

Efficacy and safety of antihyperglycemic drugs in patients with nonalcoholic fatty liver disease with or without diabetes: an updated systematic review of randomized controlled trials

Short title: Antihyperglycemic drugs for NAFLD treatment

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ABSTRACT

AIM: There are no approved drugs for the treatment of nonalcoholic fatty liver disease (NAFLD).

However, many randomized controlled trials (RCT) have examined the effect of antihyperglycemic agents on NAFLD in patients with and without type 2 diabetes mellitus (T2DM), since both T2DM and insulin resistance are closely linked to this burdensome liver disease.

METHODS: We systematically searched publication databases using predefined keywords to identify head-to-head or placebo-controlled RCTs (published until September 30, 2019) of NAFLD individuals testing the efficacy of antihyperglycemic drugs to specifically treat NAFLD or nonalcoholic steatohepatitis (NASH). Outcomes of interest included changes in serum aminotransferase levels, liver fat, liver fibrosis, or histologic resolution of NASH.

RESULTS: We included 29 RCTs involving a total of 2,617 individuals (~45% had T2DM) that have used metformin (n=6 studies), glitazones (n=8 studies), glucagon-like peptide-1 receptor agonists (n=6 studies), dipeptidyl peptidase-4 inhibitors (n=4 studies) or sodium-glucose cotransporter-2 inhibitors (n=7 studies) to treat NAFLD. Although most antihyperglycemic drugs improved serum liver enzymes, only glitazones (especially pioglitazone) and liraglutide showed an improvement of histologic features of NAFLD, with a mild beneficial effect also on liver fibrosis for pioglitazone only.

CONCLUSION: RCT evidence supports the efficacy of some antihyperglycemic agents (especially pioglitazone) in patients with NAFLD or NASH, though weight gain with pioglitazone may warrant caution. Further well-designed RCTs are needed to better characterize the efficacy and safety of monotherapy and combination therapy with antihyperglycemic agents in patients with NAFLD.

Key-words: antihyperglycemic drugs; NAFLD; NASH; type 2 diabetes

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide, affecting up to nearly 25-30% of adults in the general population, nearly 55-60% of patients with type 2 diabetes mellitus (T2DM) and the large majority of those with severe obesity. Worryingly, the prevalence of NAFLD is expected to rise further over the next decade (1,2).

The pathophysiology of NAFLD is complex and intricate, but NAFLD and T2DM form part of a vicious spiral of disease affecting both conditions. On the one hand, NAFLD is strongly associated with T2DM and obesity, *i.e.*, two pathologic conditions that predict the development of nonalcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis, which are the histological features more consistently associated with adverse hepatic and extra-hepatic outcomes in NAFLD (1,2). On the other hand, NAFLD is also associated with an approximate twofold increased risk of incident T2DM (3,4).

The management of NAFLD is essentially based on lifestyle modification(s) and early treatment of associated metabolic co-morbidities (5,6). Although currently there are no approved drug treatments for NAFLD, seeing that T2DM is linked to NAFLD and its more advanced forms (1,2), an ever-increasing number of non-randomized interventional studies and randomized controlled trials (RCTs) have focused on testing the efficacy of antihyperglycemic agents in patients with NAFLD (7,8). Such antihyperglycemic agents include metformin, glitazones, glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase 4 (DPP-4) inhibitors and sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

Therefore, our aim was to undertake an updated systematic review of published RCTs that have evaluated the efficacy and safety of the aforementioned antihyperglycemic agents to specifically treat NAFLD or NASH.

MATERIALS AND METHODS

Search strategy and study selection

We followed systematic review methodology and procedures that are in accordance with current guidance for systematic reviews [*i.e.*, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA); <http://www.prisma-statement.org/>] (9).

We included head-to-head or placebo-controlled RCTs of adults or children with NAFLD, which used a European Medicines Agency (EMA)-approved antihyperglycemic drug for treatment of NAFLD or NASH. We included only RCTs that had at least 20 patients per treatment arms of interest.

Relevant studies were identified by systematically searching PubMed, ClinicalTrials.Gov and Cochrane Database of Systematic Reviews from January 1, 1990 to 30 September, 2019 (date last searched) using the free text terms ‘nonalcoholic fatty liver disease’ (OR ‘NAFLD’ OR ‘nonalcoholic steatohepatitis’ OR ‘NASH’) AND ‘metformin’ OR ‘thiazolidinediones’ OR ‘glitazones’ OR ‘glucagon-like peptide-1 receptor agonists’ OR ‘dipeptidyl peptidase-4 inhibitors’ OR ‘sodium-glucose cotransporter-2 inhibitors’. Searches were restricted to head-to-head or placebo-controlled RCTs where the diagnosis of NAFLD was based on liver biopsy or imaging techniques. Reference lists of relevant papers and previous review articles were hand searched for other relevant studies.

Studies reported only in conference abstracts, unpublished studies, retrospective observational

studies and non-randomized interventional studies were excluded. Studies in languages other than English were also excluded. Placebo-controlled RCTs examining the efficacy of sulphonylureas, acarbose or insulin on NASH resolution, liver fat content and other liver function parameters were not available in the literature.

One investigator screened citations and a second investigator assessed excluded citations. Two investigators independently evaluated full-text articles by applying the inclusion criteria and resolved disagreements by consensus.

Data extraction and quality assessment

For all RCTs, we extracted information on participants' characteristics, interventions, methods used for diagnosing/staging NAFLD, and results for effectiveness and harms outcomes. In particular, the primary outcomes of interest included changes in serum alanine-aminotransferase (ALT) and aspartate-aminotransferase (AST) levels, liver fat content, or histologic resolution of NASH and changes in individual histologic scores of NASH (i.e., steatosis, necro-inflammation and fibrosis). We also extracted information on weight loss, changes in hemoglobin A1c and serious adverse events, as well as percentage of withdrawals due to adverse events.

Each RCT was assessed for quality by two independent reviewers, with disagreements resolved through consensus. Study quality was assessed according to predefined criteria that are based on those used by the US Preventive Services Task Force (USPSTF) and the National Health Service Centre for Reviews and Dissemination (9,10). Specifically, these criteria focus on methods of randomization, allocation concealment, blinding of providers, outcome assessors, and patients; similarity of group characteristics at baseline; attrition rate; and use of intention-to-treat analysis.

RCTs that met all criteria were rated as good quality; RCTs with an element at high risk of bias or failed to meet combinations of criteria were rated as poor quality; and the remainder were rated as fair quality.

RESULTS

Supplementary Figure S1 displays the flow diagram of the literature research and study selection.

Overall, we included 29 placebo-controlled or active-controlled RCTs for a total of 2,617 individuals (45% of them had established T2DM), who were treated for a median period of 6 months (inter-quartile range [IQR]: 5-12 months). Baseline characteristics of the eligible RCTs on metformin (n=6), glitazones (n=8), GLP-1RAs (n=6), DPP-4 inhibitors (n=4) or SGLT-2 inhibitors (n=7) are summarized in **Tables 1 to 4**, respectively. The eleven RCTs excluded at the stage of eligibility according to the flow diagram are listed in **Supplementary Table S1**.

Most eligible RCTs were small ($n < 40$ per treatment arm) and rated as fair quality, primarily due to unclear blinding, unclear allocation concealment, high attrition or lack of liver histology endpoints. All eligible RCTs in NAFLD patients with and without T2DM included treatment with an antihyperglycemic drug in one or more treatment arms.

Metformin

We included a total of six placebo-controlled or active-controlled RCTs that used metformin to treat NAFLD (**Table 1**)(11-16). These studies enrolled 573 individuals, most of whom (>90%) did not have diabetes (76% men; mean age 38 ± 15 years; BMI 30 ± 2.5 kg/m², AST 55 ± 11 UI/L, ALT 86 ± 27 UI/L), who were treated for a median of 9 months (IQR 6-12 months). Of the eligible RCTs,

one was conducted in obese children/adolescents with biopsy-proven NASH (the TONIC trial), whereas the remaining five RCTs involved adults with or without T2DM. Three of the eligible RCTs were conducted in Europe, two in Asia and one in United States. Among the four RCTs including patients with biopsy-proven NAFLD (except for the TONIC trial that failed to show any beneficial effect), metformin showed small beneficial effects on liver steatosis and inflammation, but no significant effects on liver fibrosis and resolution of NASH (11-14). In the two remaining RCTs involving patients with imaging-defined NAFLD, metformin showed a neutral effect on liver steatosis, when compared to placebo or reference therapy (15,16). In most of these eligible RCTs, metformin showed a significant reduction of serum aminotransferase levels (especially serum ALT). The effect of metformin on body weight was neutral, whereas there was a substantial improvement of HbA1c levels (~0.8-1%). Metformin was generally well tolerated, although a study reported a higher withdrawal due to adverse effects (mostly gastrointestinal symptoms) in the metformin group when compared to placebo (12).

