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Dyslipidemia in Patients with Nonalcoholic Fatty Liver Disease

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Abstract

Patients with nonalcoholic fatty liver disease (NAFLD) often have dyslipidemia along with other features of metabolic syndrome such as obesity, diabetes mellitus, and hypertension. The dyslipidemia in NAFLD is characterized by increased serum triglycerides, increased small, dense low-density lipoprotein (LDL nontype A) particles, and low high-density lipoprotein (HDL) cholesterol. The pathogenesis of dyslipidemia in NAFLD is not well understood, but it is likely related to hepatic overproduction of the very low-density lipoprotein particles and dysregulated clearance of lipoproteins from the circulation. There is unequivocal evidence that cardiovascular disease is the most common cause of mortality in patients with NAFLD. Aggressive treatment of dyslipidemia plays a critical role in the overall management of patients with NAFLD. Statins are the first-line agents to treat high cholesterol and their dosage should be adjusted based on achieving therapeutic targets and tolerability. Although all statins appear to be effective in improving cholesterol levels in patients with NAFLD, there is more experience with atorvastatin in patients with NAFLD; furthermore, it is the only statin to date to show a reduced cardiovascular morbidity in patients with NAFLD. The risk for serious liver injury from statins is quite rare and patients with NAFLD are not at increased risk for statin hepatotoxicity. Omega-3 fatty acids are perhaps the first choice to treat hypertriglyceridemia because of their safety, tolerability, and efficacy in improving serum triglycerides, as well as their potential to improve liver disease.

Keywords

Dyslipidemia; nonalcoholic fatty liver disease; cardiovascular disease; statin hepatotoxicity

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in the Western world.[1,2] Its incidence is increasing in both adults and children, and it is expected to become the most common cause for liver transplantation in the United States by 2020.[3] It encompasses a spectrum of liver disease, ranging from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH) and cirrhosis.[4] It is generally believed that NAFL is benign from the liver standpoint with minimal risk of cirrhosis whereas NASH can progress to cirrhosis, liver failure, and liver cancer.[4] Patients with NAFLD are heavily enriched with metabolic risk factors such as obesity, type2 diabetes, and dyslipidemia.[5,6]Metabolic syndrome is highly prevalent in patients with NAFLD[7–9]; it has been suggested that NAFLD should be considered as the part of the spectrum of metabolic syndrome.[10]

Dyslipidemia in patients with NAFLD is atherogenic in nature and it is characterized by increased levels of serum triglycerides and decreased levels of HDL

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cholesterol.[11–13]Although low density lipoprotein (LDL) cholesterol levels may not be different in patients with NAFLD, there are important differences in the subpopulations of LDL particles. Higher levels of small, dense LDL particles (nontype A), which are more atherogenic than type A LDL particles, are seen in patients with NAFLD.[11,13]Studies have also demonstrated that patients with NAFLD have significantly increased levels of oxidized LDL, which is highly atherogenic.[9,14,15] There are also important differences in the HDL subfractions in patients with NAFLD.[16] In a study consisting of 16 patients with fatty liver and 24 control subjects, Kantartzis et al demonstrated that fatty liver is significantly and independently associated with lower levels of high density lipoprotein 2 (HDL_2) cholesterol, which is more potently antiatherogenic, but had no effect on HDL_3 cholesterol levels.[16] The mechanisms for these profound alterations in lipid and lipoprotein profiles in NAFLD are not well understood, but they have generally been attributed to hepatic overproduction of the very low density lipoprotein (VLDL) particles and dysregulated clearance of various lipoproteins from the circulation.[17]

