



Review Article



# Pharmacotherapy for Non-alcoholic Fatty Liver Disease Associated with Diabetes Mellitus Type 2

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) and diabetes mellitus type 2 commonly coexist as a manifestation of metabolic syndrome. The presence of diabetes promotes the progression of simple fatty liver to non-alcoholic steatohepatitis (NASH) and cirrhosis, and the presence of NAFLD increases the risk of diabetic complications. This coexistence affects a large part of the population, imposing a great burden on health care systems worldwide. Apart from diet modification and exercise, recent advances in the pharmacotherapy of diabetes offer new prospects regarding liver steatosis and steatohepatitis improvement, enriching the existing algorithm and supporting a multifaceted approach to diabetic patients with fatty liver disease. These agents mainly include members of the families of glucagon-like peptide-1 analogues and the sodium-glucose co-transporter-2 inhibitors. In addition, agents acting on more than one receptor simultaneously are presently under study, in an attempt to further enhance our available options.

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## Introduction

Non-alcoholic fatty liver disease (NAFLD) and diabetes mellitus type 2 (DM2) constitute two very common entities, around the globe, being especially prevalent in the Western hemisphere. NAFLD can progress to non-alcoholic steatohepatitis (NASH) and subsequently to cirrhosis and hepatocellular carcinoma (HCC). NAFLD leads to a 2-3-fold

increased risk of DM2 development,<sup>1,2</sup> since liver fat accumulation is a crucial pathogenetic component.<sup>3</sup> The coexistence of DM2 in a patient with NAFLD increases the risk of developing the aforementioned outcomes disproportionately and contributes to deterioration of kidney and cardiovascular functions as well.<sup>4</sup> It is estimated that 25–35% of patients with obesity and diabetes also have NASH.<sup>5,6</sup>

It is widely recognized that obesity and insulin resistance are major determinants for the development of both DM2 and NAFLD.<sup>6</sup> Various mechanisms could be involved, both in the early and later stages of NAFLD, from lipid metabolite accumulation and mounting oxidative stress to the release of several pro-inflammatory cytokines.<sup>6</sup> The coexistence of underlying predisposing genes, such as PNPLA3, TM6SF2 and others, seems to increase the risk for development of DM2 as well as of NAFLD.<sup>7</sup>

The emergence of very efficient antiviral regimens for the treatment of chronic hepatitis B and C infections has brought to the forefront the need for tackling the most common and most commonly ignored NAFLD-related liver disease. Multiple therapeutic approaches are in the pipeline for NASH itself; however, while outcomes are still awaited, the treatment strategies followed for DM2 seem to provide some means to treat NASH and, certainly, prevent or improve it to some degree, by targeting the molecular mechanisms underpinning NAFLD.<sup>8,9</sup>

## Current and future treatment approaches for NAFLD/NASH associated with DM2

Currently, the most effective way to improve NAFLD and NASH is through weight loss. This can be achieved through diet and lifestyle modifications, such as adoption of the Mediterranean diet/lifestyle<sup>10–12</sup> and bariatric surgery.<sup>13–17</sup> Several, if not all, antidiabetic medications have been utilized as possible NAFLD treatments. Metformin was a major candidate, but multiple trials showed no improvement regarding steatosis, inflammation or fibrosis, despite a significant reduction of liver enzymes;<sup>18,19</sup> thus, this therapeutic option was rejected for NASH, despite its possible beneficial effects on HCC prevention.<sup>20</sup> Additionally, various dipeptidyl peptidase IV inhibitors have been utilized, such as sitagliptin, which was found not to improve liver enzymes, liver fat content or liver fibrosis in patients with NAFLD.<sup>21,22</sup> Similarly unimpressive results were published from the J-LINK study, regarding linagliptin.<sup>23</sup> Saxagliptin was found, in a randomized trial vs. glimepiride, to exhibit encouraging results, as far as liver steatosis reduction was concerned.