Glitazones

As shown in **Table 2**, we included a total of eight placebo-controlled or active-controlled RCTs that used either pioglitazone (n=6) or rosiglitazone (n=2) to treat NAFLD (14,16-22). These RCTs included 828 individuals, most of whom (~85%) did not have diabetes (57% men; mean age 47±7 years; BMI 31±3 kg/m²; AST 54±8 UI/L; ALT 80±15 UI/L), who were treated for a median of 12 months (IQR 6-14 months). Only one study was undertaken in patients with imaging-defined NAFLD (15), whereas all other RCTs included patients with biopsy-proven NAFLD. Four RCTs were conducted in United States, two in Europe and two in Asia. When compared to placebo or reference therapy, both pioglitazone and rosiglitazone significantly improved liver fat content and even NASH (15,17-23). With regard to a possible improvement of liver fibrosis, glitazones were not

superior to placebo or other active molecules, except for one RCT using pioglitazone 45 mg/day for 18 months in patients with biopsy-proven NASH and T2DM/prediabetes (23). A significant reduction of serum aminotransferase levels was observed in most patients treated with glitazones, when compared to placebo or reference therapy. Glitazones had a similar adverse event profile to placebo or reference therapy, with the exception of a weight gain (*e.g.*, ~2-3 kg at a dosage of 45 mg/day of pioglitazone) (23). Withdrawals due to serious adverse effects were not increased in the glitazone group compared to either placebo or other active agents.

GLP-1RAs

We included a total of six placebo-controlled or active-controlled RCTs that used liraglutide (n=4) or exenatide (n=2) to treat NAFLD (**Table 3**)(24-29). These RCTs included 396 individuals, the large majority (73%) of whom had diabetes (51% men; mean age 49±5 years; BMI 32±4 kg/m²; AST 47±39 UI/L; ALT 65±52 UI/L) and who were treated for a median of 6 months (IQR 5.5-7.0 months). Four RCTs were undertaken in patients with T2DM, one RCT was conducted in both patients with and without T2DM, whereas one RCT involved non-diabetic women with polycystic ovary syndrome.

Three RCTs were conducted in Europe and three in China. Only a small phase-2b RCT (*i.e.*, the LEAN trial) included patients with biopsy-proven NASH (25), whereas in the other five RCTs, NAFLD was diagnosed by imaging techniques (ultrasonography or magnetic resonance imaging). When compared to placebo or reference therapy, GLP-1RAs (especially liraglutide) improved liver fat and reduced serum aminotransferase levels in a dose-dependent way, as well as body weight (~3-5 kg) and HbA1c levels (~1-1.2%). Data on liver fibrosis were available only in the LEAN trial and liraglutide failed to produce any significant histological improvement in liver fibrosis compared to placebo (25). GLP-1RAs were well tolerated and had a similar adverse event profile to placebo (or

reference therapy), except for an increased frequency of gastro-intestinal symptoms, such as loss of appetite, nausea, constipation or diarrhea. These events tended to be transient and mild-to-moderate in severity across most of the included RCTs.

DPP-4 inhibitors

We included a total of four placebo-controlled or active-controlled RCTs that used either sitagliptin (n=3) or vildagliptin (n=1) to treat NAFLD (**Table 3**)(29-32). These RCTs included a total of 241 individuals with T2DM or prediabetes (68% men; mean age 56±9 years; BMI 29±3 kg/m²; AST 31±3 UI/L; ALT 37±7 UI/L), who were treated for a median of 6 months (IQR 5.5-8.0 months). In these four RCTs, NAFLD was detected exclusively by imaging techniques. Two RCTs were undertaken in China, one in United States and another one in United Kingdom. When compared to placebo or reference therapy, vildagliptin had a marginal significant effect on liver fat, whereas sitagliptin did not. Given the absence of liver histological data, we are unable to comment on the effect of DPP-4 inhibitors on histological resolution of NASH or other histologic features of NAFLD. When compared to placebo or reference therapy, DPP-4 inhibitors showed a reduction of HbA1c (~0.5-0.8%), but a neutral effect on body weight and serum liver enzymes, except for vildagliptin that showed a reduction (~7 IU/L) in serum ALT levels. DPP-4 inhibitors were well tolerated with a similar adverse event profile to placebo or reference therapy.

SGLT-2 inhibitors

We included a total of seven placebo-controlled or active-controlled RCTs that used empagliflozin (n=2), dapagliflozin (n=3), canagliflozin (n=1) or ipragliflozin (n=1) to treat NAFLD (**Table 4**)(33-39). These RCTs included only individuals with T2DM (n=579; 58% men; mean age 58±5 years; BMI 31±2 kg/m²; AST 34±10 UI/L; ALT 43±16 UI/L), who were treated for a median of ~6 months (IQR

5.5-6.5 months). In these seven RCTs the diagnosis of NAFLD was based on imaging techniques (ultrasonography, magnetic resonance imaging or FibroScan®). One RCT included an international cohort, three RCTs were performed in Asia, one in United States and two in Europe. When compared to placebo or reference therapy, empagliflozin, canagliflozin or ipragliflozin (not available in Europe) showed a small improvement of liver fat content, along with a reduction of body weight (~2-3 kg) and HbA1c (~0.8-1.0%). By contrast, in the RCT of Bolinder *et al.*, despite the lowering of body weight and glucose parameters, a 24-week treatment with dapagliflozin 10 mg once daily did not show any significant reduction of liver fat content (on magnetic resonance imaging) when compared to placebo (34). In all RCTs, SGLT-2 inhibitors showed a significant reduction of serum aminotransferase levels. SGLT-2 inhibitors were well tolerated with a similar adverse event profile to placebo or reference therapy, except for increased risk of genitourinary infections.

DISCUSSION

Compared with other narrative review articles published on this topic, our systematic review provides the most updated evidence of placebo-controlled or active-controlled RCTs that examined the efficacy and safety of antihyperglycemic agents (including newer antihyperglycemic drugs, i.e., the SGLT-2 inhibitors, DPP-4 inhibitors and GLP-1RAs) to specifically treat NAFLD or NASH. Our systematic review includes 29 head-to-head or placebo-controlled RCTs (published until September 30, 2019), involving a total of 2,617 NAFLD individuals with and without T2DM. The primary outcomes of interest included changes in serum aminotransferase levels, liver fat, or histological resolution of NASH and changes in individual histologic scores of NASH. We did not attempt to pool these RCTs into a meta-analysis due to the highly variable mechanisms of actions

of the antihyperglycemic agents in this analysis, as well as the high heterogeneity of the interventions, populations included and the outcome measures.

From our systematic review, it clearly emerges that the major issue in this field of research is the scarcity of high-quality, adequately powered RCTs of sufficient duration that include clinically relevant hepatic endpoints (i.e., liver histologic data). Some concerns also remain about the long-term safety of the available drugs, necessitating thoughtful balancing for the clinician and the patient of the potential risks and benefits. Therefore, to date, drug treatment for NAFLD is best targeted at patients with biopsy-confirmed NASH, who are at the highest risk of progressive liver disease (5,6).

Specifically, while most of RCTs using metformin or glitazones have investigated the efficacy of these drugs on the histologic features of NAFLD or resolution of NASH in biopsied patients (11-14,17-23), almost all of the published RCTs testing the hepatic effects of the newer antihyperglycemic agents did not have any adequate liver histological endpoints (15,16,24,26-39), with the only exception of the LEAN trial, which is a phase 2b placebo-controlled RCT, enrolling 52 UK patients with biopsy-proven NASH, who were randomly assigned to liraglutide 1.8 mg/day or placebo (25). This is an important weakness to consider in the interpretation of the main results of these published RCTs. RCTs of pharmacologic treatments aimed at improving liver disease severity in NAFLD should always include patients with biopsy-confirmed NASH or fibrosis, not the least because liver fibrosis is the histological feature most strongly associated with increased risk of adverse clinical outcomes (1,5,40). Histological endpoints are still considered the best predictors of cirrhosis and other liver-related outcomes, although they can only be reliably tested in phase 2 and 3 RCTs (but not during post-marketing monitoring trials) (40-42). To date, phase 3 RCTs

require a histological end-point of NASH resolution without fibrosis progression. Additionally, although magnetic resonance imaging-estimated proton density fat fraction can accurately quantify changes in liver fat content, its efficacy for detecting NASH and advanced fibrosis is rather limited (40). Moreover, although liver steatosis assessed by magnetic resonance imaging-estimated proton density fat fraction is increasingly used in the early phase trials examining drugs with anti-steatotic effects, the prognostic significance of a reduction in liver steatosis remains unclear (40-42). Based on these considerations, most RCTs included in our systematic review have obtained a fair quality according to the USPSTF criteria.

Metformin is a biguanide, glucose-lowering drug that represents the first-line choice for treatment of T2DM (43). Our systematic review corroborates the conclusion that metformin, despite its beneficial effects on serum liver enzymes, does not exert any beneficial effect on liver histology features, NAFLD activity score, or resolution of NASH in both adults and children with NAFLD (11-16). This finding confirms the American and European practice guidelines that recommended against the use of metformin to specifically treat NAFLD or NASH (5,6). That said, however, it is also important to underline that some evidence is now suggesting a possible hepato-protective role of metformin for reducing risk of cirrhosis and hepatocellular carcinoma (7,8).

