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Treating nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a review of efficacy and safety

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Abstract

Objective: To review current literature for the efficacy and safety of treatment for nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM).

Data sources: A PubMed literature search from January 1990 to June 2017 was conducted using the search terms nonalcoholic fatty liver disease, diabetes mellitus, type 2, therapy, treatment, treat, therapeutics, nonalcoholic fatty liver, nonalcoholic hepatosteatosis, NASH, NAFLD, metformin, and statin. Bibliographies of chosen articles were reviewed.

Study selection and data extraction: Relevant articles on metformin, thiazolidinediones (TZD), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and statins for the treatment of NAFLD which included patients with T2DM were reviewed. A total of 23 relevant studies were found and included randomized controlled, observational, and open-label designs, as well as three meta-analyses.

Data synthesis: Metformin combined with weight loss provides a modest improvement in steatosis and no improvement in fibrosis in patients with NAFLD and T2DM. TZDs showed positive results on fibrosis and resolution of NASH but at least half of patients studied were nonresponders. GLP-1 RAs also showed favorable results on reductions in transaminases and steatosis and improvements in insulin sensitivity and weight loss but lack efficacy data for resolution of NASH or improvement in fibrosis scores. Statins showed favorable results on reductions in transaminases but mixed results for improvement in steatosis and fibrosis scores.

Conclusion: All reviewed treatment options are safe for management of NAFLD in patients with T2DM but long-term histological improvements are minimal. TZDs are efficacious for resolution of NASH and improvements in fibrosis but long-term use is required to maintain these results.

Keywords: diabetes, glucagon-like peptide 1 receptor agonists, nonalcoholic fatty liver disease, statin, steatohepatitis, thiazolidinediones, treatment, type 2

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes in adults in the United States. The term NAFLD is used to encompass a wide range of liver damage from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis.[1,2] Although the pathogenesis of NAFLD and the role of insulin resistance on its progression has not been fully defined, the 'multiple-hit' hypothesis was recently developed to explain the role of multiple insults on the liver which may induce NAFLD.[3] This hypothesis replaces the previously defined 'two-hit' hypothesis, where a sedentary lifestyle, obesity, and insulin resistance lead to hepatic steatosis (first hit), which promotes liver inflammation and cellular injury (second hit).[4,5] The multiple-hit hypothesis defines insulin resistance as a key

contributor to the development of NAFLD because of its impact on increases in *de novo* lipogenesis and dysfunction in the release of free fatty acids (FFAs) and triglycerides from the liver.[3,5] These risk factors are also associated with the development of type 2 diabetes (T2DM), explaining the high rate of these diseases occurring concomitantly. Studies estimate the prevalence of hepatic steatosis in patients with T2DM to be 30–50%.[6] The prognosis for patients with concomitant NAFLD and T2DM is worsened due to increased risk for life-threatening sequela such as cardiovascular disease and hepatocellular carcinoma, highlighting the need for improved treatment options.

The American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association published joint practice guidelines in 2012 which recommend lifestyle interventions (hypocaloric diet and increased physical activity) and a body weight reduction of 3–5% to achieve improvement of steatosis; however, up to 10% weight loss is needed to demonstrate improvements in necroinflammation.[7] While there are no drugs approved for the treatment of NASH by the US Food and Drug Administration (FDA), guidelines recommend vitamin E as a first-line treatment in individuals without diabetes. The guidelines also recommend pioglitazone, but warn most clinical studies were conducted in patients without diabetes. At the time of guideline publication, there was not enough evidence to support a recommendation for the use of metformin or statins as a treatment for NASH, but the use of statins for dyslipidemia in patients with NASH is encouraged as they appear safe.

Clinicians often question the safety of common drug treatments for patients with T2DM and NASH. In recent years, numerous trials have been conducted utilizing insulin sensitizers and statins to treat NASH, which included patients with T2DM in the study design. The objective of this literature review is to evaluate the safety and efficacy of medications for the treatment of NASH in patients with T2DM.

Methods

A review of published studies using PubMed was conducted to identify reports pertaining to the safety and efficacy of pharmacologic treatments of NAFLD commonly used in patients with T2DM. One author conducted the search and assessed eligibility, and all authors contributed to the review of data, drafting, and editing of the manuscript. MeSH terms used in various combinations included non-alcoholic fatty liver disease, diabetes mellitus, type 2, therapy, treatment, treat, therapeutics, nonalcoholic fatty liver, nonalcoholic hepatosteatosis, NASH, NAFLD, metformin, and statin. PubMed search filters were applied for published dates between 1 January 1990 and 30 June 2017, English language, adults (age ⩾19 years), clinical trial, meta-analysis, or observational studies. Other articles of interest were obtained from bibliographies of included articles.

Results

A total of 397 abstracts were initially reviewed for possible inclusion. Only 23 articles met inclusion criteria based on relevancy to the study population and outcomes relevant to safety and efficacy of treatment.

Metformin

Metformin has several mechanisms by which it helps to reduce blood glucose and improve insulin sensitivity, including decreasing gluconeogenesis in the liver, increasing glucose uptake in the periphery, and increasing fatty acid oxidation, all leading to a decrease in cellular insulin production.[8,9] Metformin promotes weight loss, is inexpensive, and has long-term data showing safety and tolerability, making it a viable option in the treatment of NAFLD.