**Keywords:** NAFLD/NASH; Diabetes mellitus type 2; Steatosis; SGLT2; GLP1.

**Abbreviations:** DM2, diabetes mellitus type 2; GCR, glucagon receptor; GIPR, glucose-dependent insulinotropic peptide receptor; GLP-1a, glucagon-like peptide-1 analogues; HbA1c, glycated hemoglobin; HCC, hepatocellular carcinoma; MRI-PDFF, Magnetic Resonance Imaging-Proton Density Fat Fraction; NAFLD, Non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCT, National Clinical Trial number; PPAR, Peroxisome Proliferator-Activated Receptor; RCT, randomized clinical trial; SGLT-2i, sodium-glucose co-transporter-2 inhibitors.

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However, the independence of this effect this medication's hypoglycemic action could not be established.<sup>24</sup>

On the other hand, the use of antidiabetic agents such as thiazolidinediones, sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 analogues (GLP-1a) are examples of pharmacologic attempts to combine glycemic control and weight loss with improvement of liver steatosis and inflammation. The efficacy of these drugs, as well as a few more under development, will be summarized and discussed in this review.

### Thiazolidinediones-peroxisome proliferator-activated receptor $\gamma$ (PPAR $\gamma$ ) agonists

PPARs are nuclear hormone receptors with various functions in metabolic homeostasis, lipid metabolism, and the inflammation process. Pioglitazone (a PPAR $\gamma$  agonist) is an anti-diabetic medication that modulates the transcription of genes involved in glucose and lipid metabolism in the adipose tissue, muscle, and liver. Treatment with pioglitazone at 30 mg/day has led to statistically important improvement of inflammation in patients with NASH, with or without diabetes.<sup>25</sup> It has been used successfully in the PIVENS study-National Clinical Trial number (NCT): 00063622, on non-diabetic patients with NASH. This study, which recruited 247 patients, showed that pioglitazone caused significant reductions in steatosis, inflammation, hepatocellular ballooning and improvement in insulin resistance and liver-enzyme levels, despite failing to achieve the primary outcome of improvement in standardized scoring of liver biopsies.<sup>26</sup> Furthermore, a single-center, parallel-group, randomized, placebo-controlled study, which included 101 patients with biopsy-proven NASH and prediabetes or DM2 (NCT00994682), showed significant improvement of non-alcoholic fatty liver disease activity score in 58% of the patients in the pioglitazone group (vs. 17% in the placebo group) after 18 months of treatment. A reduction in fibrosis progression was also observed in the same group.<sup>27</sup> This is the first antidiabetic agent to achieve relative success in treating NAFLD in both diabetic and non-diabetic patients. Currently, a randomized clinical trial (RCT) is going to examine the effect of pioglitazone and empagliflozin combination in patients with NAFLD and DM2 (NCT03646292). Pioglitazone is a cheap alternative for the treatment of NASH, with or without DM2, but must be used with caution, considering the long-term adverse effects of weight gain, osteopenia, and aggravation of congestive heart failure.<sup>28</sup>

### Other PPAR agonists

Multiple agents of this family have been used in trials regarding NAFLD. The most well-known examples, apart from pioglitazone, are fenofibrate, pemafibrate, seladelpar, elafibranor and lanifibranor, which have been studied in various trials regarding their effect on liver inflammation and fibrosis, without particular success, with the exception of lanifibranor, a pan-PPAR agonist, which was shown in a phase 2b RCT (NATIVE-NCT03008070) to improve ballooning and inflammation, without worsening of fibrosis.<sup>29,30</sup> The focus of those trials was on the presence and possible positive effects on NAFLD, irrespectively of the coexistence of DM2, although 103 out of 247 patients included in the NATIVE RCT with lanifibranor were diabetic. Further evaluation of possible NASH resolution and improvement of liver fibrosis in the case of lanifibranor will be conducted in the phase 3 study NATIV3 (NCT04849728), which will include both diabetic and non-diabetic patients, as well.

