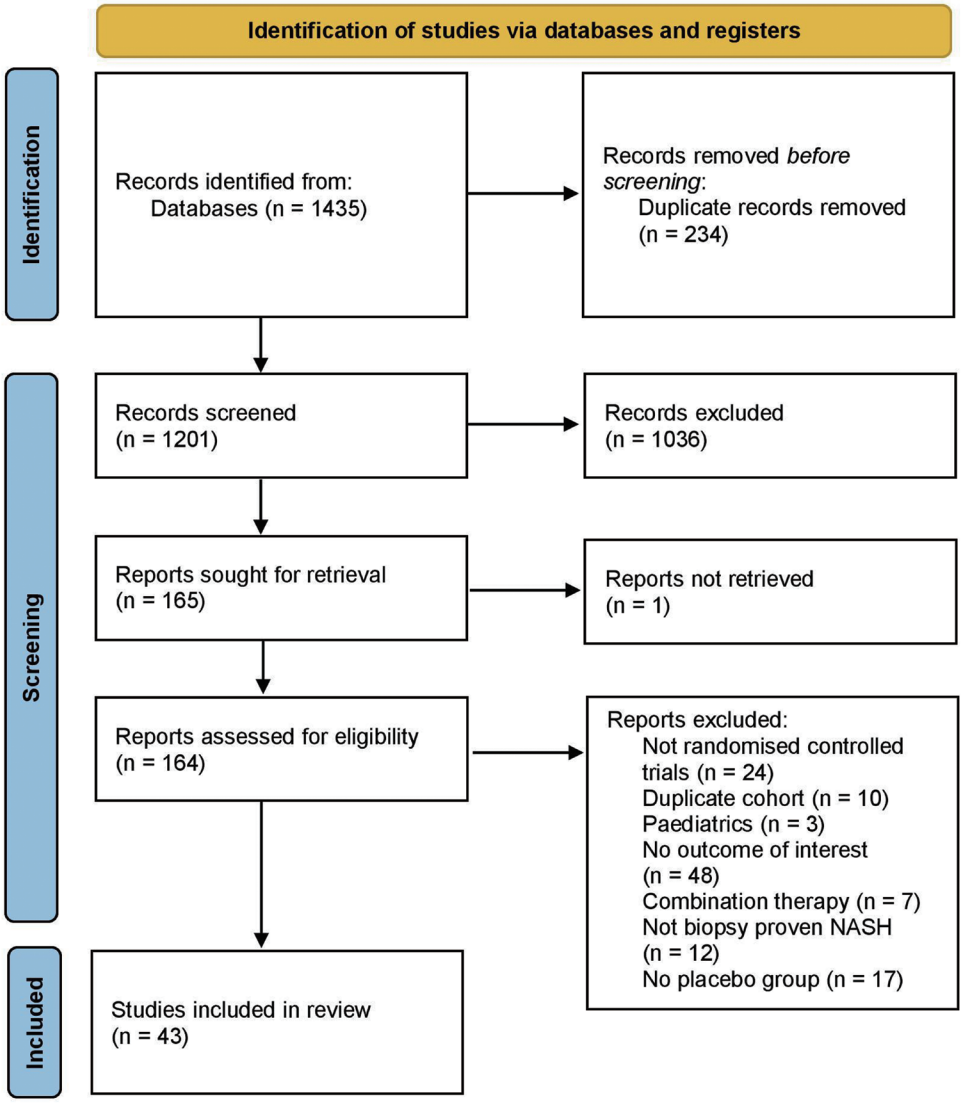

Fig. 1. PRISMA 2020 flow diagram.

bias was assessed by visual examination of funnel plots for asymmetry.

Results

Summary of included articles

1,435 articles were retrieved form the initial search strategy, with 1,201 remaining after duplicate removal. After screening of titles and abstracts, 164 full text publications were reviewed, of which 121 were excluded. The articles were excluded by title and abstract filters or full text screening if they did not qualify for inclusion based on the eligibility criteria. A total of 43 RCTs comprising 5,188 participants were included in the meta-analysis, with 2,862 participants in experimental groups and 2,326 participants in the control groups. Thirteen experimental groups were included in the inflammation subset, 24 in the energy subset, and eight in the bile acids subset. A summary of the included articles can be found in Supplementary Table 1. The majority of the RCTs were found to have low to moderate risk of bias in at least half of the domains assessed (Supplementary Fig. 1). Funnel plot analysis found no evidence of publication bias. A summary of results is shown in Figure 2.