A meta-analysis completed by Li and colleagues analyzed data from nine studies involving 417 participants on the use of metformin dosed at 0.5–3 g/day for NAFLD.[4] The primary outcome was histological response to therapy, including steatosis, inflammation, hepatocellular ballooning, and fibrosis. No significant difference was seen in any of the variables between metformin and diet and exercise alone; this was also true for a subgroup analysis of patients with diabetes *versus* those without. A limitation of this meta-analysis is that only five of the nine studies could be assessed for the primary outcome due to provision of insufficient data in the individual studies. A study completed by Nair and colleagues included patients with NAFLD who took metformin (20 mg/kg/day in three divided doses) for 48 weeks and compared pre- and post-treatment liver biopsies.[8] Ten of 15 patients completed both biopsies; of these only three saw a reduction in steatosis at the study's conclusion.

Although the data on improvements in histologic outcomes with metformin in NAFLD have been poor, improvements in metabolic markers have been seen in two meta-analyses and several smaller studies (Table 1). An important benefit of metformin therapy is its contribution to weight loss, possibly through its impact on insulin sensitivity and the gastrointestinal adverse effects associated with its use.[9] Improvements in body mass index (BMI) from baseline were seen in the meta-analysis by Li and colleagues with a weight loss of –0.82 kg/m^2 ($p < 0.04$).[4] Significant improvements in the homeostatic model assessment for insulin resistance (HOMA-IR) scores were seen in the meta-analysis by Li and colleagues ($p = 0.04$)[4] and Mazza and colleagues ($p = 0.003$)[9], indicating improvements in insulin sensitivity. A study completed by Loomba and colleagues found that patients with a lower baseline BMI responded more significantly to metformin therapy than those with a baseline BMI of at least 40 in terms of weight loss, reductions in HOMA-IR, and histological improvements.[5] The authors concluded that there is a positive correlation between weight loss and improvements in hepatocellular injury and inflammation. Mild to moderate increases in alanine aminotransferase (ALT) is the most common laboratory finding in NAFLD, and improvements in ALT and aspartate aminotransferase (AST) have been seen with metformin treatment in almost all patients in the reviewed studies.[4,8–10] These decreases do tend to be more significant after the first three months of treatment, at which time AST/ALT levels generally plateau.[8]

Another contributing factor to obesity and NAFLD is leptin, a hormone produced by adipose tissue to indicate fullness during mealtime as well as to regulate the collection of lipids to the adipose sites.[3] Patients with obesity can experience leptin resistance, and high serum levels of leptin were seen in patients with NAFLD.[3,11] Increases in leptin can impact proinflammatory responses and fibrogenesis as well as modify the effects of insulin on hepatic fat metabolism and increase insulin resistance.[3,11] A small study ($n = 34$) looked at the effects of metformin in patients with NAFLD in regards to decreases in serum leptin in comparison to a lifestyle modification intervention.[11] Leptin was significantly reduced in both groups from baseline to month 6 ($p = 0.039$ in the lifestyle group and $p = 0.047$ in the metformin group), but there was no difference between the groups. Leptin levels were reduced in correlation with amount of weight loss in both groups, further emphasizing the importance of a focus on weight management in patients with NAFLD.

Thiazolidinediones

It could be hypothesized that thiazolidinediones (TZDs) are well suited for use in the treatment of NASH due to their powerful insulin-sensitizing properties. TZDs bind to peroxisome proliferator-activated receptor γ receptors and improve insulin sensitivity in the liver, skeletal muscle, and adipose tissue.[12,13] In addition, they increase plasma adiponectin levels[14] and decrease proinflammatory cytokines,[15] all of which are primary processes involved in NASH. Several studies examined the use of rosiglitazone and pioglitazone in patients with impaired glucose tolerance or T2DM and biopsy proven NASH (Table 2).

Efficacy. Two trials[16,17] examined rosiglitazone use in patients with biopsy-confirmed NASH. In one trial,[16] rosiglitazone was studied in an open-label design in 30 subjects, half of those with either T2DM or impaired glucose tolerance, to determine if rosiglitazone would improve insulin sensitivity, improve hepatic steatosis, and reduce serum liver aminotransferases. At the end of 48 weeks, serum levels of ALT and AST decreased significantly from baseline. Significant improvements in histologic markers, specifically steatosis ($p = 0.004$) and ballooning ($p = 0.003$), were observed. While significant changes in the characteristic and pattern of fibrosis were seen, no significant difference in the global fibrosis score was observed ($p = 0.583$). Importantly, approximately half of the participants were nonresponders. For those who did respond to rosiglitazone, transaminases returned to baseline values 6 months after stopping treatment. The second study, a randomized controlled trial completed by Ratziu and colleagues, compared rosiglitazone with placebo in 63 subjects, 20 with T2DM.[17] At the end of 12 months, significantly more patients in the rosiglitazone group achieved over 30% reduction in steatosis (47% *versus* 16%, $p = 0.014$) and normalized serum ALT levels (38% *versus* 7%, $p = 0.005$) compared with placebo. Additional clinical improvements in HOMA-IR, fasting insulin level, and adiponectin level were noted. Similar to the first trial, there were no significant improvements seen in fibrosis, and 50% of subjects were nonresponders. Nonresponders had higher γ-glutamyltransferase levels, higher instances of

Table 1. Efficacy and safety trials of metformin for NAFLD in patients with T2DM.