Another member of this drug family, saroglitazar, a

PPAR $\alpha/\gamma$  agonist, has shown promise in diabetic patients with dyslipidemia, while it has also been utilized in experimental models and clinical trials for the treatment of NASH in India,<sup>31,32</sup> exhibiting promising results.<sup>33</sup>

### GLP-1 analogues

GLP-1 is an incretin hormone that stimulates insulin secretion and inhibits glucagon secretion, after ingestion of glucose.<sup>34</sup> Other actions include reduction of gastrointestinal motility and appetite. It is a 30-amino acid peptide produced by the intestinal epithelial endocrine L-cells and subsequently inactivated by dipeptidyl peptidase IV.<sup>34</sup> GLP-1 analogues, with a longer duration of action than the original enzyme, offer a potent option for the treatment of DM2. Numerous drugs of this class have been developed in recent years, including exenatide, lixisenatide, dulaglutide, liraglutide and semaglutide. As far as NASH is concerned, liraglutide has been most studied, demonstrating significant improvement of steatohepatitis (histological resolution of NASH in 39% of the patients in the treatment group vs. 9% in the placebo group) and reduced frequency of progression of fibrosis during the phase 2 RCT (LEAN study-NCT01237119), irrespectively of the presence of diabetes mellitus (9% of patients in the treatment group exhibited worsening of fibrosis vs. 36% in the placebo group).<sup>35</sup> Furthermore, the RCT LIGHT-ON (NCT02147925) compared the effect of liraglutide, sitagliptin and insulin glargine, when added to metformin in diabetic patients, exhibiting statistically significant results, in favor of liraglutide and sitagliptin, regarding body weight, visceral adipose tissue and liver fat content reduction.<sup>36</sup> Liraglutide seems to offer a body-weight loss of 4–6 kg compared to placebo,<sup>37</sup> while the protective effect on cardiovascular outcomes (lower rates of myocardial infarction, stroke and death) is notable,<sup>38</sup> as is the lower rates of diabetes nephropathy development and progression.<sup>39</sup> As shown in the LEADER study (NCT01179048), the secondary composite outcome of persistent doubling of the serum creatinine level, new-onset persistent macroalbuminuria, end-stage renal disease or death due to renal disease occurred significantly less frequently in the treatment group than in the placebo group, with a hazard ratio of 0.78.<sup>39</sup>

Dulaglutide is currently being tested in the single-blind RCT REALIST (NCT03648554) in patients with NASH and DM2. Patients will be randomized to receive either dulaglutide at 1.5 mg in combination with dietary monitoring or dietary monitoring alone for 52 weeks. The primary outcome consists of histological improvement of NASH ( $\geq 2$  points of NASH activity score). An additional study will assess the combined effect of dulaglutide and empagliflozin on noninvasive liver steatosis and fibrosis markers on patients with NAFLD and DM2 (NCT05140694).

Similarly, a recently approved antidiabetic agent of the same drug family, semaglutide, has been assessed in a double-blind phase 2 RCT in 320 patients with NASH without DM2, given subcutaneously once daily, at various doses, for 72 weeks (NCT02970942). Semaglutide proved to be significantly superior to placebo, as far as resolution of NASH was concerned (59% achieved this outcome in the maximum dose group vs. 17% in the placebo group), but without achieving improvement of fibrosis.<sup>40</sup> A dose-dependent pattern of body-weight reduction was observed, with the patients receiving the maximum dose of 0.4mg per day achieving a mean 13% weight loss, while the Placebo group exhibited a mean loss of 1%. Two phase 3 RCTs (STEP1 and STEP 2) regarding overweight or obese patients with diabetes mellitus, proved that semaglutide 2.4mg subcutaneously weekly was superior to placebo, as far as body-weight reduction is concerned,<sup>41,42</sup> while similar results were derived

