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## Review

# Beneficial effect of anti-diabetic drugs for nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder and is associated with various metabolic diseases, including type 2 diabetes mellitus. There are no approved drugs for NAFLD, and the only approved treatment option is weight reduction. As insulin resistance plays an important role in the development of NAFLD, many anti-diabetic drugs have been evaluated for the treatment of NAFLD. Improvement of liver enzymes has been demonstrated by many anti-diabetic drugs, but histological assessment still remains insufficient. Pioglitazone could become the first-line therapy for T2DM patients with NAFLD, based on evidence of histological improvement in patients with biopsy-proven nonalcoholic steatohepatitis (NASH). Liraglutide, another promising alternative, is not yet recommended in patients with NAFLD/NASH due to limited evidence. Therefore, well-designed randomized controlled trials should be performed in the near future to demonstrate if and how anti-diabetic drugs can play a role in the treatment of NAFLD. (**Clin Mol Hepatol 2020;26:430-443**)

**Keywords:** Anti-diabetic drug; Diabetes mellitus; Metabolic diseases; Non-alcoholic fatty liver disease; Treatment

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is associated with liver-related morbidity, including progression to nonalcoholic steato-

hepatitis (NASH), advanced fibrosis, and hepatocellular carcinoma (HCC). NAFLD is the fastest growing cause of HCC in liver transplant candidates,<sup>1</sup> and it is projected that NAFLD is becoming the leading cause of liver transplantation.<sup>2</sup> NAFLD can be coexistent

### Abbreviations:

ALT, alanine aminotransferase; AMPK, adenosine monophosphate-activated protein kinase; AST, aspartate aminotransferase; AWARD, Assessment of Weekly Administration of LY2189265 (dulaglutide) in Diabetes; BMI, body mass index; CV, cardiovascular; DEAN, Dapagliflozin Efficacy and Action in NASH; DPP-4, dipeptidyl peptidase-4; E-LIFT, Effect of Empagliflozin on Liver Fat Content in Patients With Type 2 Diabetes; EFFECT-II, Effects of Omega-3 Carboxylic Acids and Dapagliflozin on Liver Fat Content in Diabetic Patients; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; GLP, glucose-dependent insulinotropic polypeptide; GLP-1 RAs, GLP-1 receptor agonists; GLP-1, glucagon-like peptide-1; HCC, hepatocellular carcinoma; LEAD, Liraglutide Effect and Action in Diabetes; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PDF, proton density fat fraction; PIVENS, Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH; PPAR- $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; RCTs, randomized controlled trials; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor; TZDs, thiazolidinediones

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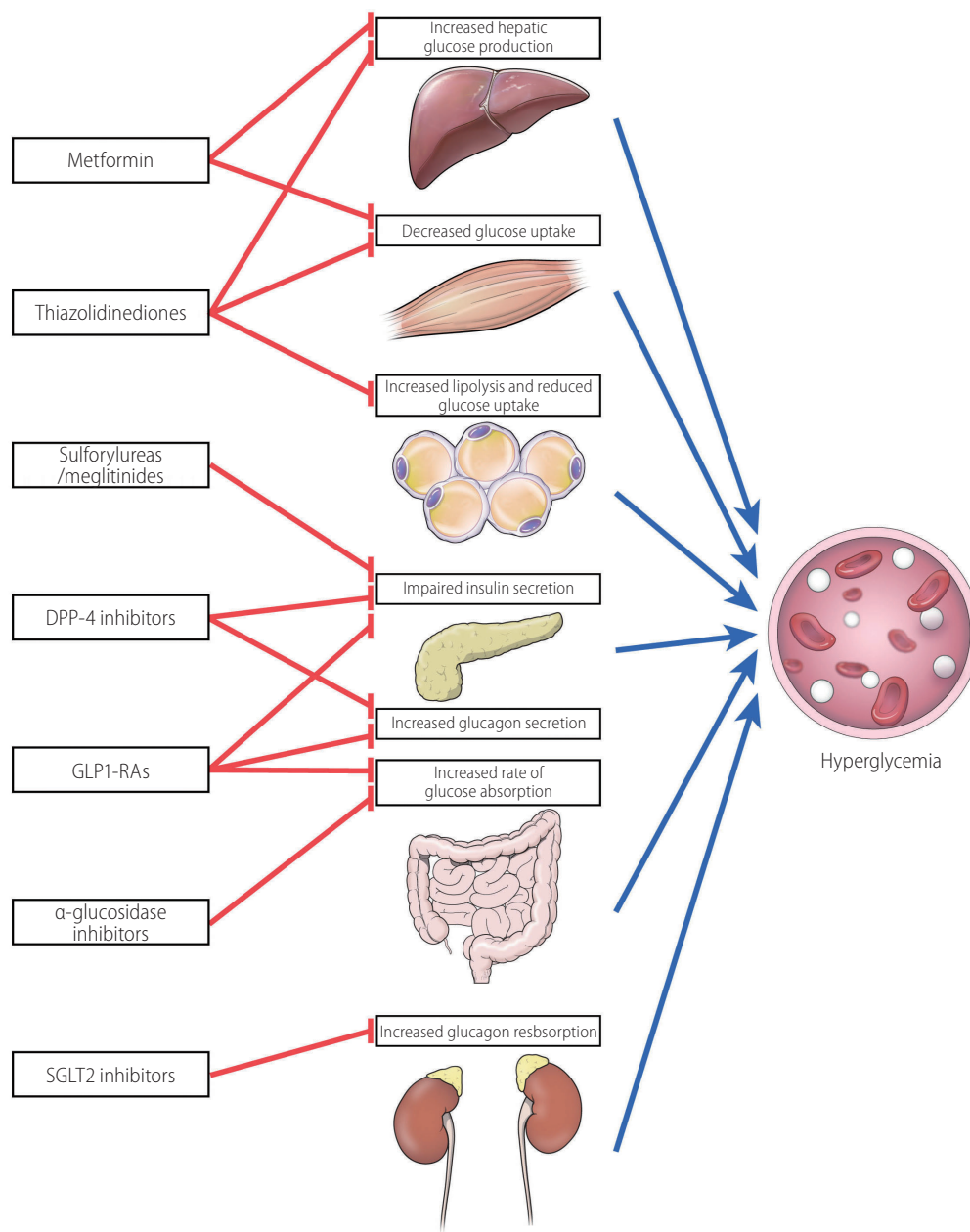
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with type 2 diabetes mellitus (T2DM), and this combination results in the undesirable consequence of cardiovascular (CV) events, which underscores the need for lifestyle modification in the management of NAFLD regardless of diabetes.<sup>3,4</sup> NAFLD is the one of the most common liver disorders, affecting approximately 20–40% of the population worldwide, with different burdens according to age, sex, ethnicity, and diagnostic tools.<sup>5,6</sup> The presence of diabetes is closely associated with the severity of NAFLD,