Study and trial design	Treatment	Comparator	Number of Participants	Duration (months unless otherwise stated)	ALT mean change from baseline	AST mean change from baseline	Imaging or histologic changes	Other significant measurements
Li *et al*.[4] Meta-analysis	MET	Diet/diet + exercise/ various PBO	417 (68 with DM or IGT)	6 or 12	–8.12 U/ liter, p = 0.03	–4.52 U/ liter, p = 0.04	No changes seen in steatosis, inflammation, ballooning, or fibrosis	HOMA-IR changes were statistically significant in patients with NAFLD but not NASH
Loomba *et al*.[5]	MET 2000 mg/day		26 (15 with DM)	48 weeks	↓ 7 U/ liter	↓ 4 U/ liter	*Presence of NASH* Pre: 26/26 Post: 18/26 *NASH activity index* Pre: 8.2 (1.5) Post: 5.9 (2.2) ($p < 0.001$)	Average weight Δ –6 kg (range +1.3 to –18.9 kg) Strong positive correlation between weight loss and changes in serum aminotransferase levels; higher baseline BMI ↓response HOMA-IR Δ –3.4 ($p < 0.04$)
Nair *et al*.[8] Open label	MET 20 mg/kg/day (max 2 g)		15 (1 with DM)	1 year	↑ 6 IU/ liter	↓ 6 IU/ liter	20% of patients showed improvement in degree of steatosis at 1 year	BMI Δ –1.7% ($p <$ 0.05) HOMA-IR Δ –0.09 ($p < 0.05$)
Haukeland *et al*.[10] RCT	MET 2500 mg/day	PBO	48 (12 with DM)	6	MET: 22 U/liter, p = 0.025 PBO: 15 U/liter, p = 0.025	MET: 8 U/ liter, p = 0.036 PBO: no change	Treatment was associated with a slight reduction of liver steatosis in both groups Age, baseline HOMA-IR, Δ in body weight: independently associated with change in liver steatosis	MET caused weight loss (–4.3 ± 4.3 kg) ($p \leqslant$ 0.001) MET group had a significant change in leptin levels ($p \leqslant 0.001$) MET significantly lowered LDL levels, mean Δ –27 mg/dl ($p <$ 0.001); no change in PBO group
Nar and Gedik[11]	MET 1700 mg/day plus diet and exercise	Diet and exercise	34 (all with DM)	6	MET: 16 U/liter, p = 0.015 Lifestyle: 7 U/liter, p = 0.047	No change (either group)	Liver echogenicity decreased significantly in both groups	MET group decreased LDL Δ –23 (p = 0.002) MET group increased HDL Δ +4 (p = 0.035)

ALT, alanine aminotransferase; AST, aspartate aminotransferase, BMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; LDL, low-density lipoprotein; MET, metformin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatits; PBO, placebo; RCT, randomized controlled trial.

Table 2. Efficacy and safety trials of thiazolidinediones for NAFLD in patients with T2DM.

Study and trial design	Treatment	Comparator	Number of participants	Duration (months unless otherwise stated)	ALT mean change from baseline	AST mean change from baseline	γ-GT mean change from baseline	Imaging or histologic changes	Other significant measurements
Neuschwander-Tetri *et al.*[16] Open label	ROS 4 mg twice daily	None	30 (8 with diabetes, 7 with IGT)	12	−54%, $p < 0.001$	−43.3%, $p = 0.003$	−62.5%, $p < 0.001$	*Steatosis* 14 improved, $p = 0.004$ 1 worsened *Ballooning* 11 improved, $p = 0.003$ *Fibrosis* 8 improved, $p = 0.583$ 3 worsened	*Mean Δ BMI* 6.5% (range −5% to 18%), $p < 0.001$ *Mean Δ HOMA-IR* −3.5, $p < 0.001$
Ratziu *et al.*[17] RCT	ROS 4 mg/day titrated to 8 mg/day after 1 month	PBO	63 (20 with DM)	12	ROS: ALT normalized in 12 subjects (38%) PBO: ALT normalized in 2 subjects (7%) $p = 0.005$			*>30% improvement in steatosis* ROS 47% PBO 16% $p = 0.014$ *Ballooning* NS *Fibrosis* ROS NS PBO NS *Inflammation* ROS NS PBO NS	*Mean Δ body weight kg (SD)* ROS: +1.5 (5.2) PBO: −1.0 (3.5) $p = 0.03$ *Mean Δ HOMA-IR* ROS −1.4 PBO 0.61 $p < 0.001$ *Mean Δ fasting insulin level (μUI/ml)* ROS −4.8 (9.2) PBO 2.1 (14.8) $p < 0.002$ *Mean Δ adiponectin level (μg/mL)* ROS 1.91 (1.39) PBO 0.94 (0.23) $p = 0.04$
Torres *et al.*[18] Randomized open label	ROS 4 mg twice daily	ROS 4 mg plus MET 500 mg twice daily ROS 4 mg twice daily plus LOS 50 mg/day	108 (18 with DM)	12	ROS −44% ROS + MET −47% ROS + LOS −52% $p < 0.001$ overall	ROS −32% ROS + MET −38% ROS + LOS −36% $p < 0.001$ overall		*Steatosis improved* ROS 27% ROS + MET 30% ROS + LOS 26% $p < 0.001$ overall *Hepatocellular inflammation* ROS 36% ROS + MET 25% ROS + LOS 21% $p < 0.001$ overall *Fibrosis improved* ROS 50% ROS + MET 50% ROS + LOS 21% $p < 0.001$ overall	Participants with diabetes had significant improvements in NAS compared with those without diabetes, $p = 0.046$ Mostly due to steatosis, $p = 0.006$ Overall, no added benefit was seen above ROS alone compared with combination groups with respect to: Steatosis, $p = 0.905$ Hepatocellular inflammation, $p = 0.46$ Fibrosis, $p = 0.302$ NAS, $p = 0.671$ Resolution of NASH (% of participants) ROS 46% ROS + MET 36% ROS + LOS 29%

(Continued)

Table 2. (Continued)

