

# Nonalcoholic Fatty Liver Disease: Dyslipidemia, Risk for Cardiovascular Complications, and Treatment Strategy

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## Abstract

Studies have shown that nonalcoholic fatty liver disease (NAFLD) is strongly associated with several metabolic disorders and diseases, such as obesity, type 2 diabetes mellitus, and dyslipidemia. In NAFLD, dyslipidemia is manifested as increased serum triglyceride and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels, all of which are key risk factors for cardiovascular disease (CVD). CVD is a leading cause of mortality in NAFLD patients. Thus, implementation of an aggressive therapeutic strategy for dyslipidemia with hypolipidemic agents may mitigate the risk for CVD among NAFLD patients. Here, we provide a current review of literature regarding NAFLD, with particular emphasis on dyslipidemia and available treatment options.

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## Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic hepatic illnesses in developed countries, and its incidence among adults and adolescents has increased rapidly in recent years. In the United States, NAFLD represented over 75% of chronic liver disease cases in 2008,<sup>1</sup> a significant increase from 47% estimated in 1998. Similarly, a high prevalence of NAFLD in the general population is found in Europe, where it is estimated to be 20–30%.<sup>2</sup> NAFLD is associated with obesity, and between 30% and 100% of NAFLD patients are obese.<sup>3</sup> The obese population is expanding at an alarming rate. For instance, a 2010

Organization for Economic Cooperation and Development report indicated that approximately 15% of adults in Germany are obese (body mass index [BMI] > 30 kg/m<sup>2</sup>) — a clear increase from 2000 (12%).<sup>4</sup> By 2020, NAFLD is projected to become one of the most prevalent illnesses requiring a liver transplant.<sup>5,6</sup>

NAFLD refers to a liver that contains an excessive amount of fat, which is not related to alcohol consumption. Histologically, NAFLD consists of a wide spectrum of liver injury, including simple steatosis, nonalcoholic steatohepatitis (NASH), and NASH-related liver cirrhosis. Hepatocellular injury and subsequent inflammation in the liver tissue are characteristic pathological features of NASH. Among NASH patients, 15–20% will adversely progress to fibrosis, cirrhosis, or even carcinoma.<sup>7,8</sup> The pathological hallmark of NAFLD is lipid accumulation in hepatocytes, suggesting there is a close link between abnormal lipid metabolism and NAFLD. Indeed, abnormal lipid metabolism due to other diseases can also lead to NAFLD.

The majority of NAFLD patients have metabolic syndrome (MS) as well.<sup>9</sup> Thus, NAFLD is considered to be the hepatic manifestation of MS.<sup>10</sup> A growing body of evidence supports an association between NAFLD and lipid MS, especially in type 7–9 NAFLD.<sup>11</sup> In addition, the role of obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia in the pathogenesis of NAFLD has been documented,<sup>12–14</sup> implying that NAFLD may be an essential component of MS. Abnormal lipid metabolism or dyslipidemia in both MS-associated and non-MS-associated NAFLD can lead to cardiovascular complications (Fig. 1). Emerging evidence has shown the increased risk for coronary heart disease, left ventricular dysfunction, hypertrophy, heart failure, valvular heart disease, and arrhythmia in NAFLD patients.<sup>15</sup> Therefore, both the liver and cardiovascular system should be closely managed in NAFLD. This review discusses dyslipidemia, the risk for cardiovascular complications, and the therapeutic strategy for NAFLD.

## Dyslipidemia and NAFLD

Dyslipidemia that is characterized by high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels predisposes patients to atherosclerosis.<sup>16</sup> Approximately 20–80% of NAFLD patients also have dyslipidemia.<sup>17</sup> A very common change in the metabolic profile among patients with T2DM, MS, and obesity is an alteration of serum lipid levels (dyslipidemia), suggesting a close relationship between T2DM, MS, and obesity and NAFLD. It has been shown that NASH significantly boosts the level of oxidized low-density lipoprotein cholesterol (LDL-C). High LDL-C is a well-established risk