progression to NASH, advanced fibrosis, cirrhosis, and even HCC,<sup>7-9</sup> independently of liver enzymes.<sup>10,11</sup> Studies on South Korean patients with T2DM who underwent ultrasonography in a university and a private clinic-based diabetes care facility showed 63.3% and 72.7% prevalence of NAFLD, respectively.<sup>12,13</sup> A recent meta-analysis reported that the global prevalence of NAFLD and NASH among patients with T2DM is 55.5% and 37.3%, respectively.<sup>14</sup> The European Association for the Study of the Liver, the European



**Figure 1.** Mechanism of action and effects of anti-diabetic drugs on glucose metabolism. DPP-4, dipeptidyl peptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2.

Association for the Study of Diabetes, and the European Association for the Study of Obesity, in their joint clinical practice guidelines for the management of NAFLD recommend screening for NAFLD in T2DM patients and vice versa.<sup>15</sup> Although weight reduction is the cornerstone of therapy among the various treatments for NAFLD,<sup>16</sup> pharmacotherapy should be administered since sufficient weight reduction can be difficult to achieve and maintain. In subjects with T2DM and NAFLD, management with anti-diabetic drugs is more effective than lifestyle modification in controlling glucose level (Fig. 1). Moreover, lifestyle changes, together with anti-diabetic medications, are likely to have an additive effect on reducing the risk factors associated with CV diseases, decreasing hepatic fat accumulation, and delaying progression to NASH and fibrosis. Although there is no approved drug of choice for managing NAFLD, many anti-diabetic drugs have been tested in patients with NAFLD due to the shared epidemiological and pathophysiological features between NAFLD and T2DM. The aim of this review is to summarize the beneficial effects of anti-diabetic drugs for NAFLD.

## METFORMIN

Metformin has been derived from the guanidine-rich *Galega officinalis* (goat's rue or French lilac), and is a kind of general insulin sensitizer.<sup>17</sup> Although its molecular mechanisms of action are complex and not completely understood, metformin has been shown to act via both adenosine monophosphate-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms, by the inhibition of mitochondrial respiration but also perhaps by the inhibition of mitochondrial glycerophosphate dehydrogenase and a mechanism involving lysosomes at the molecular level (Table 1).<sup>18</sup> Physiologically, metformin reduces blood glucose level by dominantly inhibiting hepatic glucose production via AMPK activation, stimulation of muscle glucose uptake, and decrease of intestinal glucose absorption.<sup>18</sup> All current guidelines recommend metformin as the first-line agent for T2DM.<sup>19,20</sup>