Rosiglitazone and pioglitazone (*i.e.*, this latter being the only glitazone drug now available on the market in most European countries) are selective ligands of the peroxisome-proliferator-activated receptor (PPAR)-gamma (43). The PPAR-gamma receptor has three isoforms. The PPAR-gamma receptor-2 isoform is highly expressed in adipose tissue, acting to redistribute adipose tissue between intra-abdominal and subcutaneous adipose tissue by promoting accumulation of triglyceride in peripheral fat depots. PPAR-gamma is also expressed in Kupffer cells and PPAR-

gamma has potent anti-inflammatory action to decrease nuclear factor-kB mediated cytokine and chemokine production, while at the same time increasing adiponectin levels (7,8), suggesting plausible biological mechanisms by which pioglitazone can improve liver disease, at least in some patients with NASH.

Our systematic review shows that pioglitazone use in patients with NASH had significant benefits in liver function, liver fat content and resolution of NASH both in patients with and without T2DM (15,17-23), though increases in body weight and lower-limb oedema may be cause for concern. Evidence for rosiglitazone was more limited and had somewhat mixed results, but results were generally comparable to those for pioglitazone (19,21). When compared to its beneficial effects on NASH, the effect of pioglitazone on liver fibrosis seems (rather) modest (15,17-23). However, in a placebo-controlled RCT of 101 United States individuals with biopsy-proven NASH and T2DM or prediabetes, who were randomly assigned to pioglitazone (45 mg/day) or placebo for 18 months, Cusi *et al.* reported that among those treated with pioglitazone, 51% had histological resolution of NASH (23). Moreover, long-term pioglitazone treatment improved individual histologic scores of NASH, including the fibrosis score. Notably, all 18-month histologic improvements persisted over 36 months of pioglitazone treatment. The overall rate of adverse events did not differ between the two groups, although weight gain was greater with pioglitazone (~2.5 kg vs. placebo) (23). Interestingly, in a meta-analysis of eight RCTs (5 evaluating pioglitazone use and 3 evaluating rosiglitazone use) enrolling 516 adults with biopsy-confirmed NASH for a duration of 6 to 24 months, Musso *et al.* reported that pioglitazone improved advanced fibrosis in NASH, even in patients without diabetes (44). Based on all the aforementioned data, the American and European guidelines recommended the use of pioglitazone in patients with biopsy-proven NASH, regardless of diabetes status (5,6,45). However, it is important to highlight that pioglitazone is not yet

approved by most national Medicines agencies outside the treatment for T2DM, and its off-label use for NAFLD/NASH treatment requires the patient's consent. Concerns about weight gain, fluid retention and risk of bone fractures (especially in women) may restrict the wider clinical use of pioglitazone in all patients with NAFLD (43). However, it is important to remember that pioglitazone may also exert some cardiovascular benefits to decrease risk of acute myocardial infarction and stroke in patients with T2DM or prediabetes (46,47). Taking into consideration that it is now well accepted that patients with NASH are at higher risk of cardiovascular disease (1,5,6), and pioglitazone is an inexpensive, generic medication, this cardiovascular-protective agent should be considered in patients with NASH. Similarly, newer selective PPAR-gamma modulators such as CHRS 131 (a.k.a. INT 131), which retain pioglitazone like efficacy without many of the pioglitazone side effects (48), including weight gain, need to be studied carefully in the context of RCTs since they may prove to be a useful addition to our therapeutic armamentarium.

DPP-4 inhibitors and GLP-1RAs are broadly prescribed as additional therapy in patients with T2DM (43). It is important to underline that GLP-1 receptors have been documented in human hepatocytes and that the activation of such receptors may concur to decrease liver steatosis by improving insulin-signaling pathways (7,8). In addition, GLP-1RAs induce significant weight loss (on average ~3-5 kg) (43). For these reasons, GLP-1RAs have also been investigated as a therapeutic option for NAFLD or NASH. Our systematic review supports the capability of GLP-1RAs to reduce serum liver enzymes and improve hepatic steatosis, as detected by either imaging techniques or liver histology (24-29). In particular, in the LEAN trial (25), patients (n=23) with biopsy-confirmed NASH who received liraglutide 1.8 mg/day for 48 weeks had a greater histological resolution of NASH with no worsening in hepatic fibrosis (39% vs. 9%) and significant improvements in hepatic steatosis and hepatocyte ballooning compared with patients (n=22) receiving placebo. The authors

suggested that the beneficial effects of liraglutide on the histological liver endpoints are possibly due to both its direct hepatic effect and to concomitant weight loss (25). Importantly, liraglutide and other long-acting GLP-1RAs have been also shown to reduce risk of developing cardiovascular and renal outcomes in patients with T2DM (49). For such reasons, if larger phase 3 RCTs will further confirm the promising findings of the LEAN trial, it is reasonable to hypothesize that liraglutide (and other long-acting GLP-1RAs) will become a suitable treatment option in NAFLD patients, especially in those who are obese or have T2DM.

Currently, no robust data exist with liver histological endpoints as a primary outcome to comment on the effectiveness of DPP-4 inhibitors as a treatment for NAFLD. In addition, DPP-4 inhibitors also have a neutral effect on cardiovascular events in T2DM patients (43), thus making this class of antihyperglycemic agents even less attractive for treatment of NAFLD.

SGLT-2 inhibitors are a newer class of antihyperglycemic agents that increase glucose reabsorption mainly by the kidney (43). SGLT-2 is expressed on renal epithelial cells that line the S1 segment of the proximal convoluted tubule, and SGLT-2 plays a key role in promoting glycosuria. In this way, this mechanism of regulation of blood glucose control is largely independent of insulin secretion (43). Experimental animal studies support a beneficial effect of SGLT-2 inhibitors on liver steatosis, hepatocyte ballooning and, in some cases, also on liver fibrosis, possibly due to a combination of negative energy balance by increased glycosuria and substrate switching towards lipids as a source of energy expenditure (7,43). Experimental animal studies also support a beneficial effect of SGLT-2 inhibitors on insulin resistance and lipotoxicity (7,43). Our systematic review supports the possibility that SGLT-2 inhibitors may improve both serum liver enzyme levels and liver fat content, as assessed by imaging techniques. However, most of RCTs are small with a short period

of treatment and, most importantly, to date, there are no head-to-head or placebo-controlled RCTs examining the long-term effects of SGLT-2 inhibitors on histologic features of NAFLD (50). By contrast, SGLT2-inhibitors have shown significant cardio-renal benefits in large RCTs of patients with T2DM (51); and this may represent an attractive bonus for the use of these drugs in NAFLD patients (50). Lastly, it is important to note there are multiple ongoing RCTs testing the effect of SGLT2-inhibitors in patients with NAFLD.

We believe that the major strength and the added value of our study are the use of systematic review processes to identify head-to-head or placebo-controlled RCTs (published until September 30, 2019) that meet pre-defined inclusion criteria. Limitations of this systematic review include restriction to RCTs, which may have limited generalizability to ‘real-world’ populations of patients with NAFLD, and also the highly variable mechanisms of actions of the antihyperglycemic agents, which limits any conclusions about any potential association between antihyperglycemic agents and improvement in NAFLD. Another limitation is the almost absence of head-to-head comparative RCTs (see Tables 1-4), making difficult a direct comparison between the different antihyperglycemic agents. Finally, although these RCTs have included different ethnic groups, in none of these RCTs it has been examined the contribution of common genetic variants related to NAFLD (i.e., *patatin-like phospholipase domain-containing protein 3* [PNPLA3] and *transmembrane 6 superfamily member 2* [TM6SF2] polymorphisms) to the efficacy of antihyperglycemic agents for treatment of NAFLD or NASH. Further studies are needed to better elucidate this issue. In addition, since sex differences do exist in the prevalence, risk factors and clinical outcomes of NAFLD (52), future studies should also be specifically designed to explore sex differences in the response to treatment for NAFLD or NASH with antihyperglycemic agents.

In conclusion, our systematic review is the most comprehensive and updated assessment of published head-to-head, or placebo-controlled RCTs, of individuals with NAFLD that used an EMA-approved antihyperglycemic drug to specifically treat NAFLD or NASH. Although it has been shown that many of the antihyperglycemic agents improve serum liver enzyme levels, convincing data on their beneficial effects on histologic features of NAFLD are very limited. Our systematic review supports the conclusion that most of the available evidence of efficacy in patients with NASH relates to the use of pioglitazone. Not only might pioglitazone also improve the natural history of liver disease by reducing its progression to cirrhosis in some patients with biopsy-confirmed NASH, but there is proven evidence that long-term pioglitazone treatment may also decrease risk of incident cardiovascular events, such as myocardial infarction and ischemic stroke. That said, long-term safety concerns from RCTs in patients with T2DM (and which have not been shown in patients with NASH), are undoubtedly limiting pioglitazone usage in clinical practice. We suggest that further well-designed RCTs with longer follow-up and adequate liver histology endpoints are needed to better characterize the efficacy and harms of this generic and inexpensive medication in patients with NAFLD. Larger phase 3 RCTs with adequate liver histology endpoints are also needed to confirm the long-term beneficial effects of GLP1 RAs and SGLT-2 inhibitors, considering their promising effects on NAFLD using magnetic resonance or other imaging techniques. Finally, we believe that tailoring pharmacotherapy to the dominant pathogenic pathway in a given patient, along with the use of combination therapies, is likely to represent the future direction in the treatment of patients with NASH (irrespective of the presence of diabetes).