from another phase 3 trial, comparing oral semaglutide with liraglutide in diabetic overweight patients, where semaglutide achieved significantly greater weight reduction than liraglutide or placebo (NCT02863419-PIIONEER 4).<sup>43</sup> On the same note, semaglutide was deemed superior to dulaglutide in a phase 3 open-label trial (SUSTAIN 7) regarding weight and glycated hemoglobin (HbA1c) reduction in diabetic patients.<sup>44</sup> Due to these promising results, as well as its established cardiovascular safety,<sup>42,45</sup> investigational interest around this agent is intense, with multiple randomized trials exploring its effects on liver fibrosis and steatosis of diabetic and nondiabetic patients, when administered alone, in combination or in comparison with other agents, such as empagliflozin (on diabetics-NCT04639414), efinopegdutide (on diabetics and non-diabetics-NCT04944992), cilofexor and firsocostat (on diabetics and non-diabetics-NCT04971785). The largest one is a phase 3, double-blind trial, by Novo Nordisk, aspiring to recruit 1,200 patients with NASH, with or without DM2, expected to be completed in 2028 (NCT04822181).

## Experimental agents

### ***GLP-1/glucagon receptor (GLP1R/GCR) and GLP-1/glucose-dependent insulinotropic peptide receptor (GLP1R/GIPR) dual agonists***

Various drugs, as noted above, originally created for the treatment of DM2, have shown promise for the treatment of NAFLD and NASH, due to their metabolic effects in lipid and glucose metabolism. Following the same principle, a more recent example is the development of GLP1R/GCR dual agonists,<sup>46</sup> such as MEDI0382 (cotadutide) or oxyntomodulin. The latter, a peptide secreted by the L-cells of the digestive track, has shown greater potency regarding weight loss, fatty acid oxidation, liver steatosis and anti-hyperglycemic activity compared to equal GLP1R agonism in obese mice.<sup>47</sup> MOD-6031, a long-acting, pegylated molecule of oxyntomodulin, has been tested in a phase 1 single-blinded RCT (NCT02692781) on overweight or obese patients, but further investigations have not taken place. On the other hand, MEDI0382 has been more extensively examined in multiple phase 2 RCTs, on diabetic obese patients, exhibiting significant reductions in blood glucose and body weight,<sup>48–50</sup> alone or in combination with other anti-hyperglycemic agents (NCT02548585, NCT03444584, NCT03645421, NCT03244800, NCT03235050, NCT03745937, NCT03596177, NCT04019561). Further evaluation in patients with NAFLD/NASH is warranted, with outcome measures such as steatosis or inflammation reduction. SAR425899, which has yielded early promising results regarding weight and hyperglycemia,<sup>51,52</sup> has undergone a phase 2 study, where it was administered in combination with metformin vs. placebo plus metformin and liraglutide plus metformin, in diabetic obese patients (NCT02973321). Another GLP1R/GCR dual agonist, named BI456906, is going to be tested in a phase 2 RCT in patients with NASH with or without diabetes (NCT04771273). Additionally, other molecules, such as pegapamodutide and efinopegdutide (GLP1R/GCR agonists), among others, are under study, for possible application in NASH and DM2 patients.<sup>53</sup>

Finally, tirzepatide is a GLP1R/GIPR dual agonist, currently being evaluated in phase 3 trials; in diabetic patients, alone or in combination with other agents, such as SGLT2 agonists and metformin, or vs. insulin glargine, insulin degludec or a GLP1R agonist (GLP1Ra) (SURPASS program: NCT03861039, NCT03861052, NCT03954834, NCT04039503, NCT04093752, NCT03987919, NCT03730662, NCT03882970) and in obese but not diabetic patients (SUR-

MOUNT-1, NCT04184622). The primary outcomes are HbA1c and body-weight reduction, respectively, seeking to confirm the impressive results of phase 2 studies,<sup>54</sup> especially in comparison with established treatments such as dulaglutide and semaglutide. This drug, with promising results for NASH-related biomarkers,<sup>55</sup> is under evaluation in a phase 2 study (SYNERGY-NASH, NCT04166773), with the primary outcome being the absence of NASH and no worsening of fibrosis on liver histology after 1 year of treatment. Recruitment addresses patients with or without DM2.