Reduction in LDL cholesterol

Summary results of the analysis can be found in Table 1. In total, 4,558 patients were assessed for reduction in LDL cholesterol after NASH treatment. In the SUCRA analysis (Supplementary Table 2), treatment modulating fibrosis (SUCRA = 96.0) was ranked as the best treatment for reduction in LDL cholesterol followed by treatment modulating inflammation (SUCRA = 79.0), energy (SUCRA = 50.0), placebo (SUCRA = 25.0) and bile acids (SUCRA = 0) respectively. Compared with placebo, treatment modulating fibrosis resulted in largest decrease in LDL cholesterol level (MD: −1.27, CrI: −1.76 to −0.79). There was a statistically significant decrease in LDL cholesterol level between treat-

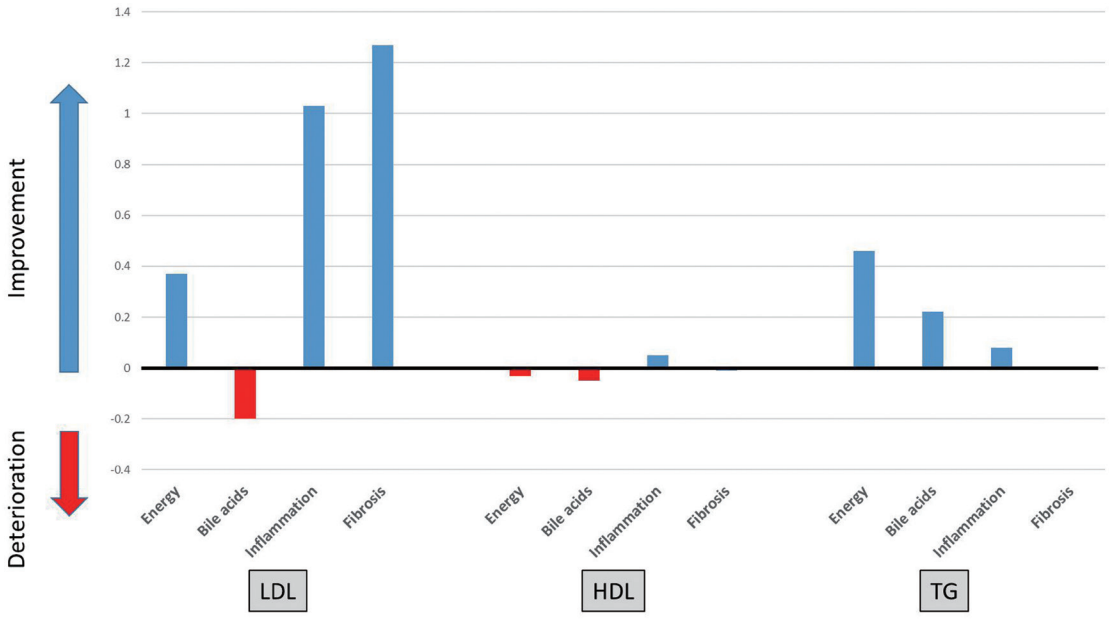

Fig. 2. Comparison of changes in triglyceride level with NASH treatment.

ment modulating inflammation (MD: −1.03, CrI: −1.09 to −0.97) and energy (MD: −0.37, CrI: −0.39 to −0.34) compared with placebo. However, treatment modulating bile acids (MD: 0.20, CrI: 0.11 to 0.28) resulted in a significant increase in LDL cholesterol levels compared with placebo.