Study and trial design	Treatment	Comparator	Number of participants	Duration (months unless otherwise stated)	ALT mean change from baseline	AST mean change from baseline	γ-GT mean change from baseline	Imaging or histologic changes	Other significant measurements
Omer *et al.*[19] Open label, randomized	MET 1700 mg/day	ROS 4 mg/day and MET 1700 mg/day + ROS 4 mg/day	64 (all with DM or IGT)	12	MET −26%, NS ROS −56%, $p < 0.0001$ MET+ROS −31%, $p = 0.017$ *p* values pre–post in-group comparison	MET −28%, NS ROS −25%, $p = 0.005$ MET+ROS −30%, $p = 0.01$	MET −49%, NS ROS +30%, NS MET+ROS −56%, $p = 0.008$	Only 35/64 subjects had follow-up biopsies *NAFLD score improvement (n)* MET (10): +0.7, $p = 0.726$ ROS (13): −2.6, $p = 0.012$ MET+ROS(12): −3.9, $p = 0.026$	*Mean Δ BMI*: MET −3.2, $p = 0.002$ ROS −0.3, NS MET+ROS −1.3, $p = 0.006$ *Mean Δ fasting plasma insulin* MET −23%, NS ROS −33%, $p = 0.005$ MET+ROS −33%, $p \leqslant 0.005$ *Mean Δ HOMA-IR* MET −18%, NS ROS −38%, $p = 0.003$ MET+ROS −28%, NS
Gastaldelli *et al.*[20] RCT	PIO 45 mg/day + hypocaloric diet	PBO + hypocaloric diet	47 with IGT or DM; 20 healthy controls	6				*Necroinflammation improved* PIO 44% PBO 12% $p \leqslant 0.001$	*Improvements in FFA metabolism* PIO *versus* PBO 20% difference, $p = 0.01$ Adipo-IR decreased by ~47% in PIO group compared with baseline $p = 0.03$ Strong correlations were found in improvement in Adipo-IR and the following for the PIO group only: Steatosis decreased ~50% ($r = 0.29$, $p = 0.049$)
Belfort *et al.*[21] RCT	PIO 45 mg/day plus hypocaloric diet	Placebo plus hypocaloric diet	48; 10 healthy controls	6	PIO −58% PBO −34% $p < 0.001$	PIO −40% PBO −21% $p = 0.04$		*Steatosis improved* PIO 65% PBO 38% $p = 0.003$ *Ballooning improved* PIO 54% PBO 24% $p = 0.02$ *Fibrosis improved* PIO 46% PBO 33% $p = 0.08$	*Mean Δ body fat % (body weight)* PIO 1.5% (+2.5±0.5 kg) PBO −4% (−3.2 ± 0.5 kg) $p = 0.005$ *Mean Δ fasting plasma insulin* PIO −34% PBO no change $p \leqslant 0.001$ *Mean Δ FFA levels* PIO −17% PBO no change $p = 0.044$

Table 2. (Continued)

Study and trial design	Treatment	Comparator	Number of participants	Duration (months unless otherwise stated)	ALT mean change from baseline	AST mean change from baseline	γ-GT mean change from baseline	Imaging or histologic changes	Other significant measurements
Cusi *et al.*[22] RCT	PIO 45 mg/day + hypocaloric diet	PBO + hypocaloric diet	101 (all with DM or IGT)	36 (18 blinded 18 open label)				*NAS improved by ⩾ 2 points* PIO 58% PBO 17% treatment difference of 41 percentage points (CI 23–59); $p < 0.001$	*Resolution of NASH* PIO 51% PBO 19% treatment difference of 32 percentage points (CI 13–51); $p < 0.001$ *Mean Δ fibrosis score* PIO −0.5 PBO 0 Treatment difference −0.5 (CI −0.9 to 0); $p = 0.039$

ALT, alanine aminotransferase; AST, aspartate aminotransferase, BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; FFA, free fatty acid; γ-GT, γ glutamyl transferase; HOMA-IR, homeostatic model assessment insulin resistance; IGT, impaired glucose tolerance; LOS, losartan; MET, metformin; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatits; NS, not significant; PBO, placebo; PIO, pioglitazone; RCT, randomized controlled trial; ROS, rosiglitazone; SD, standard deviation; IGT impaired glucose tolerance.

diabetes, lower adiponectin levels, and lower amounts of steatosis. Four months after treatment, serum transaminases returned to baseline levels.

Combination treatments with rosiglitazone and metformin have been investigated. Torres and colleagues compared rosiglitazone with metformin or with the combinations rosiglitazone plus metformin or rosiglitazone plus losartan and reported significant within-group improvements in steatosis, necroinflammation, ballooning and fibrosis ($p < 0.001$ for all); there was no significant between-group difference suggesting no benefit to adding metformin or losartan to rosiglitazone in NASH treatment.[18]

When data from subjects with diabetes were analyzed separately, NAFLD Activity Score (NAS) significantly improved in patients with diabetes compared with those without, mostly due to improvement in steatosis ($p = 0.006$). Omer and colleagues compared metformin with rosiglitazone or the combination of rosiglitazone plus metformin for the treatment of NASH in 64 subjects with T2DM or impaired glucose tolerance.[19] Significant within-group differences were observed for reductions in serum ALT and AST levels and NAS scores for the rosiglitazone and rosiglitazone plus metformin groups but not for the metformin group. HOMA-IR reduced significantly in the rosiglitazone group ($p < 0.05$) only. No significant change in fibrosis was noted in any treatment group.