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FIGURE LEGEND

Supplementary Figure S1. Flow-chart of the literature research and study selection.

Table 1. Placebo-controlled or active-controlled RCTs of metformin for treatment of NAFLD (ordered by publication year).

Investigator, Year, Country, Trial name (Quality rating)	Population, Demographics	Interventions (group sizes), Duration	Efficacy/effectiveness outcomes A vs. B (vs. C)	Adverse effects
Bugianesi, 2005 (11) multicenter Italy (Fair)	Non-diabetic adults with biopsy-confirmed NAFLD Age: 43 y Sex: 85% male BMI, kg/m ² : 28.5 Diabetes: 8.1% newly diagnosed Mean AST 45 U/L, ALT 90 U/L	A: Metformin 2000 mg/d (n = 55) B: Vitamin E 400 IU/d (n = 28) C: Prescriptive diet (n = 27) Duration: 12 months A second liver biopsy was programmed at the end of the study, but was considered optional	Serum aminotransferase levels improved in all groups, in association with weight loss. The effect in the metformin arm was larger (p<0.0001), and serum ALT levels normalized in 56% of cases A control biopsy in 17 metformin-treated cases (14 non-responders) showed a significant decrease in liver fat (p<0.001), necro-inflammation, and fibrosis (p=0.012 for both)	No patients on metformin or vitamin E stopped treatments because of AEs
Haukeland, 2009 (12) Norway (Good)	Adults with biopsy-confirmed NAFLD Age: 47.4 y Sex: 73% male Ethnicity: 86.4% white BMI, kg/m ² : 30.8 Diabetes: 27% Mean AST and ALT: NR	A: Metformin 2500 mg/d (3000 mg if weight >90 kg) (n = 24) B: Placebo (n = 24) Duration: 6 months	Percentage with improvement (p-value change from baseline); between-groups p-value: Steatosis: 25% (p=0.10) vs. 38% (p=0.03); p=0.052 Fibrosis: 5% (p=0.99) vs. 17% (p=0.17); p=0.36 NAFLD activity score: 20% (p=0.23) vs. 50% (p=0.12); p=0.06 Changes from baseline (p-value); between-groups p-value: Weight: -4.3 (p<0.001) vs. 0.3 kg (p=0.45); p<0.001 BMI: -1.3 (p<0.001) vs. 0.1 kg/m ² (p=0.59); p<0.001	Serious AEs: NR Withdrawal due to AEs: 2/24 (8.3%) vs. 0/24 (0%)
Omer, 2010 (13) Turkey (Fair)	Adults with type 2 diabetes or impaired glucose tolerance and	A: Metformin 1700 mg/d plus	Changes from baseline (p-value):	NR

	biopsy-confirmed NAFLD Age: 48.9 y Sex: 54.7% male BMI, kg/m ² : 30.6 Diabetes: NR Mean AST 50 UI/L, ALT 67 UI/L	rosiglitazone 4 mg/d (n = 22) B: Metformin 1700 mg/d (n = 22) C: Rosiglitazone 4 mg/d (n = 20) Duration: 12 months	NAFLD score: -3.9 (p=0.026) vs. 0.7 (p=0.73) vs. -2.6 (p=0.012) AST: -15.4 (p=0.01) vs. -13.0 (p=NS) vs. -13.2 UI/L (p=0.005) ALT: -22.7 (p=0.017) vs. -16.7 (p=0.62) vs. -36.2 UI/L (p<0.0001) BMI: -1.3 (p =0.006) vs. -3.2 (p=0.002) vs. -0.3 kg/m ² (p=0.29)	
Lavine, 2011 (14), multicenter United States, TONIC trial (Good)	Children/adolescents with biopsy-proven NAFLD Age: 13.1 y Sex: 81% male Ethnicity: White 74% BMI, kg/m ² : 34 Diabetes: 0% NASH: 42% Mean AST 71 UI/L, ALT 123 UI/L	A. Metformin 1000 mg/d (n = 57) B. Vitamin E 800 IU/d (n = 58) C. Placebo (n = 58) Duration: 96 weeks	Neither vitamin E nor metformin was superior to placebo in attaining the primary outcome of sustained reduction in ALT level or the secondary endpoint (improvements in histological features of NAFLD and resolution of NASH) Change in ALT level from baseline at week 96: -41.7 vs -48.3 vs. -35.2 IU/L, p=NS Change in hepatocellular ballooning scores: +0.1 with placebo (95% CI, -0.2 to 0.3) vs. -0.5 with vitamin E (95% CI, -0.8 to -0.3; p=0.006) vs. -0.3 with metformin (95% CI, -0.6 to -0.0; p=0.04); and in NAFLD activity score, -0.7 with placebo (95% CI, -1.3 to -0.2) vs. -1.8 with vitamin E (95% CI, -2.4 to -1.2; p=0.02) and -1.1 with metformin (95% CI, -1.7 to -0.5; p=0.25) Resolution of NASH: 41% vs. 58% vs. 28%, p=NS There was an overall mean increase in weight and BMI, but there were no significant differences	NR

Razavizade, 2013 (15) Iran (Fair)	<p>Adults with NAFLD assessed by ultrasonography and predictive formula</p> <p>Age: 35.3 y Sex: 85% male</p> <p>BMI, kg/m²: 27.7</p> <p>Diabetes: 7.5%</p> <p>Mean AST and ALT: NR</p>	<p>A: Metformin 1000 mg/d (n = 40) B: Pioglitazone 30 mg/d (n = 40)</p> <p>Duration: 4 months</p>	<p>Changes from baseline (p-value), between-groups p-value:</p> <p>Liver fat fraction (on ultrasound): -2.53 (p<0.01) vs. -3.23 (p<0.01), p=0.48</p> <p>AST: -10.8 (p<0.01) vs. -13.8 UI/L (p<0.01), p=0.56</p> <p>ALT: -21.8 (p<0.01) vs. -37.5 UI/L (p<0.01), p=0.07</p> <p>Weight: -2.7 (p<0.01) vs. -1.2 kg (p=0.04), p=0.05</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: None</p>
Rana, 2016 (16) India (Fair)	<p>Adults with ultrasound-detected NAFLD without history of use of insulin sensitizers or hypolipidemic drugs</p> <p>Age: NR Sex: NR</p> <p>Mean AST 55 IU/mL, ALT 64 UI/mL (AST and ALT were different at baseline between treatment groups)</p> <p>BMI, kg/m²: 27.9</p> <p>Diabetes: NR</p>	<p>A. Metformin (n = 31) B. Rosuvastatin (n = 34) C. Pioglitazone (n = 33)</p> <p>Duration: 24 weeks</p> <p>NB: daily dosage of three drugs was not reported</p>	<p>Change in ultrasound score (fatty liver) at 24 weeks: our analysis</p> <p>A vs. B: 0.07 vs. -1.27 (p<0.001)</p> <p>A vs. C: 0.07 vs. -0.70 (p<0.001)</p> <p>Weight change at 24 weeks: our analysis</p> <p>A vs. B: -4.8 vs. -4.3 kg (p 0.13) A vs. C: -4.8 vs. 0.03 kg (p< 0.001)</p> <p>AST change at 24 weeks: our analysis</p> <p>A vs. B: -14.1 vs. 8.4 UI/L (p<0.001) A vs. C: -14.1 vs. -23.7 UI/L (p=0.04)</p> <p>ALT change at 24 weeks: our analysis</p> <p>A vs. B: -15.6 vs. 8.1 UI/L (p<0.001) A vs. C: -15.6 vs. -24.7 UI/L (p=0.13)</p>	NR

Abbreviations: AEs, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported; NS, not significant.

Table 2. Placebo-controlled or active-controlled RCTs of glitazones for treatment of NAFLD (ordered by publication year).