Since metformin improves insulin resistance, which is the major pathogenesis of NAFLD, it has been widely tested in both animal NAFLD models and human clinical trials. In the insulin-resistant *ob/ob* mouse model with hepatic steatosis, metformin improved fatty liver disease and reversed the hepatomegaly, steatosis, and alanine aminotransferase (ALT) level by decreasing the expression of tumor necrosis factor-alpha (TNF- $\alpha$ ) and TNF-inducible factors that promote hepatic lipid accumulation and adenosine triphos-

phate depletion<sup>21</sup> or autophagy activation.<sup>22</sup> In a pilot study of 20 non-diabetic patients with NAFLD, metformin treatment for 4 months reduced liver enzymes and improved insulin sensitivity and liver volume as detected by ultrasound.<sup>23</sup> However, among well-designed randomized controlled trials (RCTs), the TONIC trial, which recruited 173 non-diabetic patients aged 8–17 years with biopsy-proven NAFLD and persistent increase in ALT, did not demonstrate reduced ALT level and improved liver histology with metformin compared to placebo.<sup>24</sup> To date, meta-analyses have shown that metformin could improve liver function, insulin resistance, and body mass index (BMI) to some extent, but does not impact histological response in NAFLD patients.<sup>25–27</sup> In this regard, current guidelines do not recommend metformin for treating NASH in adult patients.<sup>15,28</sup> Despite the lack of known benefits to treat NAFLD, metformin aids in reducing CV risks related to diabetes. Furthermore, a meta-analysis of case-control studies found that metformin use was associated with a reduced risk of HCC, which is the final sequence of NAFLD, and it may be a relevant factor in preventing HCC in diabetic patients.<sup>29</sup> Based on these studies, metformin could be beneficial for NAFLD patients with T2DM.

## THIAZOLIDINEDIONES

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) agonists that act as insulin sensitizers on adipose tissue, muscle, and liver. TZDs improve insulin and glucose parameters, modulate adipose tissue distribution while decreasing visceral fat and increasing subcutaneous fat, and reduce lipotoxicity in the liver. In addition, TZDs have demonstrated anti-inflammatory and antioxidant properties.

### Pioglitazone

Pioglitazone was widely evaluated for the treatment of NAFLD. Many RCTs have shown histological improvement in steatosis and lobular inflammation after pioglitazone treatment. In a pilot study, pioglitazone treatment for 48 weeks showed histological improvement (steatosis, parenchymal inflammation, cellular injury, and Mallory bodies) in 18 non-diabetic patients with biopsy-proven NASH.<sup>30</sup> In 55 patients with impaired glucose tolerance or T2DM (mean HbA1c 6.2%), pioglitazone treatment (45 mg daily) with a hypocaloric diet for 6 months resulted in improvements in insulin sensitivity, ALT levels, steatosis, ballooning necrosis, and inflam-

**Table 1.** Molecular mechanisms of anti-diabetic drugs and their effects on nonalcoholic fatty liver disease

Anti-diabetic drugs	Molecular mechanisms	Weight change	Effects on NAFLD
Metformin	<p>AMPK-dependent mechanisms</p> <ul style="list-style-type: none"> <li>- Inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity (via effects on fat metabolism), and lowering cAMP, and thereby reducing the expression of gluconeogenic enzymes</li> </ul> <p>AMPK-independent mechanisms</p> <ul style="list-style-type: none"> <li>- Inhibits fructose-1,6-bisphosphatase by AMP</li> </ul>	Neutral (potential modest loss)	- Improvement of liver enzymes and liver fat content
Thiazolidinediones	<p>Activation of the transcription factor PPAR-<math>\gamma</math> involved in the transcription of genes regulating glucose and fat metabolism</p> <ul style="list-style-type: none"> <li>→ When activated by a ligand, PPAR-<math>\gamma</math> binds to the retinoid X receptor (RXR) to form a heterodimer.</li> <li>→ This binds to DNA to regulate the genetic transcription and translation of various proteins involved in cellular differentiation as well as glucose and lipid metabolism.</li> </ul>	Gain	<p>Pioglitazone</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> <li>- Some improvement on histological features of NASH</li> </ul> <p>Rosiglitazone and lobeglitazone</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> </ul>
GLP1-RAs	<p>Binding of GLP-1 receptor (pancreatic <math>\beta</math>-cells)</p> <ul style="list-style-type: none"> <li>→ Elicits its effects via acute elevation in cAMP levels</li> <li>→ Subsequent protein kinase(s) activation</li> <li>→ Elevated <math>Ca^{2+}</math> and ATP</li> <li>→ Stimulates insulin secretion</li> </ul>	Loss	<p>Liraglutide</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> <li>- Potential beneficial effect on histological features of NASH</li> </ul> <p>Exenatide and dulaglutide</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> </ul> <p>Lixisenatide and semaglutide</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes</li> </ul>
DPP-4 inhibitors	<p>Competitively inhibits the enzyme DPP-4; this enzyme breaks down the incretin GLP-1 and GIP, which are released in response to a meal (DPP-4 is a 766 amino acid amino peptidase, and is a tetramer with each subunit consisting of two domains: N-terminal <math>\beta</math>-propeller domain &amp; C-terminal catalytic domain).</p>	Neutral	<p>Sitagliptin and vildagliptin</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> </ul>
SGLT2 inhibitors	<p>Inhibits SGLT2 action and causes reduction in renal glucose reabsorption (SGLT2 is expressed in the luminal membrane of the proximal tubule [mainly S1 and S2 segment]. It reabsorbs ~97% of filtered glucose under normoglycemic conditions).</p>	Loss	<p>Dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, and luseogliflozin</p> <ul style="list-style-type: none"> <li>- Improvement of liver enzymes and liver fat content</li> </ul>
$\alpha$ -glucosidase inhibitors	<p>Inhibits intestinal <math>\alpha</math>-glucosidase (Enzyme <math>\alpha</math>-glucosidase is located in the brush border of the enterocytes of the jejunum in the small intestine, and happens to be a key enzyme in carbohydrate synthesis and breakdown. It is an exo-type carbohydrase, which cleaves glycosidic bonds in complex carbohydrate to release absorbable monosaccharides).</p>	Neutral	No study in human
Sulfonylureas	<p>Binds to sulfonylurea receptors and causes closing of <math>K_{ATP}</math> channels on <math>\beta</math>-cell plasma membranes, influx of <math>Ca^{2+}</math>, and stimulation of insulin release</p>	Gain	No study in human
Meglitinides	<p>Binds to sulfonylurea receptors, but at different binding sites to sulfonylurea causes closing of <math>K_{ATP}</math> channels on b-cell plasma membranes, influx of <math>Ca^{2+}</math>, and stimulation of insulin release</p>	Gain	No study in human

NAFLD, nonalcoholic fatty liver disease; AMPK, adenosine monophosphate-activated protein kinase; cAMP, cyclic adenosine monophosphate; PPAR- $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; NASH, nonalcoholic steatohepatitis; ATP, adenosine triphosphate; GLP1-RAs, GLP-1 receptor agonists; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; SGLT2, sodium-glucose cotransporter 2.

mation of liver biopsy-confirmed NASH patients.<sup>31</sup> Meta-analyses agreed with the beneficial effects of pioglitazone on lobular inflammation.<sup>26,32,33</sup> However, there were conflicting results for hepatic fibrosis. The landmark phase 3 PIVENS (Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with NASH) trial was conducted as a multicenter, randomized, placebo-controlled, double-blind clinical trial of pioglitazone compared to vitamin E in the treatment of NASH, by enrolling 247 adults without diabetes who had biopsy-confirmed NASH.<sup>34</sup> After a 96-week treatment period, 45 mg/day pioglitazone treatment was associated with reductions in serum ALT levels ( $P<0.001$ ), hepatic steatosis ( $P<0.001$ ), and lobular inflammation ( $P=0.004$ ), but there was no improvement in fibrosis scores. On the contrary, another RCT was conducted in 101 patients with biopsy-proven NASH to investigate whether 45 mg/day pioglitazone treatment for 18 months could achieve the primary outcome with an improvement of at least two points in NAFLD activity score (NAS) and no worsening of fibrosis.<sup>35</sup> Pioglitazone treatment showed 58% achievement in the primary outcome and 51% resolution of NASH ( $P<0.001$  for each). Pioglitazone treatment also was associated with improvement in individual histologic scores, including fibrosis score ( $P=0.039$ ); reduced hepatic triglyceride content from 19% to 7% ( $P<0.001$ ); and improved adipose tissue, hepatic, and muscle insulin sensitivity ( $P<0.001$  vs. placebo for all). In advanced fibrosis (stages F3–F4), meta-analysis showed that pioglitazone use improved fibrosis in patients with NASH and T2DM, as well as in patients without diabetes.<sup>36</sup> Therefore, pioglitazone could be a first-line therapy for patients with NASH and T2DM. However, due to limited evidence, pioglitazone should be cautiously used in subjects without T2DM to treat NAFLD without biopsy-proven NASH.<sup>28</sup> It is important to remember that weight gain, fluid retention, and bone loss are common side effects of pioglitazone treatment. In this regard, the risks and benefits should be considered before starting therapy.

### Rosiglitazone

Rosiglitazone was once a popular TZD, but it was withdrawn from some markets in 2010 due to a high risk of myocardial infarction. In many RCTs, rosiglitazone demonstrated a biochemical improvement in liver enzymes and glycemic control in both diabetic and nondiabetic patients with NAFLD, whereas evidence of histological improvement was less clear.<sup>37</sup> Although no firm association was found after an extensive review of all evidence by the United States Food and Drug Administration, rosiglitazone is no

longer available in most countries, and its prescribing remains severely restricted in the United States.

### Lobeglitazone

Lobeglitazone is a novel PPAR- $\gamma$  agonist developed in South Korea, and it has been used for patients with T2DM in several countries. It exhibited similar beneficial effects to other TZDs, such as glucose-lowering, anti-inflammatory, and antioxidant actions.<sup>38</sup> Regarding NAFLD, lobeglitazone treatment has limited evidence. In high-fat diet-induced obese mice, lobeglitazone decreased hepatic steatosis, attenuated lipogenesis-induced oxidative liver injury, and reversed hepatic lipid dysregulation.<sup>39,40</sup> In a multicenter, prospective, open-label, exploratory clinical trial, 43 patients with NAFLD and T2DM who were treated daily with 0.5 mg lobeglitazone for 24 weeks experienced improved liver enzymes and ameliorated hepatic fat content, as assessed by vibration-controlled transient elastography, with controlled attenuation parameters.<sup>41</sup> Recommendations for the use of lobeglitazone are similar to those of pioglitazone.