In a randomized placebo-controlled trial by Gastaldelli and colleagues, histologic and metabolic effects of pioglitazone were compared with placebo for the treatment of NASH in patients with T2DM or impaired glucose tolerance.[20] Patients in both groups maintained a calorie-restricted diet by reducing their intake by 500 kcal/day. Changes in glucose and lipid metabolism, as well as adipose tissue insulin resistance (Adipo-IR) were reported. At baseline, in comparison to a control group without NASH, patients with NASH were found to have significantly lower plasma adiponectin levels, two to three times the concentration of plasma insulin levels, and significantly higher plasma FFA concentrations. These metabolic differences are indicative of systemic and adipose tissue insulin resistance and were found to be true for obese as well as lean subjects with NASH. At the end of six months, pioglitazone significantly reduced FFA

concentrations and reduced Adipo-IR by around 47% ($p = 0.03$). According to Belfort and colleagues, pioglitazone, compared with placebo, significantly reduced serum transaminases, decreased fasting plasma insulin, and decreased FFA levels.[21] Additionally, pioglitazone treatment resulted in significantly greater improvements in steatosis (65% *versus* 38%, $p = 0.003$), ballooning (54% *versus* 24%, $p = 0.02$), and combined mean necroinflammation score (44% *versus* 12%, $p = 0.001$) over placebo. Consistent with other trials assessing TZDs, there was no significant difference in reduction of fibrosis for pioglitazone over placebo (46% *versus* 33%, $p = 0.08$).

A recently published trial by Cusi and colleagues describes the results from a three-year study of efficacy and safety of pioglitazone in participants with prediabetes or T2DM and biopsy-proven NASH.[22] After the initial 18 months, more patients randomized to pioglitazone achieved the primary endpoint of at least two points' improvement in the NAS than placebo (58% *versus* 17%, $p < 0.00$). In addition, pioglitazone was more effective than placebo at NASH resolution (51% *versus* 19%, $p < 0.001$) and mean change in fibrosis scores (–0.5 *versus* 0, $p = 0.039$). Despite this, progression of any fibrosis continued in both groups but was significantly lower in the pioglitazone group compared with placebo (12% *versus* 28%, $p = 0.039$). Histologic and metabolic improvements were maintained for the entire study period of three years.

Safety. While it has been observed that long-term treatment with a TZD is necessary to sustain clinical improvements, concern exists over the safety of prolonged use. No serious adverse events reported were related to TZD treatment.[16–22] In the three-year study, no osteoporosis, osteoporotic bone fractures, or bladder cancer was detected.[22] The most notable adverse events reported were reduction in hemoglobin, median decrease 0.7 g/dl (0.1–3.1 g/dl),[16] lower limb edema,[17,21,22] and weight gain (1.5–6.4 kg).[16,17,21]

Glucagon-like peptide-1 receptor agonists

Agents in the glucagon-like peptide-1 receptor agonist (GLP-1 RA) class improve glycemic control in individuals with T2DM through multiple mechanisms, including glucose-dependent insulin secretion, decreased glucagon secretion, slowed gastric emptying, and enhanced satiety.[23] Historically, GLP-1 receptors have been identified in the pancreas, kidney, lung, gastric mucosa, heart, hypothalamus,[24] and most recently in the liver.[25] In murine models, GLP-1 RAs were shown to improve transaminase levels, reduce oxidative stress, and reduce hepatic steatosis, making them viable options for the treatment of NASH (Table 3).[26–28]

Efficacy. Two trials assessed the metabolic and hepatic effects of exenatide immediate release. Fan and colleagues compared exenatide with metformin in participants with T2DM and NAFLD.[27] At baseline, 52% of participants had abnormal liver function, with 46 participants having an ALT over 2.5 times the upper limit of normal (ULN). The second study, conducted by Shao and colleagues, compared exenatide plus insulin glargine U-100 with intensive insulin treatment with insulin glargine U-100 plus insulin aspart.[28] Included patients had hepatic injury biomarkers between 2.5 and 5 times the ULN; 'normal' for each was defined as ALT or AST up to 40 U/liter and γ glutamyl transferase (γ-GT) up to 50 U/liter. Exenatide was initiated at 5 μg twice daily for the first 4 weeks to minimize gastrointestinal effects and titrated to 10 μg twice daily for the remaining 8 weeks in both studies.

All arms of both studies showed improvement in hepatic markers. Fan and colleagues found exenatide to be superior to metformin in improving ALT, AST, and γ-GT.[27] Additionally, C-reactive protein (CRP) was significantly decreased and adiponectin was significantly increased in the exenatide arm, suggesting improved oxidative stress. Mean reductions in body weight and BMI were statistically significant for the exenatide group compared with the metformin group. Lastly, both exenatide and metformin improved insulin resistance similarly, measured by HOMA-IR. In the study by Shao and colleagues comparing exenatide plus glargine with glargine plus aspart, body weight and waist circumference were significantly decreased in the exenatide arm, but increased in the intensive insulin arm.[28] The post-treatment mean for ALT, AST, and γ-GT levels was statistically lower in the exenatide arm compared with the insulin only arm. Exenatide in combination with glargine was also superior to insulin alone in the reversal rate of fatty liver disease, which was 93.3% and 66.7% ($p < 0.01$), respectively.

The efficacy of liraglutide in patients with T2DM and NASH was assessed in two separate trials by the same primary investigator. In the first published

Table 3. Efficacy and safety trials of glucagon-like peptide 1 receptor agonists for NAFLD in patients with T2DM.