Investigator, Year, Country, Trial name (Quality rating)	Population, Demographics	Interventions (group sizes), Duration	Efficacy/effectiveness outcomes A vs. B (vs. C)	Adverse effects
Belfort, 2006 (17) US (Good)	<p>Adults with type 2 diabetes or impaired glucose tolerance and biopsy-confirmed NASH</p> <p>Age: 51 y Sex: 45% male</p> <p>Ethnicity: NR</p> <p>HbA1c: 6.2%</p> <p>BMI, kg/m²: 33.2</p> <p>Diabetes: NR</p> <p>Mean AST 44 U/L, ALT 64 U/L</p>	<p>A: Pioglitazone 30 mg/d for 2 months, then 45 mg/d (n = 29)</p> <p>B: Placebo (n = 25)</p> <p>Duration: 6 months</p>	<p>Percent with liver fibrosis improvement: 46% vs. 33%, p=0.08</p> <p>Changes from baseline (p-value), between-groups p-value:</p> <p>AST: -19 (p<0.001) vs. -9 U/L (p=0.08), p =0.04</p> <p>ALT: -39 (p<0.001) vs. -21 U/L (p=0.03), p<0.001</p> <p>Weight: 2.5 (p<0.001) vs. -0.5 kg (p=0.53), p=0.003</p> <p>BMI: 1.1 (p<0.001) vs. -0.2 kg/m² (p=0.62), p=0.005</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: 1/29 (3.5%) vs. 1/25 (4.0%)</p>
Aithal, 2008 (18) UK (Good)	<p>Non-diabetic adults with biopsy-confirmed NASH</p> <p>Age: 53 y Sex: 61% male</p> <p>Ethnicity: white</p> <p>BMI, kg/m²: 30.3</p>	<p>A: Pioglitazone 30 mg/d (n = 37)</p> <p>B: Placebo (n = 37)</p> <p>Duration: 12 months</p>	<p>Number (%) with improvement (p-value), between-groups p-value:</p> <p>Liver fibrosis: 9/31 (29%) (p=0.006) vs. 6/30 (20%) (p=0.81), p=0.05</p> <p>Steatosis: 15/31 (48%) (p=0.001) vs. 11/30 (37%) (p=0.03), p=0.19</p> <p>Changes from baseline (p-value), between-groups p-value:</p> <p>Weight: 2.6 (p=0.005) vs. -3.5 kg (p=0.69), p=0.02</p> <p>ALT: -37.7 (p=0.02) vs. -6.9 U/L (p=0.41), p=0.01</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: 3/37 (8.1%) vs. 4/37 (10.8%)</p>

Ratziu, 2008 (19) France FLIRT (Good)	<p>Adults with biopsy-confirmed NASH</p> <p>Age: 53.6 y</p> <p>Sex: 59% male</p> <p>Ethnicity: NR</p> <p>BMI, kg/m²: 31</p> <p>Diabetes: 32%</p>	<p>A: Rosiglitazone 8 mg/d (4 mg/d for 1st month) (n = 32)</p> <p>B: Placebo (n = 31)</p> <p>Duration: 12 months</p>	<p>Changes from baseline, between-groups p-value:</p> <p>NAFLD activity score: -1 vs. 0, p=0.60</p> <p>Steatosis, % reduction: -20% vs. -5%, p=0.02</p> <p>Fibrosis: 0.03 vs. -0.18, p=0.43</p> <p>ALT, number (%) achieving normalization: 12/32 (38%) vs. 2/31 (7%), p=0.005</p> <p>ALT, mean % change from baseline: -28% vs. -2%; mean reduction, -44% vs. 0%, p<0.001</p> <p>AST, mean % change from baseline: -8% vs. 9%; mean reduction, -62% vs. +15%, p<0.001</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: 1/32 (3.1%) vs. 0/31</p> <p>Dose reduction due to AEs: 5/32 (15.6%) vs. 1/31 (3.2%)</p>
Sanyal, 2010 (20) US PIVENS (Good)	<p>Non-diabetic adults with biopsy-confirmed NASH</p> <p>Age: 46.3 y %</p> <p>Sex: 40% male</p> <p>Ethnicity, % white: 88</p> <p>BMI, kg/m²: 34</p> <p>Mean AST 56 U/L, ALT 83 U/L</p>	<p>A: Pioglitazone 30 mg/d (n = 80)</p> <p>B: Vitamin E 800 IU/d (n = 84)</p> <p>C: Placebo (n = 83)</p> <p>Duration: 96 weeks</p>	<p>Changes from baseline (p-value vs. placebo):</p> <p>NASH improvement, n (%): 27/80 (34%) (p=0.04) vs. 36/84 (43%) (p=0.001) vs. 16/83 (19%)</p> <p>NAFLD activity score: -1.9 (p<0.001) vs. -1.9 (p<0.001) vs. -0.5</p> <p>Steatosis: -0.8 (p<0.001) vs. -0.7 (p<0.001) vs. -0.1</p> <p>Fibrosis: -0.4 (p=0.10) vs. -0.3 (p=0.19) vs. -0.1</p> <p>AST: -20.4 (p<0.001) vs. -21.3</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: None</p>

			<p>($p < 0.001$) vs. -3.8 UI/L</p> <p>ALT: -40.8 ($p < 0.001$) vs. -37.0 ($p = 0.001$) vs. -20.1 UI/L</p> <p>Weight: 4.7 ($p < 0.001$) vs. 0.4 ($p = 0.65$) vs. 0.7 kg</p>	
Torres, 2011 (21) US (Good)	<p>Adults with biopsy-confirmed NASH</p> <p>Age: 49.4 y Sex: 44% male</p> <p>Ethnicity, %: Caucasian: 65</p> <p>BMI, kg/m²: 33.2</p> <p>Diabetes: 17%</p> <p>HbA1c: 5.9%</p> <p>Mean AST 56 U/L, ALT 86 U/L</p>	<p>A: Rosiglitazone 8 mg/d (n = 50)</p> <p>B: Rosiglitazone 8 mg/d + metformin 1000 mg/d (n = 50)</p> <p>C: Rosiglitazone 8 mg/d + losartan 50 mg/d (n = 50)</p> <p>Duration: 48 weeks</p>	<p>Subjects with final biopsy: 26 vs. 28 vs. 35</p> <p>Changes from baseline, between-groups p-value:</p> <p>Resolution of definite NASH, n (%): 12/26 (46%) vs. 10/28 (36%) vs. 10/35 (29%), $p = \text{NR}$</p> <p>NAFLD activity score: -1.77 vs. -1.32 vs. -1.37, $p = 0.67$</p> <p>Steatosis: -0.85 vs. -0.82 vs. -0.74, $p = 0.91$</p> <p>Fibrosis: -0.70 vs. -0.59 vs. -0.32, $p = 0.30$</p> <p>AST: -39.6 vs. -35.0 vs. -48.7 UI/L, $p = \text{NS}$ (exact p-value NR)</p> <p>ALT: -17.4 vs. -19.9 vs. -21.7 UI/L, $p = \text{NS}$ (exact p-value NR)</p> <p>Weight: 0.9 vs. -1.2 vs. 3.7 kg, $p = 0.051$</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: NR by group</p>
Sharma, 2012 (22) India (Fair)	<p>Adults with biopsy-confirmed NASH</p> <p>Age: 38.9 y Sex: 54% male</p>	<p>A: Pentoxifylline 1200 mg/d (n = 29)</p> <p>B: Pioglitazone 30 mg/d (n = 30)</p> <p>Duration: 24 weeks</p>	<p>Changes from baseline (p-value), between-groups p-value:</p> <p>Brunt's score: -0.34 ($p = 0.10$) vs. -1.2 ($p = 0.005$), $p = 0.04$</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: None</p>

	<p>Ethnicity: NR</p> <p>BMI, kg/m²: 24.9</p> <p>Diabetes: NR</p> <p>Mean AST 65 U/L, ALT 96 U/L</p>		<p>Steatosis: -0.83 (p=0.02) vs. -1.18 (p=0.005), p=0.60</p> <p>Fibrosis: 0.08 (p=0.70) vs. -0.46 (p=0.19), p=0.26</p>	
Razavizade, 2013 (15) Iran (Fair)	<p>Adults with NAFLD assessed by ultrasonography</p> <p>Age: 35.3 y</p> <p>Sex: 85% male</p> <p>BMI, kg/m²: 27.7</p> <p>Diabetes: 7.5%</p> <p>Mean AST 50 U/L, ALT 91 U/L</p>	<p>A: Metformin 1000 mg/d (n = 40)</p> <p>B: Pioglitazone 30 mg/d (n = 40)</p> <p>Duration: 4 months</p>	<p>Changes from baseline (p-value), between-groups p-value:</p> <p>Liver fat fraction: -2.53 (p<0.01) vs. -3.23 (p<0.01), p=0.48</p> <p>AST: -10.8 (p<0.01) vs. -13.7 UI/L (p<0.01), p=0.56</p> <p>ALT: -21.7 (p<0.01) vs. -37.5 UI/L (p<0.01), p=0.07</p> <p>Weight: -2.7 (p<0.01) vs. -1.2 kg (p=0.04), p=0.05</p>	<p>Serious AEs: NR</p> <p>Withdrawal due to AEs: None</p>
Cusi, 2016 (23) United States (Good)	<p>Patients with type 2 diabetes or prediabetes and biopsy-confirmed NASH</p> <p>Age: 50.5 y</p> <p>Sex: 70.3 % male</p> <p>Ethnicity: 67.3% Hispanic</p> <p>BMI, kg/m²: 34.4</p> <p>Diabetes: 51%</p> <p>HbA1c in those with diabetes (n = 51): 6.9%, or those with prediabetes: 5.7% (n = 50)</p> <p>Mean ALT 59 UI/L</p>	<p>A. Pioglitazone 45 mg per day (n = 50)</p> <p>B. Placebo, (n = 51)</p> <p>All patients were prescribed a hypocaloric diet. Both groups followed with an open-label phase with pioglitazone for 18 months</p> <p>Duration: 18 months (36 months for open-label phase)</p>	<p>Greater than 2-point reduction of NAS without worsening fibrosis: 58% vs. 17%, p<0.001</p> <p>NASH resolution: 51% vs. 19%, p<0.001</p> <p>Fibrosis; greater than 1-point improvement: 39% vs. 25%, p = 0.13</p> <p>Fibrosis mean change in score improved with pioglitazone: 0 vs. -0.5, p<0.05</p> <p>Weight: pioglitazone group gained 2.5 kg, p=0.039</p>	NR

Abbreviations: AE, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported.