## SGLT2 inhibitors

The SGLT2i family represents anti-hyperglycemic agents acting independently of insulin. Their effectiveness, regarding reduction of hyperglycemia, has been demonstrated in multiple trials and the class is extensively utilized in the treatment of patients with DM2 and cardiovascular disease.<sup>56–59</sup> The currently approved drugs are empagliflozin, dapagliflozin, ertugliflozin, tofogliflozin, and canagliflozin. Inhibition of SGLT2 emerges as a potential approach for NAFLD/NASH treatment both by reduction of hyperglycemia and body weight and, possibly, through reduction of oxidative stress and inflammation.<sup>60–63</sup> Members of the SGLT2i family exhibit cardioprotective effects for patients with atherosclerotic cardiovascular disease. This was shown by the reduced rate of relevant events in large studies, such as the EMPA-REG OUTCOME, among others.<sup>64</sup> Similar results of significant reduction in a composite of cardiovascular death or heart failure-associated hospitalization of patients, with or without diabetes, receiving an SGLT2i, were observed in the EMPEROR-Reduced, EMPEROR-Preserved (empagliflozin) and the DAPA-HF (dapagliflozin) studies.<sup>65–67</sup> Furthermore, these agents have been shown to exhibit renal benefits in patients with chronic kidney disease.<sup>68,69</sup> Therefore, an extra incentive exists for using them in patients suffering from multiple comorbidities.

Regarding NAFLD, empagliflozin, in particular, has shown positive effects regarding liver fat content, as measured by Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) and Control Attenuation Parameter (CAP),<sup>60,61</sup> and liver fibrosis, as measured by liver stiffness determination<sup>63</sup> and various indexes, such as the FIB4 index and NAFLD fibrosis score.<sup>70</sup> Of note is that the benefits of this agent were shown both in diabetic and non-diabetic patients.

The combination of this particular class with thiazolidinediones presents an interesting concept, currently under trial in a phase-4, open-label study, where empagliflozin is being evaluated alone and in conjunction with pioglitazone on diabetic patients, with the primary outcome being the measurement of liver fat content by MRI-PDFF (NCT03646292). It has already been mentioned that empagliflozin is currently being studied as adjunct to GLP1a, as well as tirzepatide.

Another drug of this class, dapagliflozin, is being examined in the DEAN trial, a phase 3 RCT addressing NASH in patients with DM2. A Japanese open-label trial, with dapagliflozin, showed positive effects regarding steatosis and fibrosis, measured with non-invasive techniques, through liver stiffness measurement (especially in patients with stiffness equal or greater than 8 kPa),<sup>71</sup> while similar results were reported from the double-blind EFFECT-II study (NCT02279407).<sup>72</sup> Both studies addressed only patients with DM2.

Lastly, tofogliflozin treatment was associated with reduction of liver steatosis, as measured by MRI-PDFF, in a Japanese randomized open-label trial (ToPiND study) that compared it with pioglitazone treatment in diabetics. Patients that took tofogliflozin exhibited weight and liver fat content reduction, although steatosis improvement was greater in the pioglitazone group.<sup>73</sup> Tofogliflozin was also selected for

**Table 1. Suggested algorithm for medical treatment of diabetic patients with NAFLD/NASH**

1. Baseline CBC, LFTs, INR, Cr, U, HbA1c, liver U/S, FibroScan
2. Avoidance of alcohol
3. Caloric restriction (especially fructose) and aerobic exercise, e.g., by adopting the Mediterranean diet/lifestyle (target body-weight loss: 7–10%)
4. Initiation of drugs
A. GLP1Ra (e.g., liraglutide or semaglutide, especially on patients with CVD) as add-on to metformin, or
B. SGLT2i (e.g., empagliflozin, especially on patients with HF or CVD) as add-on to metformin, or
C. Both GLP1Ra and SGLT2i
D. Pioglitazone as an alternative or add-on, in selected patients, without osteopenia/osteoporosis or CHF
5. Regular follow-up every 3 months until diabetes control and target weight loss achievement
6. Consider enrollment in clinical trial involving dual GLP1R/GCPR or GLP1R/GIPR agonists
7. If target weight is unachievable, consider bariatric surgery for patients with BMI >30 kg/m <sup>2</sup>