Cardiovascular Disease in Patients with NAFLD

Adults and children with NAFLD are enriched with risk factors that are generally accepted as surrogates for the risk of cardiovascular disease.[11,18] Different surrogates have been investigated in clinical studies to establish heightened risk of cardiovascular disease in NAFLD and these include Framingham Risk Score, carotid artery intima-media thickness, high sensitivity C-reactive protein, premature atheroma formation, mediastinal fat pad, endothelial dysfunction, and coronary calcium scores.[11,18] A detailed discussion of these studies is beyond the scope of this article, but interested readers are alerted to excellent reviews published recently on this subject.[11,13] Several longitudinal studies have unequivocally established that cardiovascular disease is the most common cause of death in patients with NAFLD (Table 1).[19–23] In a seminal study, Matteoni et al reported the natural history of 132 patients with biopsy-proven NAFLD seen at the Cleveland Clinic. Over a mean follow-up duration of 8.3 ± 5.4 years, their mortality rate cohort was 36% and cardiovascular disease was the most common cause of the death.[24] More recently, Rafiq et al reported the outcomes of the same cohort over an extended follow-up duration (median duration of 18.5 years) and it confirmed cardiovascular disease as the most common cause of death in patients with NAFLD.[23] These data underscore the importance of aggressively managing various cardiovascular risk factors including dyslipidemia in patients with NAFLD. A recent survey from the United States showed that primary care physicians continue to harbor significant concerns about the hepatotoxicity from statins, and it is our anecdotal experience that primary care physicians underprescribe statins to this patient population.[25]

Management of Dyslipidemia

The management of dyslipidemia in patients with suspected or proven NAFLD should be according to the same principles that are applied to other populations with dyslipidemia. Several practice guidelines are available to assist practicing clinicians in managing their patients with dyslipidemia, but their discussion is beyond the scope of this review article.[26,27]

Aggressive management of dyslipidemia plays a pivotal role in the primary and secondary prevention of cardiovascular disease. The general principles of managing dyslipidemia in patients with NAFLD include (a) diagnosing and characterizing dyslipidemia; (b) risk stratifying patients into high, medium, and low risk for cardiovascular disease based on published criteria; (c) establishing treatment targets for serum lipids; (d) lifestyle modification; and (e) pharmacotherapy. The National Cholesterol Education Project IV

Adult Treatment Protocol IV (NCEP ATP IV) guidelines for the management of dyslipidemia are expected to be published in 2012; they will likely provide state-of-the art criteria for risk stratification and therapeutic targets. The 2009 Canadian Cardiovascular Society/Canadian guidelines[27] risk stratify patients into high, medium, and low risk based on the Framingham Risk Score (or Reynolds Risk Score) and the presence of diabetes, coronary artery disease, peripheral vascular disease, or any atherosclerosis (Table 2). The lifestyle changes recommended in these guidelines can be applied with some modifications to patients with NAFLD to manage the dyslipidemia and their overall cardiovascular risk:

- A diet low in sodium and simple sugars, with substitution of unsaturated fat for saturated and transfats, and increased consumption of fruits and vegetables. In individuals with hypertriglyceridemia, consumption of food products enriched omega-3 fatty acids should be encouraged.
- Caloric restriction to achieve and maintain ideal body weight
- Moderate to vigorous exercise for 30 to 60 minutes per day most days of the week
- Smoking cessation
- Psychological stress management
- Although alcohol consumption in moderation is not contraindicated in the general population, it should be avoided in patients with NAFLD except on ceremonial occasions.

Pharmacotherapy for Dyslipidemia in NAFLD

Several lipid-lowering agents are currently approved in the United States for use either as monotherapy or in combination with other agents. Agents that have been evaluated in patients with NAFLD include statins (3-hydroxy-3-methylglutaryl-coenzyme inhibitors), fibrates, ezetimibe, omega-3 fatty acids, and niacin.