Study	Treatment	Comparator	Number of participants	Duration	ALT mean change from baseline (SD)	AST mean change from baseline (SD)	γ-GT mean change from baseline (SD)	Imaging or histologic changes	Other significant measurements
Armstrong *et al.* (LEAD)[25]	LIR 0.6, 1.2, and 1.8 mg	PBO GLI 4 mg/day	149 (all with DM)	26 weeks				LSAR improvement with LIR *versus* PBO: mean difference +0.10 (95% CI −0.01 to 0.20; $p = 0.07$)	
Armstrong *et al.* (LEAN)[26]	LIR 1.8 mg	PBO	45 (17 with DM)	48 weeks	LIR: 26.6 (34.4); PBO: 10.2 (35.8); $p = 0.16$	LIR: 15.8 (21.8); PBO: 8.6 (28.3); $p = 0.29$	LIR: 33.7 (42.5); PBP: 7.2 (28.3); $p = 0.01$		Mean Δ BMI (SD): LIR, 1.8 (1.67); PBO, 0.3 (1.7); $p = 0.005$ Mean Δ HOMA-IR (SD): LIR, 1.8 (3.7); PBO, 0.70 (9.49); $p = 0.23$
Fan *et al.*[27]	EXE 5 μg twice daily for 30 days, increased to 10 μg twice daily	MET 500 mg twice daily, adjusted up to 2 g/day	117 (all with DM)	12 weeks	EXE: 27.32 (15.96); MET: 12.85 (11.38); $p = 0.002$	EXE: 7.89 (7.87); MET: 5.11 (6.98); $p = 0.048$	EXE: 26.48 (17.34); MET: 10.26 (14.11); $p = 0.000$		Mean Δ CRP (SD): EXE, 0.89 (0.59); MET, 0.61 (0.54); $p = 0.018$ Mean Δ adiponectin (SD): EXE, 1.86 (2.22); MET, 0.76 (1.3); $p = 0.001$ Mean Δ BMI (SD): EXE, 1.31 (0.98); MET, 0.69 (0.94); $p = 0.000$ Mean Δ HOMA-IR (SD): EXE, 0.57 (0.36); MET 0.56 (0.49); $p = 0.367$
Shao *et al.*[28]	iGLAR daily (+) EXE 5 μg twice daily for 30 days, increased to 10 μg twice daily	iGLAR daily (+) iASP three times daily	60 (all with DM)	12 weeks	EXE: 42.51 (13.12); INS only: 67.37 (15.78); $p < 0.001$	EXE: 32.28 (8.71); INS only: 42.90 (10.0); $p < 0.001$	EXE: 34.37 (10.05); INS only: 43.36 (3.60); $p < 0.001$	Reversal rate of fatty liver (regression from greater to lower degree of fatty liver): EXE, 93.3%; INS only, 66.7%; $p < 0.01$	Mean Δ BMI (SD):

ALT, alanine aminotransferase; AST, aspartate aminotransferase, BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; EXE, exenatide; INS, insulin; iASP, insulin aspart; iGLAR, insulin glargine; γ-GT, γ glutamyl transferase; GLI, glimepiride; HOMA-IR, homeostatic model assessment insulin resistance; LEAN, liraglutide efficacy and action in NASH; LIR, liraglutide; LSAR, liver-to-spleen attenuation ratio; MET, metformin; NS, not significant; PBO, placebo; SD, standard deviation; DM diabetes mellitus.

study, the investigators performed a meta-analysis of the LEAD (liraglutide efficacy and action in diabetes) program.[25] For the purposes of this article, only the LEAD-2 substudy is reviewed as it is the only trial with confirmed presence of fatty liver disease. In the LEAD-2 substudy, hepatic steatosis was measured by computer tomography (CT) imaging at randomization and conclusion of the study and confirmed in 64.4% of individuals at baseline. A liver-to-spleen attenuation ratio (LSAR) of less than 1.0 defined hepatic steatosis and an improvement in steatosis was an increase in the LSAR. Participants were given metformin in combination with liraglutide 0.6, 1.2, or 1.8 mg/day or active placebo (glimepiride 4 mg/day or placebo). A dose-dependent increase in LSAR was seen with liraglutide 1.8 mg, but it was nonsignificant. No significant differences in LSAR were seen between the lower doses of liraglutide and placebo.

The second study on liraglutide by Armstrong and colleagues, the LEAN (liraglutide efficacy and action in NASH) study, is a more robust assessment of liraglutide in participants with biopsy-confirmed NASH.[26] The study enrolled 52 participants, but only nine participants (35%) in the liraglutide arm and eight participants (31%) in the placebo arm had a diagnosis of T2DM. Liraglutide was titrated over 14 days to 1.8 mg per day and participants were allowed to remain on previous treatment with metformin, sulfonylurea, or a combination. Three participants (38%) with T2DM in the treatment group achieved the primary outcome of resolution of NASH with no worsening of fibrosis whereas none of the participants with T2DM in the placebo arm were able to achieve this outcome. Progression of fibrosis was observed in two participants (9%) in the liraglutide group and eight participants (36%) in the placebo group. Compared with placebo, the relative risk for participants with T2DM taking liraglutide achieving resolution of NASH without worsening fibrosis was 4.7 [95% confidence interval (CI) 0.3–75.0; $p = 0.20$]. Participants in the liraglutide arm did have statistically significant decreases in body weight, BMI, and γ-GT levels. Interestingly, this study included participants with stage 3 fibrosis and cirrhosis; study investigators observed that participants with more advanced disease had positive treatment effects from liraglutide, but not as pronounced as participants with mild to moderate disease.