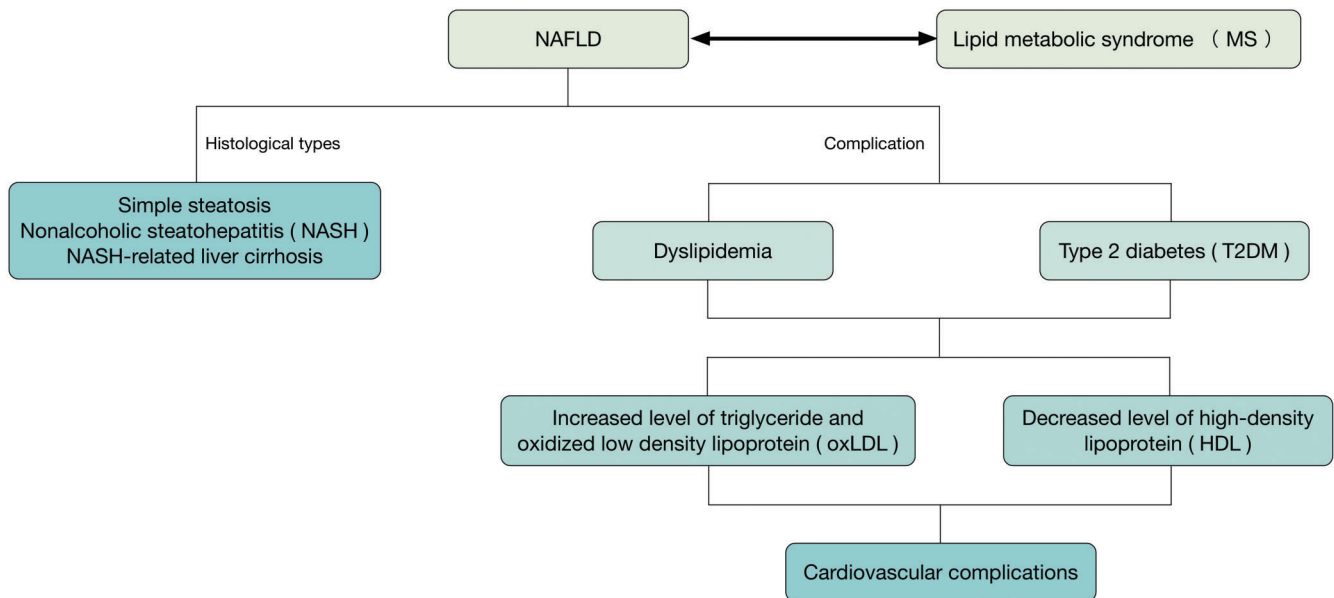
**Keywords:** Nonalcoholic fatty liver disease; Dyslipidemia; Cardiovascular disease; Hypolipidemic agents.

**Abbreviations:** ApoB/AI, apolipoprotein B/apolipoprotein AI; BMI, body mass index; CVD, cardiovascular disease; EASL, European Association for the Study of the Liver; FDA, Food and Drug Administration; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; MS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPAR $\alpha$ , peroxisome proliferator-activated receptor alpha; T2DM, type 2 diabetes mellitus; TG, high triglyceride; TLC, therapeutic lifestyle changes; TZDs, thiazolidinediones; VLDL, very low-density lipoprotein.

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**Fig. 1. The interrelationship among NAFLD, NASH, dyslipidemia, MS, and cardiovascular complications.**

factor for atherosclerosis.<sup>18</sup> The most common form of dyslipidemia in NAFLD patients is atherogenic dyslipidemia, which is characterized by hypertriglyceridemia, low HDL-C levels, and high LDL-C levels.<sup>19</sup> Long-term dyslipidemia may increase the expression and activity of sterol regulatory element binding protein-1c, a transcription factor, which adversely affects the profiles of lipid and lipoprotein synthesis in the liver, including increased TG, LDL, and very low-density lipoprotein (VLDL) levels and decreased HDL-C levels.<sup>20,21</sup> There is a strong link between insulin resistance and metabolic dyslipidemia in T2DM. Insulin resistance facilitates the increase of free fatty acid (FFA) flux. The increased FFA level boosts TG and VLDL production as well as triggers oxidative stress and lipid peroxidation, all of which are closely associated with the development of NAFLD.<sup>22,23</sup> Consequently, this physiological dysfunction also increases the risk for atherogenesis, thereby predisposing patients to cardiovascular diseases (CVDs). Direct evidence from a recent study supports a role of dyslipidemia in the development of steatosis. In an apolipoprotein E/low-density lipoprotein receptor double-knockout mouse model with obvious dyslipidemia, a western diet adversely led to hepatic steatosis and fibrosis of the liver.<sup>24</sup> Therefore, dysfunction of fat metabolism consequently leads to fat accumulation in the liver. In addition, circulating adipokines and cytokines as well as associated lipotoxicity, mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress are involved in steatosis.<sup>25</sup> It was recently demonstrated that the apolipoprotein B/apolipoprotein AI (ApoB/AI) ratio is a useful predictor of the risk of CV disease<sup>9,12</sup> and is associated with the prevalence of NAFLD.