BMI, body mass index; CBC, complete blood cell count; CHF, congestive heart failure; Cr, creatinine; CVD, cardiovascular disease; HF, heart failure; INR, international normalized ratio; LFTs, liver function tests; U, urea; U/S, ultrasound.

a phase 4 trial, vs. glimepiride, where the improvement in histological features of NAFLD in diabetic patients will be measured (NCT02649465). Results from this trial have not yet been published.<sup>74</sup> Histologically proven improvement of fibrosis has not yet been presented.

### Conclusions and thoughts for the future of NASH treatment in diabetic patients

The current scarcity of effective treatments for NASH in combination with its rising prevalence worldwide led to an extraordinary interest for related research. An exponentially expanding discovery of lipid metabolism mechanisms contributed to the development of multiple candidate drugs under trial in various populations with NASH. The available approaches focus on metabolic pathway modifiers (e.g., the Farnesoid X-receptor agonists obeticholic acid and cilofexor, the acetyl-CoA carboxylase inhibitor firsocostat, the PPAR agonist elafibranor) on the one hand, and agents with anti-inflammatory and/or antifibrotic action (e.g., the CCR2/5 inhibitor cenicriviroc and the ASK-1 inhibitor selonsertib) on

the other.

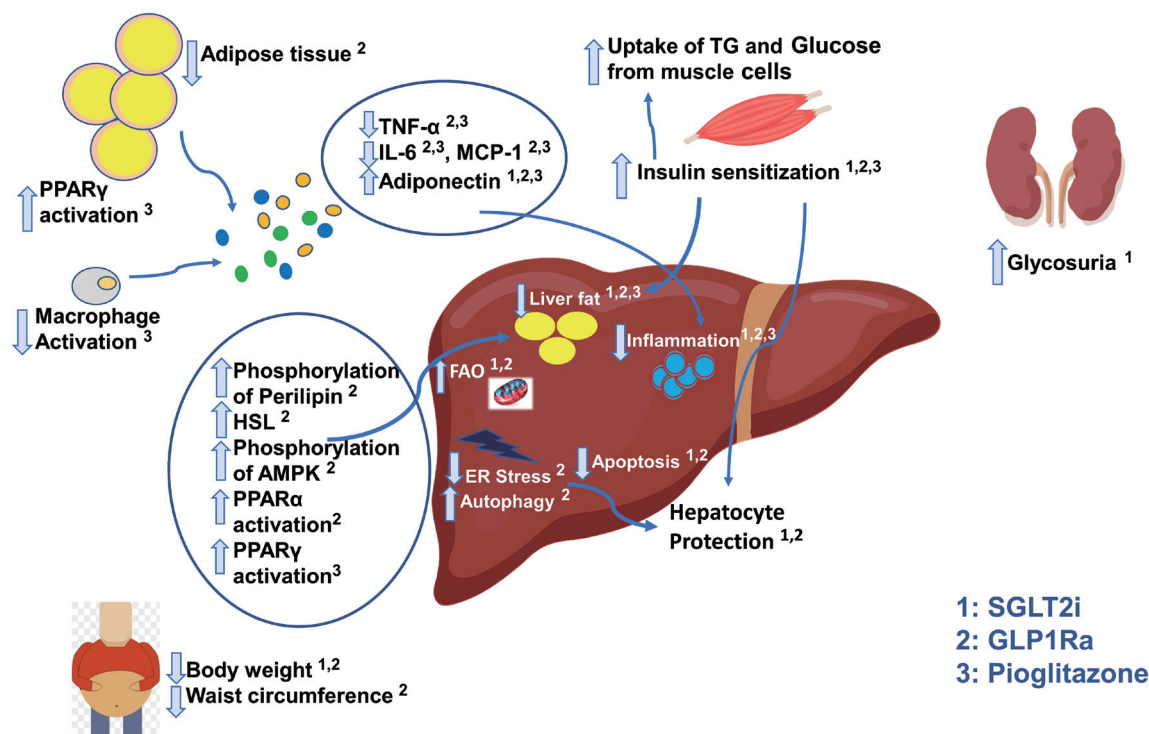
However, none have yet been approved for the treatment of NASH, while many others have already been deemed ineffective (e.g., elafibranor, seladelpar, emricasan, selonsertib and elobixibat). Despite high hopes that new agents will soon be added to the few available drugs for the treatment of NASH, antidiabetic agents remain the sole alternative, apart from vitamin E, offering a multi-target and relatively effective approach to the treatment of patients with both NAFLD/NASH and DM2.