Safety. Despite the slow titration of exenatide over 4 weeks, gastrointestinal side effects were listed in both exenatide trials as the predominant side effect in the treatment arm, but did not contribute to study withdrawl.[27,28] Adverse events were similar between liraglutide and placebo in the LEAN study, with the exception of gastrointestinal disorders, which were more common in the liraglutide-treated arm.[27] The information provided on safety from the LEAD-2 substudy is underwhelming and not delineated between the main LEAD program analysis and LEAD-2 substudy; available safety data indicate that gastrointestinal side effects and hepatobiliary serious adverse events were comparable for liraglutide 1.2, liraglutide 1.8, and placebo for participants with normal and abnormal ALT levels at baseline.[25]

Antihyperlipidemics

In addition to the benefits HMG-CoA (3-hydroxy-3-methyl-glutaryl-coenzyme A) reductase inhibitors (statins) have on lipids, they improve insulin sensitivity, decrease production of advanced glycation endproducts (AGEs), and display anti-inflammatory effects, all of which may be helpful in treating the steatosis and inflammation associated with NASH.[29,30] Several studies evaluate the use of lipid medications as treatment options for NASH, including atorvastatin, simvastatin, rosuvastatin, pitavastatin, ezetimibe/simvastatin combination, and ursodeoxycholic acid (UDCA), a bile acid used to reduce cholesterol absorption (Table 4).[30]

Efficacy. In 2003, Kiyici and colleagues completed a prospective study comparing UDCA with atorvastatin in the treatment of NASH.[30] In a small study of 44 patients, both groups saw significant lowering in ALT and γ glutamyl transferase (GGT), an enzyme used as a diagnostic marker for liver disease ($p < 0.02$). The atorvastatin group at baseline had higher cholesterol levels; after the study period, a decrease in serum cholesterol was seen in the atorvastatin group as well as a statistically significant normalization of transaminases post treatment ($p = 0.021$). Imaging studies found that liver densities did increase in the atorvastatin group. There was no change in BMI, serum glucose, or triglyceride levels in either group.

The PITCH study, a 2012 prospective randomized open-label trial by Han and colleagues compared pitavastatin (2–4 mg per day) with atorvastatin (10–20 mg/day).[31] Over 12 weeks, the 135 study participants showed a statistically significant lowering ($p < 0.05$) in serum GGT

Table 4. Efficacy and safety trials of HMG CoA reductase inhibitors for NAFLD in patients with T2DM.

Study	Treatment	Comparator	Number of participants	Duration (months)	ALT mean change from baseline	AST mean change from baseline	γ-GT mean change from baseline	Imaging or histologic changes	Other significant measurements
Kimura *et al.*[29]	ATO 10 mg		43 (31 with IGT or DM)	12	−33.5 U/liter; $p <$ 0.001	−15.8 U/liter; $p <$ 0.001	−25.3 U/liter; $p <$ 0.001	Liver density increased; $p <$ 0.001 Necroinflammatory grade improved; $p <$ 0.05 *NAS* Improved: 68% Unchanged: 27% Worsened: 5%	Δ BMI, FBG: unchanged *Fibrosis stage* Improved: 9% Unchanged: 59% Worsened: 32%
Kiyici *et al.*[30]	UDCA 13–15 mg/kg/day in normolipidemic patients	ATO 10 mg/day in hyperlipidemic patients	44 (10 with DM)	6	UDCA: −19 U/liter; p = 0.002 ATO: −37 U/liter; p = 0.0001 UDCA *versus* ATO: NS	UDCA: NS ATO: −13 U/liter; p = 0.004 UDCA *versus* ATO: p = 0.033	UDCA: −15.6 U/liter (p = 0.016) ATO: −27 U/liter (p = 0.014) UDCA *versus* ATO: NS	UDCA: NS ATO: significant increase in liver density (improved steatosis); p = 0.0001 UDCA *versus* ATO: NS change in steatosis	BMI, serum glucose and TG level changes: NS for both groups
Han *et al.*[31]	PIT 2–4 mg/day	ATO 10–20 mg/day	189 (53 with DM)	12 weeks	PIT: −5 U/liter, p = 0.047 ATO, NS	PIT, NS ATO, NS	PIT: −10.9 U/liter, p = 0.034 ATO: −11.1 U/liter, p = 0.040	Hepatic steatosis improvement: PIT, p = 0.008 ATO, NS	Equal reduction in LDL, $p <$ 0.0001 Increase in ALT: 17 patients; 2 severe (>3 × ULN)
Hyogo *et al.*[32]	ATO 10 mg/day		31 (22 with IGT or DM)	24	−53.5 U/liter, $p <$ 0.001	−25.3 U/liter, $p <$ 0.001	−36 U/liter, $p <$ 0.001	Steatosis grade and NAS: improved, $p <$ 0.001 Fibrosis: worsened in 4 patients	Transaminases normalized in 74.2% of patients Δ BMI, FBG, HbA1c, NS Δ HS CRP: decrease, $p <$ 0.05 Δ HOMA-IR, NS
Abel *et al.*[33]	SIM 20 mg/day	EZE/SIM 10/10 mg/day	45 (all with DM)	6	SIM: −37 7 U/liter, $p <$ 0.0001 EZE/SIM: −31 U/liter, $p <$ 0.0001 SIM *versus* EZE/SIM, $p <$ 0.0112	SIM: −35.6 U/liter, $p <$ 0.0001 EZE/SIM: −27.1 U/liter, $p <$ 0.0001 SIM *versus* EZE/SIM, $p <$ 0.0001	NR		Δ TC, HDL, TG: NS in either group or between groups Δ LDL: SIM *versus* EZE/SIM, p = 0.0063 Δ CK U/L: NS in either group
Nelson *et al.*[34]	SIM 40 mg/day	PBO	16 (7 with DM)	12	SIM, NS PBO, NS SIM *versus* PBO, NS	SIM, NS PBO, NS SIM *versus* PBO, NS	NR	Δ hepatic steatosis, necroinflammatory activity, fibrosis stage: NS in either group or between groups	Δ TC, LDL, TG: NS in either group or between groups

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATO, atorvastatin; BMI, body mass index; CK, creatine kinase; CRP, C-reactive protein; DM, diabetes mellitus; EZE/SIM, ezetimibe/simvastatin; FBG, fasting blood glucose; γ-GT, γ glutamyl transferase; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; HS CRP, high-sensitivity C-reactive protein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NAS, NAFLD Activity Score; NR, not reported; NS, not significant; PBO, placebo; PIT, pitavastatin; TG, triglyceride; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; SIM simvastatin TC total cholesterol.

concentrations and LDL cholesterol ($p < 0.0001$) from baseline in both treatment groups. Only the pitavastatin group had significantly reduced ALT, which was the primary endpoint. Tomography revealed that both groups reduced hepatic steatosis severity in patients with overt fatty liver before randomization.