### CVDs and NAFLD

Clinically, most NAFLD patients also have MS, thus predisposing these individuals to abnormal lipid metabolism in hepatocytes, leading to hepatocellular injury and inflammation. Therefore, NAFLD patients with MS exhibit a high tendency to develop NASH.<sup>8,26</sup> Moreover, CVD risk factors,

such as a high Framingham risk score, carotid intima media thickness, and high-sensitivity C-reactive protein level as well as early forms of atherosclerosis, endothelial dysfunction of the pericardial fat pads, and coronary artery calcification, are significantly elevated in NAFLD patients.<sup>27</sup> Several longitudinal studies have demonstrated that cardiovascular events are the leading cause of mortality in NAFLD patients.<sup>28,29</sup> In an eight year study, Matteoni *et al.* found that the mortality rate among 132 NAFLD patients was 36%, and that most of them died of cardiovascular complications.<sup>30</sup> The contribution of cardiovascular complications to the mortality of NAFLD patients was further confirmed by another clinical trial involving 132 NAFLD patients followed for 18 years.<sup>31</sup> The aforementioned findings highlight the increased risk of developing secondary cardiovascular complications among NAFLD patients. However, the exact underlying mechanisms of this complex relationship remain not well understood. Some studies have suggested that inflammation, oxidative stress, insulin resistance, ectopic adipose tissue distribution, dyslipidemia, and endothelial dysfunction might be risk factors that link NAFLD and CVD.<sup>32</sup> Regarding dyslipidemia as the plausible link between NAFLD and CVDs, aggressive management of dyslipidemia and prevention of cardiovascular deterioration may represent a promising addition to the treatment of NAFLD, thus reducing patient mortality. Liver fat deposition and oxidative stress result in the increased secretion of inflammatory markers, such as interleukin-6, tumor necrosis factor- $\alpha$ , C-reactive protein, and fibrinogen.<sup>33</sup> The inflammatory reaction boosts the expression of plasminogen activator inhibitor-1 and adhesion molecules in endothelial cells. Thus, the ideal therapeutic strategy for NAFLD management should not only reverse the excessive lipid accumulation in hepatocytes but also attenuate the hepatic inflammatory reaction, endothelial dysfunction, and insulin resistance in the liver, eventually preventing the progression of simple steatosis to NASH. A better understanding of the role of these factors in the pathogenesis of NAFLD is imperative for future studies.

## Management of dyslipidemia in NAFLD patients

Management of abnormal lipid profiles is an important component of primary and secondary programs for preventing CVDs. Currently, a consensus on managing such lipid metabolic abnormalities in NAFLD patients, as adopted by the general guidelines, includes (a) individual patient assessment of lipid abnormalities; (b) stratification of patients according to the severity of the cardiovascular risk factors they have when admitted (high, medium, or low); (c) set target lipid levels for NAFLD; (d) aggressive lifestyle changes; and (e) hypolipidemic agents.

### Risk stratification

The Canadian Cardiovascular Society has recommended risk stratification guidelines for the diagnosis and treatment of dyslipidemia and prevention of CVD. The stratification criteria utilize the Framingham risk score of patients who have concurrent diseases, such as T2DM, coronary artery disease, periphery vascular disease, and atherosclerosis.<sup>34</sup> Patients with a Framingham risk score greater than 20%, 10–19%, or less than 10% fall in the high-, medium-, and low-risk CVD risk categories, respectively.