### GLUCAGON-LIKE PEPTIDE-1 (GLP-1) RECEPTOR AGONISTS

GLP-1 is released from intestinal epithelial L-cells in response to meals and secreted into circulation.<sup>42</sup> Circulating active GLP-1 induces insulin secretion in pancreatic  $\beta$ -cells and reduces glucagon secretion in pancreatic  $\alpha$ -cells in a glucose-dependent manner. Since GLP-1 has a very short half-life, GLP-1 receptor agonists (GLP-1 RAs) were developed, and they showed a glucose-lowering effect by stimulating GLP-1 receptors. In addition to the glucose-lowering effect, GLP-1 RAs decrease appetite, delay gastric emptying, and induce weight loss. Therefore, GLP-1 RAs are an attractive candidate for the treatment of NAFLD, as they can reduce weight and enhance insulin action. However, according to the American Association for the Study of Liver Disease 2018 practice guideline, it is premature to consider GLP-1 RA for the treatment of liver disease in patients with NAFLD or NASH, due to limited evidence.<sup>28</sup> However, several meta-analyses showed that GLP-1 RAs have additional roles in reducing the risk of major adverse CV events and CV deaths in high-risk patients with T2DM, especially in the Asian population.<sup>43</sup>

## Exenatide

Exenatide is a synthetic form of a hormone isolated from Gila monster saliva, and the first agent of GLP-1 RA to be approved for the treatment of T2DM. In an observational pilot study, exenatide showed more qualitative ultrasonographic improvements in patients with NAFLD and T2DM compared with gliclazide, pioglitazone, sitagliptin, and liraglutide, although these differences were not significant.<sup>44</sup> Several RCTs have found that exenatide alone or combined with other anti-diabetic drugs reduced liver enzymes, hepatic content, hepatic triglycerides, and epicardial fat.<sup>45-48</sup> However, no well-designed placebo-controlled, double-blind study with histology-proven outcomes has evaluated the effect of exenatide on NAFLD.

## Liraglutide

Liraglutide is a long-acting GLP-1 RA, and is used for T2DM therapy at doses of up to 1.8 mg daily. It has also been approved for obesity management at the dose of 3 mg daily, and has been included in the largest number of studies on NAFLD among the GLP-1 RAs. Many studies showed that liraglutide reduced liver enzymes.<sup>49,50</sup> In a meta-analysis of six RCTs conducted by the "Liraglutide Effect and Action in Diabetes (LEAD)" program, 26 weeks of liraglutide treatment (1.8 mg/day) improved ALT and hepatic steatosis in 4,442 patients with T2DM.<sup>49</sup> However, these effects were likely mediated by weight loss and glycemic control, since they were lost after adjustment for weight reduction and HbA1c. In a prospective, single-center study (LIRA-NAFLD), liraglutide treatment (1.2 mg/day) for 6 months decreased liver fat content, as measured by proton magnetic resonance spectroscopy (MRS), in 68 patients with uncontrolled T2DM.<sup>51</sup> The study also concluded that the effect of liver fat content reduction was mainly driven by body weight reduction. In a randomized trial which defined NAFLD as liver fat fraction >5% on magnetic resonance imaging (MRI), liraglutide (3 mg/day) improved hepatic steatosis and hepatocellular apoptosis after 26 weeks in 30 obese patients; however, the benefits were not sustained after discontinuation, in contrast to lifestyle modification.<sup>52</sup> Histological features were evaluated in two trials, LEAN (Liraglutide Safety and Efficacy in Patients With Non-Alcoholic Steatohepatitis) and LEAN-J (Liraglutide Effects in Non-Alcoholic Steatohepatitis and Non-Alcoholic Fatty Liver Disease With Glucose Intolerance in Japanese Patients). In the LEAN study, which was a randomized, placebo-controlled phase 2 trial consisting of 52 patients with biopsy-proven

NASH, 48 weeks of liraglutide (1.8 mg daily) was reported to resolve biopsy-proven NASH in nine out of 23 patients, whereas this was observed in only two out of 22 patients in the placebo group.<sup>53</sup> In the LEAN-J study, which enrolled 19 Japanese patients with biopsy-proven NASH, repeated liver biopsy was performed in 10 subjects who continued liraglutide therapy (0.9 mg/day) for 96 weeks. Seven subjects showed improved histological inflammation, six showed reduced liver fibrosis, and eight had improved NAS.<sup>54</sup> As expected, in both LEAN and LEAN-J studies, liraglutide was associated with significant reductions in body weight and BMI compared with placebo. However, their effects for NASH are not solely explained by the improvements in weight and metabolic phenotype. Liraglutide seems to be the most promising GLP-1 RA for NAFLD/NASH prevention and/or treatment, although large RCTs are needed to confirm its effects.