Improvement in HDL cholesterol

Summary results of the analysis can be found in Table 1. A total of 4,400 patients were assessed for improvements in HDL cholesterol. In the improvement of HDL cholesterol, treatments ranked in descending order were modulating bile acids (SUCRA = 89.9), energy (SUCRA = 68.7), fibrosis (SUCRA = 51.2), placebo (SUCRA = 35.7), and inflammation (SUCRA = 4.5). Treatment modulating bile acids (MD: 0.05, CrI: 0.03 to 0.07) and energy (MD: 0.03, CrI: 0.02 to 0.04) resulted in similar improvement of HDL cholesterol compared with placebo. There was no significant improvement in HDL cholesterol levels resulting from treatment modulating fibrosis (MD: 0.01, CrI: −0.12 to 0.14) compared with placebo. Treatment modulating inflammation, on the other hand, resulted in a statistically significant decrease in HDL cholesterol (MD: −0.05, CrI: −0.07 to −0.03) compared with placebo.

Reduction of triglycerides

Summary results can be found in Table 1. A total of 4,406 patients were assessed for reduction in triglyceride levels after the respective NASH treatments. SUCRA analysis ranked treatment modulating energy (SUCRA = 99.6) as the best for reducing serum triglyceride levels, followed by bile acids (SUCRA = 70.6), inflammation (SUCRA = 41.8), fibrosis (SUCRA = 25.4), and placebo (SUCRA = 12.6). Statistically significant decreases in triglyceride levels was observed with treatments modulating energy (MD: −0.46, CrI: −0.49 to −0.43), bile acids (MD: −0.22, CrI: −0.35 to −0.09), and inflammation (MD: −0.08, CrI: −0.13 to −0.03) compared with placebo (Fig. 2). However, treatment modulating fibrosis did not result in a significant decrease in triglycerides (MD: 0.00, CrI: −0.41 to 0.42, Fig. 2).

Discussion

Cardiovascular disease remains the leading cause of mortality in NASH. The proinflammatory state in NASH contributes to the formation of atherosclerotic plaques, and an estimated 55.4% of NAFLD patients experience clinically significant coronary artery disease.[23] Given the association of the[24] pathophysiology of NASH and dyslipidemia[25] (Fig. 3), along with the associated increased risk for cardiovascular morbidity and mortality, targets of NASH treatment should encompass optimization of atherogenic dyslipidemia in NASH patients. Resolution of NASH has also been found to be tied to improvements in HDL and triglyceride level.[24] Broadly, we previously classified NASH treatments with expert consensus into four classes of agents that modulated bile acids, energy, inflammation, and fibrosis.[26] In this network meta-analysis of 43 RCTs, bile acid and energy-modulating treatments were significantly better than placebo in improving HDL cholesterol and reducing triglyceride levels. However, treatment modulating bile acids increased LDL cholesterol and fibrosis, inflammation, and energy-modulating treatments significantly reduced LDL cholesterol.

Lipids play an integral part in NASH pathophysiology. In this study, energy and bile acid modulating treatment were the most effective agents in triglyceride reduction. Derangement of lipid metabolism contributes to the subsequent manifestation of NAFLD and NASH.[27,28] The accumulation of lipids, mainly triglycerides, in hepatocytes participates in the pathogenesis of hepatic inflammation and fibrosis characteristic of NASH. Triglycerides in hepatic tissues are derived from free fatty acids (FFAs) contributed by adipose tissues, dietary FFAs, and *de novo* synthesis.[29] In hepatocytes, FFAs are channeled toward beta oxidation to produce energy, and excess FFAs are esterified to triglycerides that are stored in hepatocytes or exported to blood as VLDL molecules. However, in the diseased state of NAFLD, entry of FFAs into hepatocytes increases and beta oxidation and se-

Table 1. Comparison of treatments for reduction in low-density lipoprotein cholesterol, improvement in high-density lipoprotein cholesterol, and reduction in triglycerides