### Therapeutic lifestyle changes

A combination of diet and exercise, collectively known as therapeutic lifestyle changes (TLC), has been found to be critical for the overall health and wellness of participants. TLC is able to bring lipid levels within the acceptable range,<sup>35</sup> which can significantly lower cardiovascular risk and favorably improve the clinical outcomes of NAFLD patients.<sup>36</sup> The current recommendations for TLC include the following: a) eating food with less sugar, salt, and saturated fatty acids; b) maintaining a healthy body weight; c) exercising 30–60 min every day. The American College of Sports Medicine recommended in 2009 that moderate-intensity exercise between 150 and 250 min a week is effective in preventing weight gain and improves NAFLD.<sup>37</sup> St George *et al.*<sup>38,39</sup> showed that NAFLD patients who increased their physical activity by at least 60 min or who maintained their physical activity at  $\geq 150$  min per week demonstrated the greater improvements in liver biochemistry compared to those who were inactive; d) quitting smoking; e) maintaining good mood and relieving pressure; and f) reducing alcohol consumption. In a one-year study, Huang *et al.* found that lifestyle changes and body weight loss resulted in significant histological improvement in patients with NASH (60% of 23 NAFLD patients).<sup>40</sup> In another study, of the enrolled 49 dyslipidemic hemodialysis patients who completed a 21-week lifestyle intervention, 17% became nondyslipidemic and in other patients, the LDL cholesterol and triglyceride levels were significantly decreased and the HDL level was significantly increased.<sup>41</sup>

### Hypolipidemic agents and NAFLD

Lipid-lowering compounds currently available are statins, fenofibrate, omega-3 fatty acids, niacin (table 1). These agents are widely used in the treatment of hyperlipidemia with mono- or combination therapy, including patients with NAFLD. There are two major concerns with respect to the pharmacotherapeutic use clinically of these compounds for dyslipidemia in NAFLD. One is whether the current lipid-lowering compounds have the

same efficacy for NAFLD as they have for other health issues accompanied with dyslipidemia. Another one is whether lipid-lowering compounds can reduce the risk of CVD in patients with NAFLD.

### Statins

Statins (or 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors) are a class of drugs that are used to lower cholesterol levels by blocking the enzyme HMG-CoA reductase. A number of statins are available on the market now: lovastatin, atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Statins inhibit the cholesterol synthesis pathway in the liver and significantly lower circulating cholesterol levels. Administration of statins induces a 20–60% reduction of LDL-C and TG levels while effectively increasing HDL-C levels by 1–10%. Clinically, atorvastatin, pravastatin, simvastatin, and pitavastatin are garnering further attention because of their enhanced ability to lower hyperlipidemia in NAFLD patients.

#### Atorvastatin

Athyros *et al.* reported a clinical trial in Greece regarding the efficacy of atorvastatin on the prevention of secondary CVDs.<sup>42</sup> A total of 1,600 subjects were enrolled in this three year follow-up study, of which 437 subjects were latent NAFLD patients without a definitive diagnosis. Among the latent NAFLD patients, 227 were administered atorvastatin (24 mg/day) whereas 210 patients were not treated with a statin. They found that the patients treated with atorvastatin demonstrated a 35%, 44%, and 32% reduction in the serum total cholesterol, LDL-C, and TG levels, respectively. Simultaneously, atorvastatin significantly increased the HDL-C level by 8% compared to the standard treatment group. Moreover, the cardiovascular risk in the atorvastatin group was significantly reduced by 68% (from 10% to 3.2%). These findings suggest that statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in potential NAFLD patients with mild-to-moderately abnormal liver tests.

#### Simvastatin

Abel *et al.* reported that simvastatin (20 mg/day) effectively improved the lipid profile of NAFLD patients in a six month nonblinded clinical trial.<sup>43</sup> By using immunohistochemistry to measure LDL-C level in the liver, it was found that LDL-C in patients treated with simvastatin was reduced by 26% compared to untreated counterparts.

#### Rosuvastatin

In another prospective cohort study, 23 NAFLD patients were treated with rosuvastatin for 8 months.<sup>44</sup> Lipid panel and liver function analyses were conducted prior to initiation of treatment and at 2 and 8 months during treatment. After 2 months, the patients showed a significant reduction of total cholesterol (33%), LDL-C (41%), TG (22%), and transaminase (50%) levels. Interestingly, all of these parameters were within the normal ranges. In addition, at 8 months of treatment, the HDL-C level was improved by 83% in NAFLD patients.

### Pravastatin

In a study with a small sample size, Rallidis *et al.* reported that pravastatin (20 mg/day) significantly affected total cholesterol level in five NAFLD patients.<sup>45</sup> Although pravastatin treatment did not significantly impact the TG level, liver function in all patients was effectively improved after treatment. Moreover, notable amelioration of hepatic inflammation and steatosis was observed.

### Fibrates

Fibrates are a class of amphipathic carboxylic acids, and they reduce lipid levels by activating peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ). PPARs are a class of intracellular receptors that modulate carbohydrate and fat metabolism as well as adipose tissue differentiation. PPAR $\alpha$  increases lipolysis and elimination of TG-rich particles from the plasma via activating lipoprotein lipase and reducing apolipoprotein CIII.<sup>46</sup> Fibrates can improve the microcirculatory system function in the liver by facilitating fatty acid oxidation. It has been shown that gemfibrozil (600 mg/day) can significantly lower serum TG level and improve liver function of NAFLD patients.<sup>47</sup> The results in this study are consistent with previous reports in which fenofibrate was found to be therapeutically beneficial on the lipid profile of NAFLD patients.<sup>48,49</sup> In short, fibrates offer a different type of therapeutic strategy for the treatment of dyslipidemia in NAFLD patients.

### Ezetimibe

Ezetimibe is a specific cholesterol absorption inhibitor, and it does not inhibit cholesterol synthesis in the liver or increase bile acid excretion. It lowers plasma cholesterol levels by decreasing cholesterol absorption in the small intestine.<sup>50</sup> However, data regarding the overall efficacy data of ezetimibe are inconclusive for use in patients with NAFLD.

### Omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fatty acids. They are essential fatty acids that cannot be endogenously synthesized. Omega-3 fatty acid monotherapy or in combination with a statin can lower the TG level without affecting the LDL-C level.<sup>51</sup> Omega-3 fatty acids have been approved by the United States Food and Drug Administration (FDA, US) as an adjunct to diet for lowering very high TG levels.<sup>52</sup> Previous studies have found that omega-3 fatty acids can effectively improve lipid profiles in NAFLD patients treated for eight to 12 months.<sup>53–57</sup> Although results from studies examining liver function tests after treatment with omega-3 fatty acids are inconsistent, all studies have strong clinical evidence in support of the benefits of omega-3 fatty acids on TG level in NAFLD patients. For example, in a clinical trial, 144 NAFLD patients were administered 29 omega-3 fatty acids or placebo daily for 24 weeks. Aminotransferase and serum TG levels as well as hepatic steatosis were significantly improved in the patients administered the omega-3 fatty acids compared to the placebo group.

### Combination Therapies

To achieve a maximal reduction in the LDL-C level, the combination of statins with other lipid-lowering agents has

been evaluated. In a study by Athyros *et al.*, 186 NAFLD patients were treated with atorvastatin (20 mg/day), fenofibrate (200 mg/day), or a combination of these for 54 weeks; and it was found that outcomes on lowering cardiovascular risk were better with atorvastatin than fenofibrate.<sup>48</sup> Interestingly, the combination treatment was also more efficacious than fenofibrate alone. In another similar study, Foster *et al.* found that the combination of atorvastatin (20 mg/day) with vitamin C (1 g/day or 1000 IU/day) greatly improved the survival of NAFLD patients at the end of the follow-up period.<sup>58</sup> Moreover, their data suggested that the beneficial effects on hepatic steatosis were closely associated with a decrease in the total cholesterol and LDL-C levels but not HDL-C or TG levels.

### Statins and the risk of serious hepatotoxicity

Although up to 2% of the patients treated with statins show elevated alanine aminotransferase levels at more than three times the upper limit of normal, the risk of serious hepatotoxicity is still very rare. However, the significant increase of aminotransferase levels in some treated patients does raise concerns regarding the potential hepatotoxicity of statins. Recently, numerous studies have demonstrated that statins are safe for treating NAFLD patients.<sup>59–62</sup> There is no clinical evidence that hyperlipidemic patients with high aminotransferase levels possess a greater risk for statin hepatotoxicity than their counterparts with normal transaminase levels. A clinical study by Chalasani *et al.* clearly confirmed this conclusion.<sup>60</sup> In this study, 342 hyperlipidemic patients with high aminotransferase levels (cohort 1) and 1,437 hyperlipidemic patients with normal aminotransferase levels (cohort 2) received statin therapy. An additional 2,245 patients with elevated liver enzyme levels (cohort 3) who did not receive statins (liver disease control) were also enrolled in this study. After 6 months of treatment, hepatotoxicity of statins was examined. The incidence of mild-moderate elevations in liver biochemistries in cohort 2 was less than cohort 1 (1.9%,  $p=0.002$ ), but there was no significant difference between cohort 2 and cohort 1 in severe elevations (0.2%,  $p=0.2$ ). There were no differences in liver biochemistries between cohorts 1 and 3. In another clinical trial that was designed to examine the safety of pravastatin, it was found that the incidence of elevated aminotransferase levels was not significantly different between pravastatin-treated and placebo-treated patients.<sup>52</sup> Overall, the available data suggest that statin-induced hepatotoxicity is quite rare.