## Lixisenatide

Similar to exenatide, lixisenatide is based on exendin-4 with an addition of six lysines and deletion of a proline at the C-terminus. To date, there has been no RCT on lixisenatide for patients with NAFLD. In a meta-analysis of 12 RCTs on lixisenatide versus placebo and three RCTs with the active comparators, lixisenatide increased the proportion of patients with normalization of ALT compared with placebo or active comparators.<sup>55</sup>

## Dulaglutide

Dulaglutide is a once-weekly GLP-1 RA and has some advantages, such as weekly injection, disposable and prefilled devices, as well as safety profiles similar to those of other GLP-1 RAs. The effect of dulaglutide on NAFLD is not well-known, as only a few studies have been conducted. In a *post hoc* analysis of AWARD (Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes) trials, dulaglutide (1.5 mg once weekly) improved liver enzymes compared with placebo in a pattern consistent with liver fat reduction.<sup>56</sup> In a Japanese retrospective study, dulaglutide (0.75 mg once weekly) significantly improved liver enzymes and liver stiffness, as measured by transient elastography after 12 weeks of therapy in T2DM patients with biopsy-proven NASH.<sup>57</sup>

## Semaglutide

Semaglutide is a human GLP-1 RA and has two forms, a once-weekly injectable agent and a once-daily oral agent. Currently,

there is limited evidence regarding the effect of semaglutide on NAFLD. In a sub-analysis of the 104-week CV outcomes trial of T2DM (semaglutide 0.5 or 1.0 mg/week) and a 52-week weight management trial (semaglutide 0.05–0.4 mg/day), semaglutide significantly reduced ALT in subjects with T2DM.<sup>58</sup> To investigate the safety and efficacy of semaglutide (once-daily subcutaneous injection) on NASH (stage 1–3 fibrosis), a phase 2, randomized, double-blind, placebo-controlled trial (SEMA-NASH study, NCT02970942) was initiated, the final results of which are currently pending. However, there is no existing data regarding the effects of an oral form of semaglutide on NAFLD.

### Tirzepatide

Tirzepatide is a novel unimolecular, multi-functional peptide that combines GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist activities. GIP is an incretin secreted from K cells in the upper small intestine in response to food. Unlike GLP-1, GIP is both glucagonotropic and insulinotropic in a glucose-dependent manner, dose-dependently stimulating glucagon secretion under hypoglycemic conditions and insulin under hyperglycemic conditions.<sup>59</sup> The number of studies conducted to demonstrate the effect of tirzepatide on NAFLD is very limited. Patients with T2DM received either once weekly tirzepatide (1, 5, 10, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. In *post hoc* analyses, significant ( $P < 0.05$ ) reductions from baseline in ALT (all groups), aspartate aminotransferase (AST) (all groups except tirzepatide 10 mg), keratin-18 (tirzepatide 5, 10, 15 mg), and procollagen III (tirzepatide 15 mg) were observed at 26 weeks.<sup>60</sup> Although one study cannot provide sufficient evidence of efficacy for tirzepatide in subjects with NASH, weight reduction along with changes in NASH biomarker suggest the need for further trials of tirzepatide in subjects with NASH.

### DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

DPP-4 inhibitors demonstrate a glucose-lowering effect by increasing the incretin effect through the delay of quick inactivation of GLP-1 in plasma. Several studies found that serum DPP-4 level was elevated in NASH patients, and also correlated with hepatic steatosis, fibrosis, and hepatocyte apoptosis.<sup>61,62</sup> These findings support the notion that DPP-4 inhibitors may improve the histological features of NAFLD/NASH; however, there has been only a few studies demonstrating the significant efficacy of DPP-4 inhibi-

tors in patients with NAFLD. DPP-4 inhibitors are not yet believed to have a beneficial effect on NAFLD.

### Sitagliptin

As a first-in-class DPP-4 inhibitor, sitagliptin has been most widely studied to evaluate its efficacy on NAFLD/NASH. However, sitagliptin has shown conflicting evidence regarding its effects on NAFLD. Sitagliptin treatment (50 mg/day) for 4 months improved liver enzymes in patients with NAFLD ( $n=30$ ) diagnosed by ultrasound.<sup>63</sup> In an observational pilot study of 15 T2DM patients with biopsy-proven NASH, sitagliptin treatment (100 mg/day) for 1 year ameliorated liver enzymes, hepatocyte ballooning, and NASH scores.<sup>64</sup> In a prospective, 24-week, single-center, open-label comparative study that enrolled 20 Japanese patients with T2DM and NAFLD, sitagliptin significantly reduced intrahepatic lipid content, as assessed by 1) H-MRS, and total body fat mass after 24 weeks.<sup>65</sup> On the other hand, in 44 patients with T2DM and biopsy-proven NAFLD, sitagliptin treatment (50 mg/day) for 12 months did not reduce liver enzymes, although HbA1c was reduced by 0.7%.<sup>66</sup> In a RCT that enrolled 50 NAFLD patients, liver enzymes and magnetic resonance elastography-derived liver stiffness were not improved by 24 weeks of sitagliptin treatment (100 mg/day).<sup>67</sup> Moreover, in many existing studies, sitagliptin treatment failed to produce any reduction in liver fat content and liver enzymes.<sup>68,69</sup> Based on previous clinical trials, sitagliptin is not yet believed to have a beneficial effect on NAFLD.