Table 3. Placebo-controlled or active-controlled RCTs of incretin-based therapies (GLP-1 receptor agonists or DPP-4 inhibitors) for treatment of NAFLD (ordered by publication year).

Investigator, Year, Country, Trial name (Quality rating)	Population, Demographics	Interventions (group sizes), Duration	Efficacy/effectiveness outcomes A vs. B (vs. C vs. D)	Adverse effects
<i>GLP-1 receptor agonists</i>				
Shao, 2014 (24) China (Fair)	<p>Obese patients with type 2 diabetes and ultrasound-defined NAFLD (and raised serum liver enzymes)</p> <p>Age: 43 y</p> <p>Sex: 48% male</p> <p>BMI, kg/m²: 30</p> <p>HbA1c: 7.6%</p> <p>Mean ALT 166 IU/L, AST 123 IU/L</p>	<p>A. Exenatide + glargine (n = 30)</p> <p>B. Intensive insulin: Insulin aspart + insulin glargine (n = 30)</p> <p>Duration: 12 weeks</p>	<p>Reversal rate of NAFLD based on liver ultrasound:</p> <p>A vs. B: 93% vs. 67%, p<0.01</p> <p>Differences in weight change post minus pretreatment:</p> <p>A vs. B: -7.8 vs. 3.3 kg, p<0.001</p> <p>No difference between groups in change in HbA1c (-1.4 vs. -1.3%)</p>	NR
Armstrong, 2016 (25) United Kingdom, LEAN (Good)	<p>Patients had biopsy-proven noncirrhotic NASH</p> <p>Age: 51 y</p> <p>Sex: 60% male</p> <p>Ethnicity: White: 88%</p> <p>ALT: 72 IU/mL</p> <p>F3-F4 on liver histology: 52%</p> <p>BMI, kg/m²: 36</p> <p>Diabetes: 33%</p> <p>Mean ALT 71 IU/L, AST 51 IU/L</p>	<p>A. Liraglutide 1.8 mg (n = 26)</p> <p>B. Placebo (n = 26)</p> <p>Duration: 48 weeks</p>	<p>Resolution of NASH: 39% vs. 9% (relative risk 4.3, 95% CI 1.0 to 17.7)</p> <p>Change in NAS score: -1.3 vs. -0.8, p=0.24</p> <p>Change in fibrosis stage: -0.2 vs. 0.2, p=0.11</p> <p>Patients with improvement in fibrosis: 26% vs. 14%, p=0.46</p> <p>Patients with worsening fibrosis: 9% vs. 36%, p=0.04</p> <p>Change in ALT: -26.6 vs. -10.2 UI/L, p=0.16</p> <p>Change in AST: -27 vs. +9 IU/L;</p>	<p>WAE: 8% vs. 4% (p = 0.56)</p> <p>SAE: 8% vs. 8%</p> <p>GI-disorders: 81% vs. 65% (p = 0.27)</p>

			p=0.02	
Dutour, 2016 (26), France (Fair)	<p>Patients with type 2 diabetes treated with metformin and/or sulphonylureas and/or DPP4 inhibitors (95% had NAFLD on MR spectroscopy)</p> <p>Age: 52 y</p> <p>Sex: 48% male</p> <p>BMI, kg/m²: 36.1</p> <p>HbA1c 7.5%</p> <p>Mean ALT 29 IU/L, AST 22 IU/L</p>	<p>A: Placebo (n = 22)</p> <p>B: Exenatide 5-10 mcg bid (n = 22)</p> <p>Duration: 26 weeks</p>	<p>Exenatide and reference treatment led to a similar improvement in HbA1c ($-0.7 \pm 0.3\%$ vs. $-0.7 \pm 0.4\%$; p=0.29)</p> <p>Significant weight loss was observed only in the exenatide group (-5.5 ± 1.2 kg vs. -0.2 ± 0.8 kg; p=0.001 for difference between groups)</p> <p>Exenatide induced a significant reduction in hepatic fat content, compared with the reference treatment (hepatic fat content: $-23.8 \pm 9.5\%$ vs. $+12.5 \pm 9.6\%$, p=0.007)</p>	19 patients concluded the trial both in the placebo and in the treatment arm
Feng, 2017 (27) China (Fair)	<p>Patients with type 2 diabetes and NAFLD assessed by ultrasonography</p> <p>Age: 47 y</p> <p>Sex: 75% male</p> <p>BMI, kg/m²: 27.6</p> <p>HbA1c: 9.1%</p> <p>Mean ALT 49 IU/mL, AST 31 IU/L</p>	<p>A. Liraglutide up to 1.8 mg/d (n = 31)</p> <p>B. Metformin up to 2000 mg/d (n = 31)</p> <p>C. Gliclazide up to 120 mg/d (n = 31)</p> <p>Duration: 24 weeks</p>	<p>Hepatic fat content (estimated by ultrasound) decreased significantly in all treatment groups, from $36.7 \pm 3.6\%$ to $13.1 \pm 1.8\%$ in the liraglutide group, from $33.0 \pm 3.5\%$ to $19.6 \pm 2.1\%$ in the gliclazide group, and from $35.1 \pm 2.3\%$ to $18.4 \pm 2.2\%$ in the metformin group (p<0.001 for all treatment groups, final vs. baseline)</p> <p>Reduction in liver fat following liraglutide treatment was greater than that following gliclazide treatment (p=0.001)</p> <p>Both liraglutide and metformin treatments significantly reduced weight and improved liver function tests</p> <p>HbA1c levels were lower in the liraglutide- and metformin-treated groups than in the gliclazide-</p>	29 patients in each study arm completed the 24-week trial

			treated group	
Frossing, 2017 (28) Denmark, LIPT-study (Fair)	<p>Obese non-diabetic women with polycystic ovary syndrome and NAFLD (assessed by MR spectroscopy)</p> <p>Age: 47 y</p> <p>Sex: 100% female</p> <p>BMI, kg/m²: 33</p> <p>Diabetes: NR</p> <p>Mean ALT and AST: NR</p>	<p>A. Placebo (n = 24)</p> <p>B. Liraglutide 1.8 mg/d (n = 48)</p> <p>Duration: 26 weeks</p>	<p>Compared with placebo, liraglutide treatment reduced body weight by 5.2 kg (-5.6% from baseline), intrahepatic triglyceride content (as measured by MR spectroscopy) by 44% and the prevalence of NAFLD by about two-thirds (all p<0.01)</p> <p>Liraglutide treatment caused significant reductions in fasting plasma glucose (liraglutide vs placebo, mean between-group difference [95% CI], -0.24 [-0.44 to -0.04] mmol/L; mean HbA1c [95% CI], -1.38 [-2.48 to -0.28] mmol/mol)</p>	<p>Nausea (liraglutide 79%; placebo 13%; P < 0.01) and constipation (liraglutide 26%; placebo 0%; P < 0.01) were the most frequent AEs</p>
Yan, 2019 (29) China (Fair)	<p>Patients with NAFLD (assessed by MRI-PDFF) and type 2 diabetes who were unable to maintain good glycemic control with metformin</p> <p>Age: 44 y</p> <p>Sex: 69% male</p> <p>BMI, kg/m²: 29.8</p> <p>HbA1c: 7.7%</p> <p>Mean ALT 43 IU/mL, AST 33 IU/mL</p>	<p>A. Liraglutide 1.8 mg/d (n = 24)</p> <p>B. Insulin glargine 0.2 IU/kg/d (n = 24)</p> <p>C. Sitagliptin 100 mg/d (n = 27)</p> <p>Duration: 26 weeks</p>	<p>In the liraglutide and sitagliptin groups, hepatic fat content, measured by MRI-PDFF, significantly decreased from baseline to week 26 (liraglutide, 15.4±5.6% to 12.5±6.4%, p<0.001; and sitagliptin, 15.5±5.6% to 11.7±5.0%, p=0.001)</p> <p>Although this change was greater with liraglutide than sitagliptin, it was not significantly different between the two groups (-4.0 vs. -3.8%; p=0.91)</p> <p>In contrast, hepatic fat content did not change significantly from baseline in the insulin glargine group</p> <p>HbA1c improved significantly in all treatment groups (liraglutide, 7.8±1.4% to 6.8±1.7%, p<0.001; sitagliptin, 7.6±0.9% to 6.6±1.1%,</p>	<p>Six patients in the liraglutide group withdrew from the study (four lost to follow-up, one for protocol violations, and one for AEs), one patient in the sitagliptin group was lost to follow-up, and three patients in the insulin glargine group withdrew for protocol violations</p>