Two pertinent questions with regards to pharmacotherapy of dyslipidemia in NAFLD are (a) if the available pharmacologic agents are as effective in NAFLD as they are in other populations with dyslipidemia and (b) if the treatment of dyslipidemia improves cardiovascular disease and outcomes in patients with NAFLD. The post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study offers some insight into these questions.[28] The GREACE study was conducted to test if atorvastatin is effective in the secondary prevention of cardiovascular disease; it consisted of 1600 participants who were followed for an average of 3 years. Of the 437 participants with suspected NAFLD at the enrollment, 227 individuals received statins (predominantly atorvastatin 24 mg daily) and 210 individuals were managed with standard care. Compared with individuals in the standard care group, participants in the statin group had significant improvement in the levels of total cholesterol (35% reduction), LDL cholesterol (44% reduction), triglycerides (32% reduction), and HDL cholesterol (8% increase). There was a 68% relative risk reduction of cardiovascular events in patients with suspected NAFLD who received statins (3.2 events/100 patient-years) compared with patients with suspected NAFLD who did not receive statin (10.0 events/100 patient-years).[28] Interestingly, among all patients who received statins, patients with suspected NAFLD derived significantly greater benefit from statins compared with those who had no biochemical evidence of NAFLD (4.6 events per 100 patient-years vs 7.6 events per 100 patient-years, respectively, $P < .0001$).[28] In another randomized controlled trial (RCT), high-dose pravastatin (80 mg/d) was compared with placebo in patients with chronic liver disease (214 out of 320 randomized had NAFLD).[29] At 4 weeks after initiating the treatment, total cholesterol (−22% mean change in pravastatin group vs 1.16% in the placebo group, $P < .001$), LDL-

cholesterol (−32.57% in pravastatin group vs 0.82% in the placebo group, $P < .001$), and triglycerides (−13.75% with pravastatin and 4.8% with placebo, $P < .001$) were significantly lower in the pravastatin group.[29] These findings show that statins are effective in improving dyslipidemia and cardiovascular outcomes in patients with NAFLD.

Statins

Statins are potent lipid-lowering agents and they act by inhibiting hepatic 3-hydoxy-3-methylglutaryl coenzyme A reductase enzyme activity. Depending on the dose and type of statin, they on average decrease LDL cholesterol by 20 to 60%, decrease triglycerides by 10 to 33% and increase HDL cholesterol by 5 to 10%. Lovastatin, atorvastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, and pitavastatin are the seven statins approved by the U.S. Food and Drug Administration (FDA) and marketed in the United States. However, specific studies in NAFLD to treat dyslipidemia or the liver disease were done only with atorvastatin, pravastatin, simvastatin, and rosuvastatin either as monotherapy or in combination with other agents (Table 3).

Atorvastatin

Several open-label studies with different doses of atorvastatin and variable duration of therapy have consistently reported an improvement in lipid profiles and liver enzymes (Table 3).[30–35]However, the treatment duration was relatively modest in most studies and none of the studies with the exception of the GREACE study examined the relationship between improvement in dyslipidemia and the cardiovascular outcomes. As detailed above, the GREACE study is the only trial to show a reduction of CVD events with statins in patients with NAFLD and it predominantly used atorvastatin.[28]

Simvastatin

In an open-label, 6-month study, Abel et al have shown that simvastatin (20 mg/d) significantly improves dyslipidemia in patients with NAFLD.[36] In another small RCT, 16 patients were randomized to receive either 40 mg of simvastatin or placebo for a duration of 12 months and participants had baseline and posttreatment liver biopsy. The simvastatin group had a 26% reduction in LDL (not statistically significant from placebo), but it was not associated with histologic improvement.[37]

Rosuvastatin

Antonopoulos et al examined the effect of rosuvastatin on the lipid profiles of 23 patients with NAFLD in a prospective study.[38] The lipid profiles and liver biochemistries were monitored at months 0, 2, and 8 after starting the treatment. By month 2, there was already a significant drop in total cholesterol (−32.69%), LDL cholesterol (−41.32%), and triglycerides levels (−22%) with improvement in transaminases by ~50%. By the end of the study, all patients had normal aminotransferases, total cholesterol, triglycerides, and LDL cholesterol, with 83% achieving the desired HDL levels.