	Energy	Bile acids	Inflammation	Fibrosis	Placebo
Reduction in LDL cholesterol					
Energy	–	0.56 (0.47, 0.65)*	−0.66 (−0.73, −0.60)*	−0.91 (−1.39, −0.42)*	0.37 (0.34, 0.39)*
Bile acids	−0.56 (−0.65, −0.47)*	–	−1.23 (−1.33, −1.12)*	−1.47 (−1.96, −0.98)*	−0.20 (−0.28, −0.11)*
Inflammation	0.66 (0.60, 0.73)*	1.23 (1.12, 1.33)*	–	−0.24 (−0.72, 0.24)	1.03 (0.97, 1.09)*
Fibrosis	0.91 (0.42, 1.39)*	1.47 (0.98, 1.96)*	0.24 (−0.24, 0.72)	–	1.27 (0.79, 1.76)*
Placebo	−0.37 (−0.39, −0.34)*	0.20 (0.11, 0.28)*	−1.03 (−1.09, −0.97)*	−1.27 (−1.76, −0.79)*	–
Improvement in HDL cholesterol					
Energy	–	0.02 (−0.01, 0.04)	−0.08 (−0.11, −0.06)*	−0.02 (−0.15, 0.11)	−0.03 (−0.04, −0.02)*
Bile acids	−0.02 (−0.04, 0.01)	–	−0.10 (−0.13, −0.07)*	−0.04 (−0.17, 0.09)	−0.05 (−0.07, −0.03)*
Inflammation	0.08 (0.06, 0.11)*	0.10 (0.07, 0.13)*	–	0.06 (−0.07, 0.19)	0.05 (0.03, 0.07)*
Fibrosis	0.02 (−0.11, 0.15)	0.04 (−0.09, 0.17)	−0.06 (−0.19, 0.07)	–	−0.01 (−0.14, 0.12)
Placebo	0.03 (0.02, 0.04)*	0.05 (0.03, 0.07)*	−0.05 (−0.07, −0.03)*	0.01 (−0.12, 0.14)	–
Reduction in triglycerides					
Energy	–	0.24 (0.11, 0.37)*	0.38 (0.32, 0.44)*	0.46 (0.05, 0.88)*	0.46 (0.43, 0.49)*
Bile acids	−0.24 (−0.37, −0.11)*	–	0.14 (0.01, 0.27)*	0.22 (−0.21, 0.66)	0.22 (0.09, 0.35)*
Inflammation	−0.38 (−0.44, −0.32)*	−0.14 (−0.27, −0.01)*	–	0.08 (−0.33, 0.49)	0.08 (0.03, 0.13)*
Fibrosis	−0.46 (−0.88, −0.05)*	−0.22 (−0.66, 0.21)	−0.08 (−0.49, 0.33)	–	−0.00 (−0.42, 0.41)
Placebo	−0.46 (−0.49, −0.43)*	−0.22 (−0.35, −0.09)*	−0.08 (−0.13, −0.03)*	0.00 (−0.41, 0.42)	–

*statistically significant, HDL, high-density lipoprotein; LDL, low-density lipoprotein.

cretion of VLDL decreases.[30] Accumulation of hepatotoxic lipid material in the hepatocytes occurs when the increased FFAs exceed the cell's capacity of triglyceride synthesis and storage, thereby inducing the characteristic NASH histological presentation.[31,32] In turn, our previous network analysis found that BA was associated with a 2-point reduction in NAFLD Activity Score (NAS) without worsening of fibrosis and a one-point reduction in fibrosis score.[26] Recent phase II and III RCTs with BA has shown similar results with significant improvements in NASH histological markers. Loomba *et al*.[33] and Younossi *et al*.[34] reported greater proportions of patients on bile acid modulating treatments with ≥2-point NAS improvements, reduction in steatosis, lobular inflammation, and ballooning compared with placebo. In the Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment (FLINT) trial, obeticholic acid (OCA) significantly improved histological features of NASH[35] and *post hoc* analysis of lipoprotein subparticle modulation found elevated LDL with increased large-buoyant LDL, increased small-dense LDL particles, and altered HDL levels resulting from OCA NASH treatment.[36] The changes developed particularly after 12 weeks of treatment and persisted until treatment discontinuation.[36]