### Vildagliptin

A few trials have demonstrated that vildagliptin has an effect on NAFLD. In 44 patients with T2DM and hepatic steatosis, vildagliptin treatment (50 mg twice daily) for 6 months decreased liver enzymes and intrahepatic triglyceride content, as assessed by MRI.<sup>70</sup> In a RCT conducted in Pakistan, vildagliptin (50 mg twice daily) for 12 weeks improved liver enzymes and steatosis grading, as assessed by ultrasound.<sup>71</sup>

### Other DPP-4 inhibitors

Not many studies have been conducted to evaluate the efficacy of other DPP-4 inhibitors, including gemigliptin, alogliptin, teneligliptin, saxagliptin, anagliptin, and linagliptin, on NAFLD. In an animal model, many DPP-4 inhibitors, including gemigliptin, alogliptin, teneligliptin, and linagliptin, were able to alleviate hepatic

steatosis and hepatic lipogenesis.<sup>72-75</sup> In human clinical trials, 12 months of alogliptin treatment (25 mg/day) in NAFLD patients with T2DM yielded a decrease in NAFLD progression.<sup>76</sup> With saxagliptin, liver enzymes and hepatic steatosis were improved after treatment for 24 weeks in 95 patients with NAFLD and T2DM.<sup>77</sup>

## **SODIUM-GLUCOSE COTRANSPORTER 2 (SGLT2) INHIBITORS**

SGLT2 is responsible for a majority of the glucose reabsorption that occurs in proximal renal tubules. SGLT2 inhibitors are a novel class of anti-diabetic drugs that improve hyperglycemia by inhibiting urinary glucose reabsorption from the kidney.<sup>78</sup> In addition to a glucose-lowering effect, SGLT2 inhibitors exert several cardiorenal and metabolic benefits, including weight loss; therefore, they are thought to be promising therapeutic agents for patients with NAFLD.<sup>79</sup> Although beneficial effects continue to be reported, SGLT2 inhibitors are not yet generally recommended for the treatment of NAFLD.

### **Dapagliflozin**

Many small-scale studies have shown that dapagliflozin treatment improved liver enzymes, liver fat content, or liver stiffness in patients with NAFLD.<sup>80,81</sup> In a single-arm, nonrandomized, open-label study, dapagliflozin treatment (5 mg/day) for 24 weeks reduced liver enzymes and metabolic parameters in 11 patients with biopsy-proven NASH.<sup>82</sup> The Effects of Omega-3 Carboxylic Acids and Dapagliflozin on Liver Fat Content in Diabetic Patients (EFFECT-II) study found that dapagliflozin (10 mg/day) combined with omega-3 carboxylic acids reduced liver fat content, as assessed by MRI-derived proton density fat fraction (MRI-PDFF), and dapagliflozin monotherapy reduced all measured hepatocyte injury markers in patients with T2DM and NAFLD.<sup>83</sup> In a randomized, active-controlled, open-label trial, dapagliflozin treatment (5 mg/day) for 24 weeks improved liver enzymes, steatosis, and fibrosis, as measured by transient elastography (FibroScan), in 57 patients with T2DM and NAFLD, as defined by ultrasound.<sup>84</sup> Furthermore, the Dapagliflozin Efficacy and Action in NASH (DEAN) study (NCT03723252) is still ongoing, with the objective to assess the efficacy and safety of dapagliflozin for improving biopsy-proven NASH and metabolic risk factors. This study is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial, and will enroll 100 participants until November 2021.

### **Canagliflozin**

Several studies have evaluated the efficacy of canagliflozin on NAFLD.<sup>85-88</sup> A meta-analysis of 11 trials with a total of 6,745 T2DM patients reported that canagliflozin significantly decreased liver enzymes.<sup>85</sup> In a RCT, canagliflozin (300 mg/day) for 24 weeks reduced liver enzymes and intrahepatic triglyceride content, as measured by proton-MRS, in 37 patients with T2DM and NAFLD.<sup>86</sup> Likewise, in a small (n=20), prospective, non-randomized, open-label, single-arm study, canagliflozin (100 mg daily) treatment for 12 months significantly reduced hepatic fat fraction, as measured by MRI, in patients with T2DM and NAFLD.<sup>87</sup> In nine patients with T2DM and biopsy-proven NASH, canagliflozin treatment (100 mg/day) for 24 weeks improved the histological features of NASH, including steatosis, lobular inflammation, ballooning, and fibrosis stage.<sup>88</sup>

### **Empagliflozin**

Only a few studies have evaluated the efficacy of empagliflozin on NAFLD. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin reduced liver enzymes (ALT>AST) in patients with T2DM.<sup>89</sup> A single-center, retrospective, observational study found that empagliflozin (5 mg/day) for 6 months significantly improved liver enzymes in 46 patients with T2DM.<sup>90</sup> The Effect of Empagliflozin on Liver Fat Content in Patients With Type 2 Diabetes (E-LIFT) trial, an investigator-initiated, prospective, open-label, randomized clinical study involving 50 patients with T2DM and NAFLD, showed that empagliflozin (10 mg daily) for 20 weeks significantly reduced liver enzymes and liver fat, as measured by MRI-PDFF.<sup>91</sup>