For the time being, the proposed treatment algorithm for patients with DM2 and NAFLD/NASH focuses on caloric restriction, especially those acquired by ingestion of fructose and alcohol, and initiation of aerobic exercise, targeting an overall body-weight reduction of 7–10%. Treatment with pioglitazone is a logical approach in patients with histologically proven NASH; however, it is associated with weight gain and deterioration of congestive heart failure. The emergence of the most effective GLP1Ra and the SGLT2i agents offers a safer approach in tackling patients with NAFLD and DM2 (Tables 1 and 2), through a variety of molecular mechanisms (Fig. 1).<sup>75–78</sup> Treatment with a combination of these agents, as add-on to metformin, along with proper control of cardio-

**Table 2. Proposed and experimental drugs for patients with DM2 and NAFLD/NASH**

Drug	Mechanism of action	Effect as shown from trials so far
Pioglitazone	PPAR $\gamma$ agonist	Reduction of steatosis and inflammation
Saroglitazar	PPAR $\alpha/\gamma$ agonist	Reduction of steatosis and inflammation
Lanifibranor	panPPAR agonist	Reduction of steatosis and inflammation
Empagliflozin	SGLT2i	Reduction of steatosis, possible positive effect on fibrosis
Dapagliflozin	SGLT2i	Reduction of steatosis, possible positive effect on fibrosis
Tofogliflozin	SGLT2i	Reduction of steatosis
Dulaglutide	GLP1a	Under investigation
Liraglutide	GLP1a	Reduction of steatosis and inflammation, possible positive effect on fibrosis
Semaglutide	GLP1a	Reduction of steatosis and inflammation
Experimental agents		
Tirzepatide	GLP1R/GIPR dual agonist	Possible reduction of steatosis and inflammation
MEDI0382	GLP1R/GCR dual agonist	Further evaluation in NASH warranted
BI456906	GLP1R/GCR dual agonist	Further evaluation in NASH warranted





**Fig. 1. Examples of possible mechanisms of NAFLD amelioration through current antidiabetic treatment.**<sup>75-78</sup> AMPK, AMP-activated protein kinase; ER, endoplasmic reticulum; FAO, fatty acid oxidation; HSL, hormone-sensitive lipase; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; TG, triglycerides; TNF-α, tumor necrosis factor-α.

vascular risk factors (e.g., hypertension, hyperlipidemia and smoking), is widely adopted for overweight diabetic patients who are diagnosed with a fatty liver, even more when their cardioprotective effects are taken into account.<sup>79</sup> Efficient control of DM2 along with their effect on body mass index reduction and improvement of liver steatosis and steatohepatitis make them, for nonce, very attractive.

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## Conflict of interest

JK has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2018. ESK has no conflict of interests related to this publication.

## Author contributions

Both authors contributed equally as far as the conception of the article is concerned. Furthermore, the authors participated equally in the relevant research, the drafting of the manuscript and the requested revisions. In conclusion, both authors had an important part in this review and have approved of the final manuscript.

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