In the analysis of NASH treatments, bile acid, and energy-modulating treatments were associated with the greatest increase in HDL cholesterol. Treatments modulating energy, including but not limited to glucagon-like peptide-1 receptor agonists (GLP1-RA), peroxisome proliferator-activated receptor gamma/alpha (PPAR-g/a), and dipeptidyl peptidase-4 inhibitors (DPP4-i) was ranked was the most likely treatment to achieve resolution in NASH.[26] GLP1-RA and PPAR-g/a were found significantly effective in reducing fatty liver,[37] and a previous network analysis by Ng *et al*.[38] also found significant improvement in lipid modulation by PPAR-g and GLP1-RA. NASH patients have altered atherogenicity profiles because of dyslipidemia characterized by increased levels of serum triglycerides, decreased levels of HDL cholesterol and elevated LDL cholesterol levels.[9] HDL is protective against atherogenesis and CVD because of its antioxidative, antithrombotic, cytoprotective, and anti-inflammatory endothelial activity.[39] These treatments in turn potentially have added benefits in reducing the risk of CVDs in NASH.

While BA have been found to be significantly associated with reduction in fatty liver, our network analysis found that BA significantly increased LDL levels. So, while BA significantly increase LDL, combination therapy may blunt the impact of some monotherapies on lipid dysgenesis. For example, statins can be considered for use as combination therapy with treatment modulating bile acids to achieve the maximal correction of dyslipidemia in NASH patients. The efficacy and safety of statins in lowering LDL cholesterol and the risk of CVDs has been widely reported in prior studies.[40,41] The recent CONTROL study showed that BA-induced LDL increase can be mitigated by concurrent administered with atorvastatin without significantly increasing adverse reactions.[42] In turn, BA combined with statins confers additional LDL and TG reduction with modest HDL improvement, which might in turn reduce CVD risk in NASH. Furthermore, use of statins in NAFLD patients have been proven safe in multiple literatures in aspects of hepatic toxicity and treatment of dyslipidemia in patients with NAFLD.[43,44] Administering statins can also improve liver function test results and reduce cardiovascular morbidity in patients with NAFLD and at high risk of cardiovascular disease.[44] However, a previous study found that neither inflammation nor fibrosis modulating treatment contributed to significant improvement in the histological endpoints of fatty liver.[19] Besides the probable combination of BA modulating treatments and statins, it is worthwhile to note that fibrosis modulating drugs similarly resulted in significant reduction in LDL cholesterol levels,

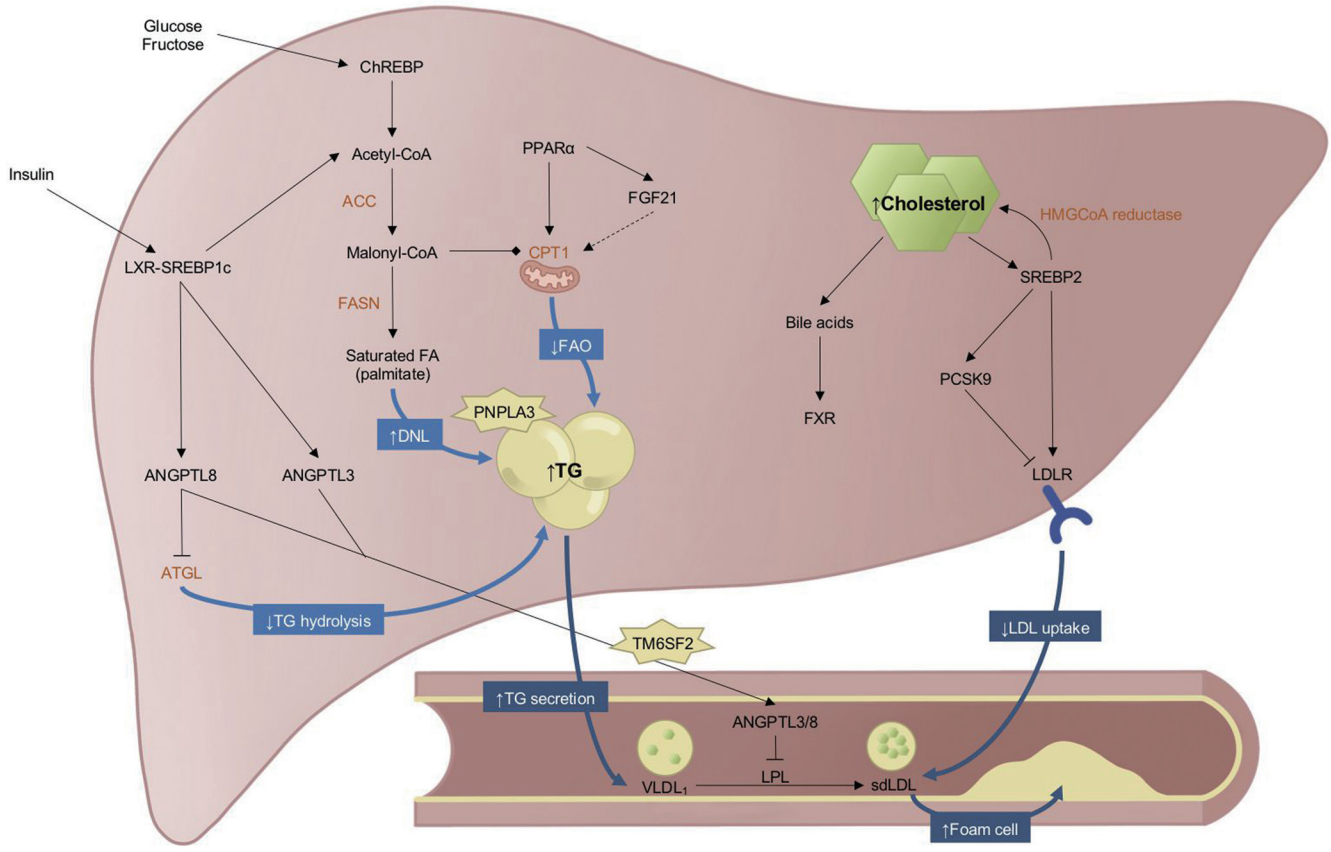

Fig. 3. Diagram of hepatic metabolism and atherosclerosis.

while inflammation modulating treatments resulted in significant improvements in all three lipid biomarkers in this analysis, suggesting potential use in combination therapy.

Strengths and limitations

This meta-analysis details a comprehensive review and comparison of various NASH treatments in modulating dyslipidemia. However, there are several limitations. Standardization of treatment definitions is not possible given the different clinical study protocols of the selected trials. However, the classification was based on a previous network analysis with expert consensus in NASH. While the classifications are not widely recognized, the comparisons between the classifications provide novel insights toward understanding the pathophysiology of disease, future drug development, and potentially aid in selection of drugs for combination therapies. Because of inter-trial heterogeneity, it was not feasible to evaluate effects of individual drugs within each class to account for variability in efficacy of different drug classes. Additionally, modulating lipids in NASH are surrogate measures of 'hard' clinical outcomes including Major adverse cardiac events (MACE) as current RCTs have yet to examine the impact of NASH treatment in MACE.

Conclusion

In conclusion, this meta-analysis compared treatments in reducing triglyceride, LDL levels, and improving HDL levels in NASH patients. Cardiovascular disease is a significant comorbidity in NASH and is a leading cause of mortality even with reversal of fibrosis. Traditional targets for treatment of NASH should be expanded to encompass optimization of atherogenic dyslipidemia. Use of combination therapy can be considered to maximize therapeutic potential and minimize the potential adverse effects of NASH treatments. However, more studies are required to evaluate longer term outcomes such as cardiovascular outcomes to justify usage of various NASH treatments.

Funding

None to declare.

Conflict of interest

AJS is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect, and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz, and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen, and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck,

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Author contributions

Conception and design (CHN, DJHT, MDM), administrative support (NC, BT, DQH, NT, RF, MYC, MN, MSS, AJS, MDM), provision of study materials or patients (NC, BT, DQH, NT, RF, MYC, MN, MSS, AJS, MDM), collection and assembly of data (JX, CHN, YHC), data analysis and interpretation (JX, CHN, YHC, DJHT, WHL, GL, JQ, ASPT, KEC, RYS), manuscript writing (all authors), and provision of final approval of manuscript (all authors)

Data sharing statement

All articles in this manuscript are available from Medline, Embase.

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