### **Ipragliflozin**

Ipragliflozin is used in several countries, including South Korea and Japan. In 43 patients with T2DM and NAFLD, ipragliflozin treatment for 24 weeks (50 mg daily) reduced liver enzymes.<sup>92</sup> Despite the small number of studies, ipragliflozin showed similar beneficial effects to pioglitazone on NAFLD. The open-label, randomized, active-controlled trial compared the efficacy of ipragliflozin (50 mg daily) versus pioglitazone (15–30 mg daily) in 66 patients with T2DM and NAFLD. At week 24, ipragliflozin exerted equally beneficial effects on NAFLD compared with pioglitazone.<sup>93</sup> Furthermore, ipragliflozin (50 mg daily) treatment for 24 weeks



significantly ameliorated liver steatosis and reduced excessive fat in 44 euglycemic patients with T2DM and NAFLD who were taking metformin and pioglitazone at baseline.<sup>94</sup>

### Other SGLT2 inhibitors

Several pre-clinical studies conducted with animal experimental models have shown that luseogliflozin and remogliflozin could be associated with improvement in hepatic steatosis.<sup>95,96</sup> In 32 patients with T2DM and NAFLD diagnosed by abdominal computed tomography or ultrasound, luseogliflozin treatment (2.5 mg daily) for 6 months reduced liver fat deposition compared to metformin.<sup>97</sup> A prospective, single-arm trial (LEAD trial) showed that luseogliflozin treatment (2.5 mg daily) for 24 weeks reduced hepatic fat content, as evaluated by MRI, in patients with T2DM and NAFLD.<sup>98</sup>

### $\alpha$ -GLUCOSIDASE INHIBITORS

$\alpha$ -glucosidase inhibitors, including acarbose, miglitol, and voglibose, are oral glucose-lowering agents that specifically inhibit  $\alpha$ -glucosidases in the brush border of the small intestine to prevent digestion of carbohydrates, such as starch and sugar. To date, only a limited number of studies have investigated the effect of  $\alpha$ -glucosidase inhibitors on NAFLD. In a mouse model of NAFLD, combination therapy with ezetimibe and acarbose for 24 weeks improved the histopathological findings.<sup>99</sup> Administration of miglitol (150 mg/day) for 12 months in 17 T2DM patients with histologically-confirmed NASH showed significantly decreased BMI and serum ALT.<sup>100</sup> Post-treatment liver biopsy of 11 patients revealed significant improvements in steatosis, lobular inflammation, portal inflammation scores, and NAFLD activity scores (from  $5.5 \pm 1.5$  to  $3.9 \pm 1.4$ ,  $P=0.012$ ). However, fibrosis and hepatocyte ballooning scores remained unchanged.

### SULFONYLUREAS AND MEGLITINIDES

Insulin resistance with hyperinsulinemia might be deleterious to the liver and associated with high intrahepatic triglyceride content.<sup>101</sup> Sulfonylureas and meglitinides are insulin secretagogues that lower glucose level by enhancing insulin secretion from pancreatic  $\beta$ -cells. Metformin and pioglitazone may be safely used in patients with NAFLD, whereas sulfonylureas and insulin itself

have been associated with NAFLD progression and adverse outcomes.<sup>102</sup> This class of drugs has rarely been studied regarding its impact on NAFLD.

### DRUGS UNDER INVESTIGATION

Various types of promising therapeutic targets for T2DM are under investigation. Protein tyrosine phosphatase 1B inhibitor, free fatty acid receptors 1, aldose reductase, glycogen phosphorylase, fructose-1, 6-bisphosphatase, glucagon receptor antagonist, and phosphoenolpyruvate carboxykinase are currently being assessed.<sup>103</sup> Among them, drugs that show weight reduction can be effective in the treatment of NAFLD. Further studies are warranted to evaluate the efficacy of novel anti-diabetic drugs for NAFLD.

### CONCLUSIONS

To this day, the only approved treatment option for NAFLD is weight reduction, although much progress has been made in the understanding, diagnosis, and treatment of NAFLD over past decades. Since T2DM and NAFLD have a partly shared pathophysiology that includes insulin resistance even genetically,<sup>104-106</sup> anti-diabetic drugs are a good candidate for the treatment of NAFLD. Most anti-diabetic drugs showed an improvement in liver enzymes, but there is limited evidence of any beneficial effect on histological outcomes. Among anti-diabetic drugs, pioglitazone has the strongest evidence for a role in NAFLD treatment, and it has shown improvement in liver histology for patients with biopsy-proven NASH. Liraglutide has also shown promising evidence, although it is premature to consider a GLP-1 RA for the treatment of liver disease in patients with NAFLD. Further well-designed RCTs should be conducted to determine the role of these anti-diabetic drugs in NAFLD treatment.

### Authors' contribution

Kyung-Soo Kim and Byung-Wan Lee contributed to the literature review and manuscript preparation.

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## Conflicts of Interest

The authors have no conflicts to disclose.

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