### Insulin sensitizing agents and NAFLD

Metformin, an inhibitor of hepatic gluconeogenesis, is used clinically as a first-line treatment of T2DM. In an open label trial consisting of 110 patients randomly assigned to receive either metformin 2 g/d (55 patients), vitamin E 800 IU/d (28 patients), or dietary-induced weight loss (27 patients) patients for 12 months, liver transaminase levels were significantly decreased in the metformin group relative to the other groups. Also, in a subset of 17 patients taking metformin, there were histological improvements in hepatic steatosis, inflammation, and fibrosis. A recent clinical trial, however, did not find any significant benefit of treatment in pediatric patients with the disease.<sup>63</sup> Meanwhile, the position statement based on an European Association for the Study of the Liver (EASL) special conference on NAFLD/NASH has not



**Table 1. Overview of dyslipidemia agents in NAFLD**

Dyslipidemia agents	Brief description	Representative drugs	Effects on the liver
Statins	A class of drugs that are used to lower cholesterol levels by blocking the enzyme HMG-CoA reductase	Atorvastatin Simvastatin Rosuvastatin Pravastatin	Inhibit the cholesterol synthesis pathway in the liver and significantly lower circulating cholesterol levels by reducing endogenous cholesterol synthesis.
Fibrates	A class of amphipathic carboxylic acids used to reduce lipid levels by activating peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ )	Fibrates	Improve serum liver enzymes without affecting liver histology and improve the microcirculatory system function in the liver by facilitating fatty acid oxidation.
Ezetimibe	A specific cholesterol absorption inhibitor	Ezetimibe	Not tested in RCTs. Lower plasma cholesterol levels by decreasing cholesterol absorption in the small intestine. The overall efficacy data are inconclusive in NAFLD.
Omega-3 fatty acids	Polyunsaturated fatty acids	Omega-3 fatty acids	Lower the TG level without affecting the LDL-C level in NAFLD.
Insulin sensitizing agents	Activates AMPK and improves peripheral insulin sensitivity	Metformin Thiazolidinediones (TZDs)	Improve liver histology, glucose, lipid, and inflammatory variables and delay progression to fibrosis in patients with NAFLD

recommended metformin for specific liver-directed therapy of NASH.<sup>64</sup>

The thiazolidinediones (TZDs) are another group of insulin sensitizing agents that improve insulin sensitivity at the level of adipose tissue, muscle, and liver and are now widely used for treatment of T2DM. Troglitazone was the first TZD to be tested for NASH in an open-label pilot clinical trial.<sup>65</sup> A recent meta-analysis showed the beneficial effects of pioglitazone on liver histology, glucose, lipid, and inflammatory variables, and progression to fibrosis in patients with NAFLD.<sup>66</sup> The drug should be considered for treatment of NAFLD, especially in patients with T2DM.

## Conclusions

NAFLD patients frequently have MS, especially dyslipidemia. The features of dyslipidemia include elevated TG and LDL-C levels accompanied with a decreased HDL-C level. NAFLD patients carry a high risk for CVDs, which are a leading cause of mortality for NAFLD patients; therefore, reducing the CVD risk could represent a pivotal strategy for effectively managing NAFLD patients. In addition, correction of abnormal lipid profiles in these patients could improve their survival by lowering the risk of CVDs. The criteria for CVD risk stratification of NAFLD patients have been established, and the corresponding management should be based on the risk status of the patients. Statins are the first line choice for treating hypercholesterolemia. The drug dosage should be adjusted individually based on tolerability and the therapeutic target. As reviewed here, all statins seem to restore the altered serum lipid levels in NAFLD patients effectively. However, physicians may prefer atorvastatin to other drugs, since atorvastatin is the only agent that has been proven to lower cardiovascular risk factors in NAFLD patients and possesses less hepatotoxicity. For the treatment of hypertriglyceridemia, omega-3 fatty acids may be the first choice, because of their enhanced ability to lowering serum TG levels

and they are well tolerated. Importantly, current evidence suggests that combination therapy with more than a hypolipidemic agent in NAFLD patients may increase efficacy in controlling dyslipidemia and improve tolerability.

## Conflict of interest

None

## Author contributions

Designing the research (ZQQ, LLG), searching the databases and writing the paper (ZQQ), making the complete guide of article (LLG).

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