			<p>p=0.016; and insulin glargine, 7.7±0.9% to 6.9% ± 1.1%, p=0.013). However, ΔHbA1c did not differ across treatment groups</p> <p>In the liraglutide and sitagliptin groups (but not in the insulin glargine groups), significant decreases in body weight and BMI were observed</p>	
<i>DPP-4 inhibitors</i>				
Macauley, 2015 (30) UK (Fair)	<p>Patients with type 2 diabetes and NAFLD (assessed by MRI-PDFF) on stable metformin therapy</p> <p>Age: 61.4 y</p> <p>Sex: 64% male</p> <p>BMI, kg/m²: 30.3</p> <p>HbA1c 6.4%</p> <p>Mean ALT 28 IU/mL</p>	<p>A. Vildagliptin 50 mg bid (n = 22)</p> <p>B. Placebo (n = 22)</p> <p>Duration: 6 months</p>	<p>Body weight decreased by 1.6±0.5 vs. 0.4±0.5 kg in the vildagliptin and placebo groups, respectively (p=0.08)</p> <p>Mean hepatic fat content (assessed by MRI-PDFF) decreased significantly with vildagliptin treatment from 7.3±1.0% at baseline to 5.3±0.9% at endpoint (p=0.001)</p> <p>No change in the placebo group (5.4±0.7% to 5.4±1.0%; p=0.48). The between-group difference in change from baseline was significant (p<0.013)</p> <p>Mean plasma ALT fell from 27.2±2.8 to 20.3±1.4 IU/L in the vildagliptin group (p=0.001), and did not change in the placebo group (29.6±3 to 29.6±3.7 IU/L; p=0.44)</p>	There were no meaningful differences between the vildagliptin and placebo groups in the overall AEs
Cui, 2016 (31) United States (Fair)	<p>Patients with NAFLD (assessed by MRI-PDFF) and with prediabetes (n = 25) or controlled type 2 diabetes (n = 25)</p> <p>Age: 54 y</p>	<p>A. Sitagliptin 100 mg (n = 25)</p> <p>B. Placebo (n = 25)</p> <p>Duration: 24 weeks</p>	<p>Sitagliptin was not significantly better than placebo in reducing liver fat content measured by MRI-PDFF (mean difference between sitagliptin and placebo arms: -1.3%, p=0.40)</p> <p>Compared to baseline, there were</p>	NR

	<p>Sex: 62% male</p> <p>BMI, kg/m²: 31.8</p> <p>HbA1c 6.2%</p> <p>Mean ALT 42 IU/mL; AST 28 IU/mL</p>		<p>no significant differences in end-of-treatment MRI-PDFF for sitagliptin (18.1% to 16.9%, p=0.27) or placebo (16.6% to 14.0%, p=0.07)</p> <p>No significant differences for changes in serum transaminase levels, HOMA-IR or MRE-derived liver stiffness between the two groups</p>	
Deng, 2017 (32) China (Fair)	<p>Patients with uncomplicated type 2 diabetes and NAFLD diagnosed by ultrasound</p> <p>Age: 64 y</p> <p>Sex: 75% male</p> <p>BMI, kg/m²: 24</p> <p>Diabetes: HbA1c 7.4%</p> <p>Mean ALT 35 IU/mL, AST 32 IU/mL</p>	<p>A. Sitagliptin 50 mg to 100 mg (n = 36)</p> <p>B. Diet and exercise (n = 36)</p> <p>Duration: 52 weeks</p>	<p>No differences for changes in serum AST (p=0.99) and ALT (p=0.97) between treatment with sitagliptin vs. diet and exercise</p> <p>Greater decrease in HbA1c with sitagliptin (-0.81% from baseline) vs. diet and exercise (-0.25%), p<0.01 at 52 weeks</p>	NR (70 patients completed the trial)
Yan, 2019 (29) China (Fair)	<p>Patients with NAFLD (assessed by MRI-PDFF) and type 2 diabetes who were unable to maintain glycemic control with metformin</p> <p>Age: 44 y</p> <p>Sex: 69% male</p> <p>BMI, kg/m²: 29.8</p> <p>HbA1c: 7.7%</p> <p>Mean ALT 43 IU/mL, AST 33 IU/mL</p>	<p>A. Liraglutide 1.8 mg/d (n = 24)</p> <p>B. Insulin glargine 0.2 IU/kg/d (n = 24)</p> <p>C. Sitagliptin 100 mg/d (n = 27)</p> <p>Duration: 26 weeks</p>	<p>In the liraglutide and sitagliptin groups, liver fat content, measured by MRI-PDFF, significantly decreased from baseline to week 26 (liraglutide, 15.4±5.6% to 12.5±6.4%, p<0.001; and sitagliptin, 15.5±5.6% to 11.7± 5%, p=0.001)</p> <p>Although this change was greater with liraglutide than sitagliptin, it was not significantly different between the two groups (-4.0 vs. -3.8; p=0.91)</p> <p>Liver fat content did not change significantly from baseline in the insulin glargine group</p> <p>HbA1c improved significantly in all</p>	Six patients in the liraglutide group withdrew from the study (four lost to follow-up, one for protocol violations, and one for AEs), one patient in the sitagliptin group was lost to follow-up, and three patients in the insulin glargine group withdrew for protocol violations

			<p>treatment groups (liraglutide, 7.8±1.4% to 6.8±1.7%, p<0.001; sitagliptin, 7.6±0.9% to 6.6±1.1%, p=0.016; and insulin glargine, 7.7±0.9% to 6.9±1.1%, p=0.013). However, ΔHbA1c did not significantly differ across treatment groups</p> <p>In the liraglutide and sitagliptin groups, significant decreases in body weight were observed</p>	
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Abbreviations: AE, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MR, magnetic resonance; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported.

Table 4. Placebo-controlled or active-controlled RCTs of SGLT2 inhibitors for treatment of NAFLD (ordered by publication year).

Investigator, Year, Country, Trial name (Quality rating)	Population, Demographics	Interventions (group sizes), Duration	Efficacy/effectiveness outcomes A vs. B (vs. C)	Adverse effects
Bolinder, 2012 (33) International (Fair)	<p>Patients with NAFLD (assessed by MRI-PDFF) and type 2 diabetes inadequately controlled on metformin</p> <p>Age: 58.6 y</p> <p>Sex: 46.7% male</p> <p>Ethnicity: 100% White</p> <p>BMI, kg/m²: 31.9</p> <p>HbA1c 7.2%</p> <p>Mean ALT and AST: NR</p>	<p>A. Placebo (n = 91)</p> <p>B. Dapagliflozin 10 mg/d (n = 91)</p> <p>Duration: 24 weeks (with a 78-wk site- and patient-blinded extension period)</p> <p>In a subset of patients (n = 42 in the placebo arm and n = 38 in the active drug arm), MRI-PDFF was also performed</p>	<p>At week 24, placebo-corrected changes with dapagliflozin were as follows: body weight, -2.08 kg [95% confidence interval (CI)= -2.84 to -1.31; p<0.0001]; waist circumference, -1.52 cm (95% CI= -2.74 to -0.31; p=0.014); total fat mass, -1.48 kg (95% CI = -2.22 to -0.74; p<0.0001)</p> <p><u>In the MR sub-study:</u> Dapagliflozin produced significantly greater mean reductions from baseline in visceral adipose tissue compared with placebo at 24-week</p> <p>Change from baseline at 24-week in mean percent hepatic fat content with dapagliflozin was -2.35% and -1.53% with placebo, resulting in a not significant placebo-corrected difference of -0.82% (95% CI = -2.97 to 1.33; p=0.45)</p>	<p>In B vs. A group: serious AEs were reported in 6.6% vs. 1.1%, respectively; events suggestive of vulvovaginitis, balanitis, and related genital infection in 3.3 vs. 0%; and lower urinary tract infections in 6.6 vs. 2.2%</p>
Ito, 2017 (34), Multicenter Japan (Fair)	<p>Patients with poorly controlled type 2 diabetes and NAFLD on ultrasound</p> <p>Age: 58 y</p> <p>Sex: 48.5% male</p> <p>BMI, kg/m²: 30</p> <p>HbA1c 8.4%</p> <p>Mean ALT 55 IU/mL, AST 41 IU/mL</p>	<p>A. Pioglitazone 15-30 mg/d (n = 34)</p> <p>B. Ipragliflozin 50 mg/d (n = 32)</p> <p>Duration: 24 weeks</p>	<p>Mean liver-to-spleen attenuation ratio on computed tomography at week 24 increased by 0.22 (from 0.80±0.24 to 1.0±0.18) in the ipragliflozin group and 0.21 (from 0.78±0.26 to 0.98±0.16) in the pioglitazone group (p=0.90)</p> <p>AST, ALT and GGT levels, HbA1c and HOMA-IR were similarly reduced in the two treatment groups</p> <p>FIB4 score was similarly reduced in</p>	<p>Serious AEs: NR</p>