Pravastatin

In a small study of five patients with NASH, 20 mg pravastatin was administered for 6 months and the hepatic histology was reexamined in four patients.[39] At the end of study duration, there was a significant reduction in cholesterol, but not in triglycerides levels. Liver enzymes normalized in all five patients and with some improvement in hepatic inflammation and steatosis.

Fibrates

Fibrates are potent peroxisome proliferator activator receptors alpha (PPARα) agonists and they can significantly increase the hepatic oxidation of free fatty acids.[40] The PPARα agonists may have additional benefits such as improving hepatic microcirculation and oxygen availability.[41] In a pilot study, Laurin et al administered clofibrate (2 g/d) to 16 patients with NASH and hyperlipidemia for 1 year and reported no significant improvement in triglycerides, cholesterol, liver tests, or hepatic histology.[42] Clofibrate has long been withdrawn from the U.S. market due to unexplained increased mortality.[43] Gemfibrozil at a 600 mg per day dose, in a controlled trial of 46 patients with NASH, resulted in significant improvement in triglyceride levels and liver tests compared with placebo.[44] Two studies evaluated fenofibrate in patients with NAFLD and reported improvement in dyslipidemia.[35,45] One of these studies also reported improvement in liver histology.[45] Overall, fibrates are an attractive option to treat hypertriglyceridemia in patients with NAFLD, but their effect on liver histology is unclear.

Ezetimibe

Ezetimibe is an inhibitor of intestinal cholesterol absorption by inhibiting the Niemann-Pick C1-like 1 protein (NPC1L1), which is involved in cholesterol transport in the liver as well as in the intestine.[46,47]Several small studies evaluated ezetimibe in patients with NAFLD patients with variable results (Table 3).[48–52]In a study of 45 patients with NAFLD associated with type 2 diabetes and metabolic syndrome, the combination of simvastatin and ezetimibe for 6 months resulted in a significant decrease in liver enzymes and significantly greater reduction in the levels of LDL cholesterol.[36] Overall, the existing data are insufficient to assess the utility of ezetimibe in patients with NAFLD.

Omega-3 Fatty Acids

Omega-3 fatty acids are approved in the United States to treat hypertriglyceridemia. They are also available over-the-counter as natural food products for the self-treatment of a variety of health conditions. There has been significant interest to explore the beneficial effects of omega-3 fatty acids in animal models of fatty liver as well as in humans with NAFLD.[53] In a recent review, Masterton et al critically appraised the published literature related to omega-3 fatty acids in NAFLD.[53] They found strong experimental evidence supporting their use in NAFLD, but the published human studies consisted of small sample size and had many methodologic flaws. Five human studies tabulated in their review had 183 subjects and used different omega-3 formulations at varying doses.[54–58] The duration of treatment ranged from 8 weeks to 12 months. Although the effect of omega-3 fatty acid treatment on serum aminotransferases and liver biochemistries was variable, they consistently led to a significant reduction in the serum triglycerides across all tabulated studies. An interesting study that was not included in the aforementioned review randomized 144 NAFLD patients with dyslipidemia to 2 g of omega-3 fatty acids from seal oils or placebo in a 24-week clinical trial.[59] Omega-3 fatty acid supplementation was associated with significant improvement in serum aminotransferases, serum triglycerides, and hepatic steatosis at 24 weeks. There is an ongoing phase 3, multicenter, randomized, controlled trial of eicosapentaenoic acid (EPA) in patients with biopsy-proven NASH in the United States, and its results are expected to shed further light on the role of omega-3 fatty acids in the management of NAFLD (ClinicalTrials.gov Identifier: NCT01154985).

Combination Therapies

Sometimes statins are used in combination with other lipid lowering agents to achieve a greater reduction in LDL cholesterol levels or maintain tolerability. However, the data specific to using combination therapies in patients with NAFLD are sparse. Several

formulations that combine a statin with another lipid lowering agent are available in the United States market, and they include niacin/lovastatin (Advicor®, Abbott Laboratories), niacin/simvastatin (Simcor®, Abbott Laboratories), and ezetimibe/simvastatin (Vytorin®, Merck Pharmaceuticals). In addition, investigators have used a combination of statins and other agents such as fenofibrates, angiotensin receptor blockers, and antioxidants in patients with NAFLD (Table 3).

Atorvastatin with Fenofibrate

Atorvastatin (20 mg/d), micronized fenofibrate (200 mg/d), or their combination were studied in a prospective, open-label, randomized study consisting of 186 patients with NAFLD and metabolic syndrome.[35] Over a 54-week treatment period, the atorvastatin–fenofibrate combination and atorvastatin monotherapy were more effective than fenofibrate alone in reducing both biochemical and ultrasonographic evidence of NAFLD. Atorvastatin–fenofibrate combination had the most beneficial effect on all lipid parameters and on estimated CVD risk.

Atorvastatin with Antioxidants

Foster et al conducted a post hoc analysis of the St. Francis Heart Study; they examined the effect of combined therapy with atorvastatin (20 mg), vitamin C (1 g), and vitamin E (1,000 IU) administered daily or matching placebo on hepatic steatosis and NAFLD.[60] In this study, liver to spleen ratio from computed tomography images at baseline and at follow-up was used to assess for the presence of NAFLD. The combination of atorvastatin with vitamins E and C significantly reduced the presence of NAFLD at the end of follow-up (70% vs 34%; OR: 0.29; 95% CI, 0.15–0.79; $P < .001$). The improvement in hepatic steatosis was associated with significant reduction in the total and LDL cholesterol levels. However, HDL cholesterol and TG levels did not differ significantly between the two groups.

Statins and the Risk of Serious Hepatotoxicity

Alanine aminotransferase levels >3 times upper limit of normal (ULN) are seen in up to 2% of the patients exposed to statins, but the risk of serious hepatotoxicity is quite rare.[61] Nonetheless, because of the information in the package inserts as well as a misunderstanding about the significance of asymptomatic elevations in aminotransferases, there is a continued misperception about statin hepatotoxicity among the health care providers. There are several studies in the literature to show that statins can be used safely in patients with NAFLD and dyslipidemia.[29,62–65]

We have previously shown that hyperlipidemic patients with elevated baseline liver enzymes are at not higher risk for statin hepatotoxicity than hyperlipidemic patients with normal transaminases.[62] In this study, the incidence of statin hepatotoxicity over a 6-month period was examined among 342 hyperlipidemic patients with elevated baseline enzymes (presumed due to NAFLD) who received statins, 1,437 hyperlipidemic patients with normal aminotransferases who received statins (statin controls), and 2,245 patients with elevated liver enzymes who did not receive statins (liver disease controls).[62] Elevations in liver biochemistries were categorized into mild-moderate or severe based on predefined criteria. Compared with statin controls, patients with elevated baseline liver enzymes had higher incidence of mild-moderate elevations (4.7% vs 1.9%; $P = .002$), but not severe elevations (0.6% vs 0.2%; $P = .2$). However, compared with liver disease controls, patients with elevated baseline liver enzymes who received statins did not have higher incidence of mild-moderate elevations (4.7% vs 6.4%; $P = .2$) or severe elevations (0.6% vs 0.4%; $P = .6$). As this study consisted atorvastatin and simvastatin almost exclusively, we have conducted a

subsequent study with lovastatin to show that hyperlipidemic patients with elevated liver enzymes are not at higher risk for hepatotoxicity.[63] These observations are also consistent with post hoc analysis of the Pravastatin Pooling Project project, which provided data on the safety and tolerability of pravastatin over a median duration of 5 years. Of the 19,592 patients evaluated, 319 pravastatin treated patients and 262 placebo-treated patients had elevated baseline ALT (between 1 and 3 times ULN). The incidence of significantly elevated ALT at any time during the postran-domization was 5% in the pravastatin group and was not different from the placebo-treated patients (7.3%).[64] In a randomized controlled trial, Lewis et al have shown that high-dose pravastatin is safe and effective in patients with chronic liver disease (214 out of 320 had NAFLD).[29] The post hoc data from the GREACE study also have confirmed that liver-related adverse events among NAFLD patients receiving statins are quite rare (<1%).[28]

Summary

Patients with NAFLD are heavily enriched with metabolic risk factors including atherogenic dyslipidemia. Dyslipidemia in NAFLD is typically characterized by increased serum triglyceride levels, increased small, dense LDL particles, and decreased HDL cholesterol. Patients with NAFLD are at heightened risk for cardiovascular disease as assessed by a variety of surrogate measures such as endothelial dysfunction and Framingham Risk Scores. More importantly, several longitudinal studies have clearly established cardiovascular disease as the most important cause of mortality in these patients. The aggressive treatment of dyslipidemia should be considered in the overall framework of cardiovascular risk reduction in patients with NAFLD. Patients with NAFLD should be risk stratified for cardiovascular disease, and their cardiovascular risk factors should be managed based on their risk status. The NCEP ATP IV guidelines for the management of dyslipidemia are expected to be published in 2012, and they will likely provide state-of-the art criteria for risk stratification and therapeutic targets. Statins are the first-line agents to treat high cholesterol and their dosage should be adjusted based on tolerability and therapeutic targets. Although all statins appear to be effective in improving cholesterol levels in patients with NAFLD, there is more experience with atorvastatin; furthermore, it is the only statin to date to show a reduction in the incidence of cardiovascular events in patients with NAFLD. The risk for serious liver injury from statins is quite rare and patients with NAFLD are not an increased risk for statin hepatotoxicity. Omega-3 fatty acids are perhaps the first choice to treat hypertriglyceridemia because of their safety, tolerability, and efficacy in improving serum triglycerides as well as their potential to improve the liver disease.

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Abbreviations

ATP	adult treatment protocol
CVD	cardiovascular disease
GREACE	Greek atorvastatin and coronary heart disease evaluation study
HDL	high-density lipoprotein

LDL	low-density lipoprotein
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCEP	National Cholesterol Education Project
PPAR	peroxisome proliferator activator receptors
RCT	randomized controlled trial
VLDL	very low-density lipoprotein

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Table 1

Incidence of Cardiovascular Disease (CVD) in Patients with Nonalcoholic Fatty Liver Disease (NAFLD) in Selected Longitudinal Studies

Author[Ref]	Number of Subjects	Diagnosis of NAFLD	Follow-Up Duration (Years)	Proportion of Deaths Due to Cardiovascular Disease (%)	Comment
Soderberg et al[19]	118	Histology	24 (median)	30	CVD is the most common cause of death.
Ekstedt et al[20]	129	Histology	13.7 ± 1.3 (mean)	16	CVD is the most common cause of death.
Adams et al[21]	421	Imaging	7.6 ± 4.0 (mean)	25	CVD is the 2nd most common cause of death after malignancy.
Dam-Larsen et al[22]	170	Histology	20.4 (median)	38	CVD is the most common cause of death.
*Rafiq et al[23]	173	Histology	18.5 (median)	12.7	CVD is the most common cause of death.

*This report presents the extended follow-up for the original cohort from the Cleveland Clinic.[24]

Table 2

Risk Stratification for Cardiovascular Morbidity and MortalityMortality [*]

Risk Category	Criteria
High risk	Evidence of cardiovascular disease Evidence of peripheral vascular disease Evidence of atherosclerosis at any location Framingham Risk Score ≥ 20% [†] Reynolds Risk Score ≥ 20% [‡]
Medium risk	Framingham Risk Score 10–19%
Low risk	Framingham Risk Score ≤10%

[*] Based on 2009 Canadian Cholesterol Guidelines.

[†] 10-year Framingham Risk Score is based on age, gender, smoking, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, and the use of antihypertensive medications. It can be calculated at http://hp2010.nhlbihin.net/atpiii/calculator.asp

[‡] Reynolds Risk Score is based on age, smoking history, systolic blood pressure, total cholesterol, HDL-cholesterol, high sensitivity C-reactive protein, and family history of heart attack before the age of 60 years. It can be calculated at http://www.reynoldsriskscore.org/

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Table 3

Lipid Lowering Agents used Therapeutically in Patients with NAFLD

Study	*N*	NASH or NAFLD	Agent	Daily Dose	Duration (Months)	Lipid Levels	Liver Histology	Steatosis by Imaging
Kiyici et al[30]	27	NASH	Atorvastatin	10mg'	6	TC – Improved TG – No improvement	–	Improved-CT
Hatzitolios et al[33]‡	28	NAFLD	Atorvastatin	20mg	6	TG, TC, LDL – Improved HDL – No improvement	–	Improved-US
Gomez-Dominguez et al[31]	22	NAFLD	Atorvastatin	Varied	12	TC,TG – Improved	–	No change-US
Hyogo et al[32]	31	NASH	Atorvastatin	10mg	24	TC, TG,LDL, HDL – Improved	Improved	-
Georgescu et al[34]	10	NASH	Atorvastatin	10mg	10	TC – Improved TG – No improvement	Only steatosis improved	-
Athyros et al[35]†	63	NAFLD	Atorvastatin	20 mg	12.5	TC,TG,LDL,HDL – Improved	–	Improved
Abel et al *	26	NAFLD	Simvastatin	20mg	6	TC,TG,LDL,HDL – Improved	–	-
Nelson et al[36,37]	16	NASH	Simvastatin	40 mg	12	TC,TG,LDL– No improvement	No improvement	-
Antonopoulos et al[38]	23	NAFLD	Rosuvastatin	10mg	8	TC, TG, LDL, HDL– Improved	–	-
Athyros et al[35]†	62	NAFLD	Fenofibrate	200 mg	12.5	TC,TG,LDL,HDL improved	–	Improved
Fernandez-Miranda et al[45]	16	NASH	Fenofibrate	200 mg	12	TG – Improved	Improved	-
Basaranoglu et al.[44]	46	NASH	Gemfibrozil	600mg	1	TG – Improved	–	-
Yoneda et al[48]	10	NASH	Ezetimibe	10 mg	6	TG, LDL – Improved		
Park et al[49]	45	NAFLD	Ezetimibe	10 mg + diet	24	TC, TG, LDL– Improved		
Chan et al[50]	25	NAFLD	Ezetimibe	10 mg + diet	22	TC, TG, LDL, HDL – Improved		
Takeshita et al[52]	29	NAFLD	Ezetimibe	10 mg	24	TC – Improved		
Shiwa et al[51]	70	NAFLD	Ezetimibe	10 mg	6	-	–	Improved-US
Hatzitolios et al[33]‡	23	NAFLD	Omega3 fatty acid	15ml	6	TG, TC, LDL – Improved HDL – No improvement	–	Improved-CT
Foster et al[60]	44	NAFLD	Atorvastatin + Vitamin E + Vitamin C	20mg	48	TC,LDL – Improved HDL, TG improved but not different from placebo	–	Improved
Abel et al[36]	19	NAFLD	Ezetimibe/ simvastatin	10/10 mg	6	TC,TG,HDL – Improved LDL decrease was significantly more than simvastatin alone.	–	-

N, number of patients; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; mg, milligrams; TG, triglycerides; TC, total cholesterol; na, not applicable; US, ultrasound; CT, computed tomography.

* Two arms of the same study.

† Two arms of the same study.

‡ Three arms of the same study.