Two additional studies investigated the use of atorvastatin 10 mg per day in combination with standard weight loss counselling.[29,32] A controlled trial by Hyogo and colleagues followed patients over 24 months, twice the length of patients followed in the open-label trial by Kimura and colleagues. Hyogo and colleagues found a mean change in both ALT and AST from baseline whereas Kimura also found a change in γ-GTP. No changes in BMI or serum glucose were found in either study; however, Hyogo and colleagues also evaluated for changes in adiponectin, tumor necrosis factor α, leptin, and long chain fatty acids. Overall, no statistically significant changes were found in these values. Both studies showed improvement in NAFLD score and liver steatosis grade. Kimura and colleagues additionally reviewed the effects of atorvastatin on AGEs, as they are commonly increased in patients with NASH. Atorvastatin was found to decrease AGEs significantly.[29,32]

A randomized, double-blind, placebo-controlled trial by Nelson and colleagues investigated the use of simvastatin 40 mg *versus* placebo in the treatment of NASH.[34] Over 12 months, 16 patients were not found to have a statistically significant improvement in ALT or AST from baseline, hepatic steatosis, necroinflammatory activity, or fibrosis stage for either the treatment or placebo group. An additional retrospective trial by Abel and colleagues compared simvastatin 20 mg with ezetimibe/simvastatin 10 mg/10 mg over six months.[33] Both groups resulted in a statistically significant change in ALT and AST from baseline ($p < 0.0001$ for all groups), and simvastatin monotherapy decreased both ALT and AST significantly more than combination therapy ($p < 0.0112$ and $p < 0.0001$, respectively). Overall, there was no difference between the two groups in regards to cholesterol decrease, triglyceride reduction, and HDL elevation.

Safety. Adverse effects of statin therapies used in the aforementioned trials ranged from elevations in ALT to a progression of fibrosis. Of the atorvastatin studies, there was no report of an elevation in transaminases.[29,30,32] However, the PITCH study reported an elevation in ALT in both the pitavastatin and atorvastatin treatment groups, with one study participant from each treatment group being excluded from analysis as a result of severely elevated ALT.[31] Progression in fibrosis staging was found in atorvastatin treatment groups in two of the studies that utilized atorvastatin.[29,32] The studies involving simvastatin did not reveal any adverse effects of the therapy.[33,34]

Discussion

Based on the reviewed studies, metformin, TZDs, GLP-1 RAs, and statins all appear to be safe options for the treatment of NAFLD/NASH in patients with concomitant T2DM, but efficacy data surrounding each vary. Metformin shows little positive impact on histological markers associated with NAFLD. The benefit from metformin treatment can be attributed to improvement in weight and metabolic profile. Data from reviewed studies on metformin reiterated that weight management in patients with NAFLD has the most benefit on steatosis.[7]

The mechanism of TZDs to improve insulin sensitivity in the liver, muscle, and adipose tissue has shown effectiveness in reversing NASH in up to half of treated patients, but may need to be continued indefinitely to avoid return to baseline.[16,17] TZDs provide significant histologic and metabolic improvements overall, but did not provide significant differences in fibrosis compared with placebo. While it is not fully understood why some patients do not respond to TZD treatment, one trial found a higher rate of nonresponders in those with T2DM.[17] Conversely, another trial reported NAS scores significantly improved in those with diabetes *versus* those without.[18]

Improvements in liver disease in patients on GLP-1 RAs were detected through reduced hepatic enzymes and liver histology *via* biopsy or imaging in patients with NAFLD and T2DM. These improvements may be attributed to the beneficial effects GLP-1 RAs have on liver inflammation, insulin resistance, and body weight. Based on the available data, GLP-1 treatment appears to be of benefit in individuals with mild to moderate NAFLD and T2DM, and may offer some advantages in advanced disease (e.g. cirrhosis), albeit a lessened effect for a very costly medication.

Atorvastatin is the most commonly studied statin in the treatment of NAFLD/NASH. Overall, atorvastatin appears to be moderately beneficial in decreasing transaminases, the severity of hepatic steatosis, and the NAS score. One study also noted the importance of reducing AGEs and the ability of atorvastatin to decrease those levels in patients with dyslipidemia. However, the overall ability of AGEs to be utilized as an indicative biomarker for NASH warrants further investigation.[29] Certain trials included patients only with dyslipidemia; therefore, the role of statins in the treatment of NASH in patients with normal lipids needs to be further investigated.[30]

Along with diet, exercise, and glycemic control, the discussed medications may be a viable option for the treatment of NAFLD. In addition to their insulin-sensitizing benefits, they may improve the prognosis of NAFLD in patients with T2DM by decreasing the risk of serious consequences, such as cardiovascular disease and hepatocellular carcinoma.[35] Conflicting trial results, small cohorts, and short study durations emphasize the need for continued studies on the most viable and efficacious pharmacologic treatment options for patients with NAFLD and T2DM.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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