			the two treatment groups	
			Body weight and visceral fat area showed significant reductions only in the ipragliflozin group compared with the pioglitazone group	
Cusi, 2018 (35) USA (Fair)	<p>Patients with type 2 diabetes who were unable to maintain glycemic control (most patients had NAFLD on MRI-PDFF)</p> <p>Age: 58 y</p> <p>Sex: 66% male</p> <p>Ethnicity: 67% White</p> <p>BMI, kg/m²: 32</p> <p>HbA1c 7.7%</p> <p>Mean ALT 30 IU/mL, AST 25 IU/mL</p> <p>Mean hepatic fat content measured by magnetic resonance spectroscopy: 12.5%</p>	<p>A. Placebo (n = 30)</p> <p>B. Canagliflozin 100 mg/d titrated up to 300 mg/d (n = 26)</p> <p>Duration: 24 weeks</p>	<p>A not significant larger absolute decrease in hepatic fat content occurred with canagliflozin (hepatic fat content: -4.6% [-6.4; -2.7]) vs. placebo (-2.4% [-4.2; -0.6]; p=0.09)</p> <p>In patients with NAFLD, the decrease in hepatic fat content was -6.9% (-9.5; -4.2) vs. -3.8% (-6.3; -1.3; p=0.05), and strongly associated with the magnitude of weight loss</p> <p>Body weight loss ≥5% with a ≥30% relative reduction in hepatic fat content occurred more often with canagliflozin (38% vs. 7%, p=0.009)</p> <p>Canagliflozin reduced HbA1c (placebo-subtracted change: -0.71% [-1.08; -0.33]) and body weight (-3.4% [-5.4; -1.4]; both p<0.001)</p> <p>Hepatic insulin sensitivity improved with canagliflozin (p<0.01), but not muscle or adipose tissue insulin sensitivity (measured by euglycemic insulin clamp)</p>	<p>Serious AEs: NR</p> <p>SAE: 3% vs. 4%</p>
Kuchay, 2018 (36) India, E-LIFT (Fair)	<p>Patients with type 2 diabetes and NAFLD (assessed by MRI-PDFF)</p> <p>Age: 50 y</p>	<p>A. Placebo (n = 25)</p> <p>B. Empagliflozin 10 mg/d (n = 25)</p> <p>Duration: 20 weeks</p>	<p>Empagliflozin was significantly better at reducing liver fat content (mean MRI-PDFF difference between the empagliflozin and control groups 24.0%; p<0.0001)</p>	<p>Serious AEs: NR</p> <p>In the empagliflozin arm, 22 patients completed the study, with 3 developing AEs related to the</p>

	<p>Sex: 60% male</p> <p>BMI, kg/m²: 29.5</p> <p>HbA1c 9%</p> <p>Mean ALT 64 IU/L, AST 44 IU/L</p>		<p>Compared with baseline, significant reduction was found in the end-of-treatment MRI-PDFF for the empagliflozin group (16.2% to 11.3%; p<0.0001) and a nonsignificant change was found in the control group (16.4% to 15.5%; p=0.057)</p> <p>The two groups showed significant differences for change in serum ALT level (p=0.005) and nonsignificant differences for AST (p=0.212) and GGT (p=0.057) levels</p>	<p>study medication</p> <p>In the control arm, 20 patients completed the study, with three lost to follow-up and two patients discontinuing because of work schedule conflicts</p>
Eriksson, 2018 (37) Multicenter, Sweden, EFFECT-II trial (Fair)	<p>Patients with type 2 diabetes and NAFLD (assessed by MRI-PDFF)</p> <p>Age: 65.5 y</p> <p>Sex: 70% male</p> <p>BMI, kg/m²: 31.2</p> <p>HbA1c 7.5%</p> <p>Mean ALT and AST: NR</p>	<p>A: Placebo (n = 21)</p> <p>B: Omega-3 carboxylic acids (OM-3CA) 4 g/d (n = 20)</p> <p>C: Dapagliflozin 10 mg/d (n = 21)</p> <p>D: Omega-3 carboxylic acids 4 g/d + dapagliflozin 10 mg/d (n = 22)</p> <p>Duration: 12 weeks</p>	<p>All active treatments significantly reduced hepatic fat content from baseline, relative changes: OM-3CA, -15%; dapagliflozin, -13%; OM-3CA + dapagliflozin, -21%</p> <p>Only the combination treatment reduced liver fat content (p=0.046) and total liver fat volume (relative change, -24%, p=0.037) in comparison with placebo</p> <p>Dapagliflozin monotherapy, but not the combination with OM-3CA, reduced serum transaminase and GGT levels</p> <p>Dapagliflozin alone and in combination with OM-3CA improved HbA1c and reduced body weight</p>	<p>All active treatment groups had similar total percentages of AE reporting (70.0–77.3%), which were higher than in the placebo group (47.6%)</p> <p>More participants reported AEs when using dapagliflozin and OM-3CA (n = 15, 68.2%) than when using dapagliflozin monotherapy (n = 7, 33.3%), OM-3CA monotherapy (n = 8, 40%) or placebo (n = 6, 28.6%)</p>
Shimitzu, 2019 (38), Japan (Fair)	<p>Patients with type 2 diabetes and NAFLD (assessed by Fibroscan and CAP measurement)</p> <p>Age: 56 y</p>	<p>A: Placebo (n = 24)</p> <p>B: Dapagliflozin 5 mg/day (n = 33)</p> <p>Duration: 24 weeks</p>	<p>In week 24, there was a significant decrease in controlled attenuation parameter (CAP) from 314±61 to 290±73 dB/m (p=0.042) in the dapagliflozin group, but not in the control group</p>	NR

	<p>Sex</p> <p>BMI, kg/m²: 28.0</p> <p>HbA1c: 7.8%</p> <p>Mean ALT 36 IU/L, AST 27 IU/L</p>		<p>Liver stiffness measurement (LSM) tended to decrease from 9.49±6.1 to 8.01±5.8 kPa in the dapagliflozin group. In 14 patients from this group with LSM values ≥8.0 kPa, LSM decreased significantly from 14.7±5.7 to 11.0±7.3 kPa (p=0.016)</p> <p>Serum ALT and GGT levels decreased significantly in the dapagliflozin group, but not in the control group</p> <p>Changes in BMI and HbA1c in the control vs. the dapagliflozin groups were 0.0 (-0.55, 0.50) vs. -0.8 (-1.25, -0.07) kg/m²; and HbA1c -0.3 (-0.5, 0.5) vs. -0.8 (-1.3, -0.5)%, respectively</p>	
Kahl, 2019 (39), Germany (Fair)	<p>Patients with well-controlled type 2 diabetes and NAFLD (assessed by MR spectroscopy)</p> <p>Age: 62 y</p> <p>Sex: 69% male</p> <p>Ethnicity: 100% White</p> <p>BMI, kg/m²: 32.2</p> <p>HbA1c 6.6%</p> <p>Mean ALT 35 IU/mL, AST 25 IU/mL</p> <p>Mean hepatic fat content measured by magnetic resonance spectroscopy: 13% (80% of patients had hepatic steatosis at baseline)</p>	<p>A: Placebo (n = 42)</p> <p>B: Empagliflozin 25 mg/day (n = 42)</p> <p>Duration: 24 weeks</p>	<p>EMPA treatment resulted in a placebo-corrected absolute of 21.8% (95% CI 23.4, 20.2%; p=0.02) and relative change in liver fat content of -22% (-36, -7%; p=0.009) from baseline to end of treatment, corresponding to a 2.3-fold greater reduction</p> <p>Weight loss occurred only with EMPA (placebo-corrected change -2.5 kg [-3.7, -1.4 kg]; p<0.001), while no placebo-corrected change in tissue-specific insulin sensitivity was observed</p> <p>EMPA treatment also led to placebo-corrected changes in uric acid (-74 mmol/L [-108, -42 mmol/L]; p<0.001) and high-molecular-weight adiponectin (36% [16, 60%]; p < 0.001) levels from 0</p>	<p>Serious AEs: NR</p> <p>All treatment groups had similar total percentages of AEs (5 events in EMPA and 7 events in placebo groups)</p>

			to 24 weeks	
			Serum ALT and GGT levels were reduced with similar effect sizes in EMPA and placebo after 24 weeks	

Abbreviations: AE, adverse effects; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MR, magnetic resonance; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported.