

The Effects of Hypoglycemic Agents on Non-alcoholic Fatty Liver Disease: Focused on Sodium-Glucose Cotransporter 2 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists

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The only known, effective intervention for non-alcoholic fatty liver disease (NAFLD) is weight loss, and there is no approved pharmacotherapy. Recently, new hypoglycemic agents, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), and their effects on NAFLD have received substantial interest. Herein, we review the currently available human studies regarding the effects of SGLT2 inhibitors and GLP-1RAs on NAFLD/non-alcoholic steatohepatitis in patients with type 2 diabetes mellitus, and we describe the possible mechanisms explaining the positive effects of these agents on NAFLD.

Key words: Sodium-glucose cotransporter 2 inhibitor, Glucagon-like peptide-1 receptor agonist, Non-alcoholic fatty liver disease, Type 2 diabetes mellitus

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the most common form of chronic liver disease worldwide, is prevalent in patients with type 2 diabetes mellitus (T2DM).^{1,2} NAFLD progresses to steatohepatitis, fibrosis, and cirrhosis.³ In addition, those with T2DM and NAFLD show a poor hepatic prognosis and have increased risk of cardiovascular disease.^{4,5} The only known, effective treatment for NAFLD is weight loss, and there is no approved

pharmacotherapy. Because NAFLD and T2DM share pathophysiologic features, such as insulin resistance, hypoglycemic agents, especially pioglitazone, have been evaluated for effectiveness in NAFLD.⁶ There is substantial growing interest in the effects of new hypoglycemic agents, such as sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs), on NAFLD.

Experimental preclinical and clinical human data suggest that SGLT2 inhibitors and GLP-1RAs have beneficial effects on

NAFLD and non-alcoholic steatohepatitis (NASH).^{7,8} To date, the effects of SGLT2 inhibitors and GLP-1RAs on hepatic steatosis or fibrosis have been largely investigated with the following information: NAFLD biochemical markers such as alanine aminotransferase (ALT), serum fibrotic markers such as ferritin, and radiologic findings evaluating hepatic fat content (ultrasonography, computed tomography [CT], magnetic resonance imaging [MRI], and transient elastography [so-called FibroScan]). Histologic evaluation has been relatively scarce until now.

The high prevalence and impact on public health of NAFLD and T2DM indicate the need for investigation of the effects of new hypoglycemic agents on NAFLD in patients with T2DM. In this review, we focus on recent human studies regarding the effects of SGLT2 inhibitors and GLP-1RAs on NAFLD/NASH in patients with T2DM, and we describe possible mechanisms to explain the positive effects of these agents on NAFLD.

SGLT2 INHIBITORS

Several studies have reported that SGLT2 inhibitors can inhibit the development of NAFLD/NASH and improve histological hepatic steatosis or steatohepatitis in experimental animal models with T2DM.⁹⁻¹¹ On the other hand, published articles on the effects of SGLT2 inhibitors on NAFLD/NASH in human were scarce until 2017, and the majority of human studies was conducted in Japan and recently published in 2018. Many reports regarding the improvement in liver enzymes after treatment with SGLT2 inhibitors have been published, whereas only a few studies have attempted to evaluate the role of SGLT2 inhibitors on liver inflammation and fibrosis histologically in T2DM patients with biopsy-confirmed NAFLD or NASH.

Dapagliflozin

In a randomized controlled trial (RCT) by Shimizu et al.,⁷ 57 patients with NAFLD and T2DM were divided into two groups, dapagliflozin 5 mg/day group or the standard treatment without SGLT2 inhibitors group, and treated for 24 weeks. The diagnosis of NAFLD was based on persistent elevation of ALT above the normal limit and fatty liver on ultrasonography. Transient elastography (FibroScan) was performed to assess liver steatosis and fibro-

sis. In week 24, only the dapagliflozin group demonstrated a significant decrease in the following: steatosis from FibroScan, serum ALT, γ -glutamyl transpeptidase (γ GT) level, and visceral fat mass. In addition, 14 patients with significant liver fibrosis underwent significantly decreased liver stiffness after dapagliflozin treatment. This was the first study to show the effect of dapagliflozin on hepatic fibrosis using FibroScan.

One large retrospective study using a Canadian diabetes register investigated the effects of dapagliflozin and canagliflozin (SGLT2 inhibitors), sitagliptin, and liraglutide on changes in ALT levels in 3,667 patients with T2DM in comparison to a control group.¹² ALT level was lower after treatment with the SGLT2 inhibitors, canagliflozin and dapagliflozin, compared to treatment with liraglutide or sitagliptin (mean follow-up, 4.8 months). In addition, only the SGLT2 inhibitor group maintained a significant ALT reduction compared with the control. Greater ALT reduction was seen in the SGLT2 inhibitor treatment group, with higher baseline ALT independent of the changes in glycated hemoglobin and body weight.

An RCT (EFFECT-II) study in Sweden investigated the effects of dapagliflozin and omega-3 carboxylic acids on liver fat content in patients with NAFLD and T2DM.¹³ NAFLD was defined according to liver fat content assessed by MRI (proton density fat fraction [PDFF]). Eighty-four patients with NAFLD and T2DM were randomly assigned to one of four treatment groups: 10 mg of dapagliflozin, 4 g of omega-3 carboxylic acids, a combination of both drugs, or placebo. Only the combination treatment group showed decreased liver PDFF and total liver fat volume in comparison with placebo. The dapagliflozin monotherapy group experienced reduced liver injury biomarkers (ALT, aspartate aminotransferase [AST], and γ GT).

Eleven Japanese patients with liver biopsy-proven NASH and T2DM were treated with dapagliflozin 5 mg/day for 24 weeks in a single-arm, nonrandomized pilot study.¹⁴ Dapagliflozin treatment was associated with significant improvement of liver-related biochemistry (serum ALT, AST, ferritin, and type IV collagen) and reduction of visceral fat.

Our group compared the effects of dapagliflozin and dipeptidyl peptidase-4 (DPP4) inhibitors in 102 patients with NAFLD and T2DM who had an abnormal ALT level > 40 IU/L.¹⁵ Patients in the dapagliflozin group experienced more weight loss and ALT re-

duction than patients in the DPP4 inhibitors group. In addition, the proportion of patients with ALT normalization after treatment was significantly higher in the dapagliflozin group, and the result was consistent even after adjustments for weight loss.

Empagliflozin

The recently published EMPA-REG OUTCOME trial, a study including pooled data from four 24-week placebo-controlled trials, and a trial of empagliflozin vs. glimepiride over 104 weeks investigated the effect of empagliflozin on liver enzymes in patients with T2DM.¹⁶ The adjusted mean difference in change of ALT was -3.2 IU/L with empagliflozin versus placebo in pooled 24-week data and -4.9 IU/L with empagliflozin versus glimepiride at week 28. These ALT improvements were independent of changes in glycated hemoglobin or body weight.

E-LIFT (Effect of Empagliflozin on Liver Fat content in 50 patients with T2DM), a prospective randomized study, examined the effect of empagliflozin 10 mg for 20 weeks on liver fat in patients with NAFLD and T2DM using MRI-derived PDF. Empagliflozin was significantly better at reducing liver fat than standard treatment without empagliflozin. The empagliflozin group showed a significant reduction in end-of-treatment MRI-PDF and ALT compared with baseline.

Canagliflozin

Data pooled from two 52-week active-controlled studies of canagliflozin 300 mg versus sitagliptin 100 mg and four 26-week placebo-controlled studies of canagliflozin 100 mg and 300 mg revealed reductions in ALT, AST, alkaline phosphatase, and γ GT in the canagliflozin treatment groups. These results were explained by the combined effects of improved glycated hemoglobin and body weight reductions with canagliflozin.¹⁸

A prospective, nonrandomized, single-arm study by Inoue et al.¹⁹ evaluated the effect of 12 months of treatment with canagliflozin 100 mg on biochemical markers, body composition measured by bioelectrical impedance analysis, and MRI-derived hepatic fat fraction (HFF). HFF decreased from a baseline of $17.6\% \pm 7.5\%$ to $12.1\% \pm 6.1\%$ after 12 months. In addition, liver enzymes and type IV collagen level were reduced.

In a study by Seko et al.²⁰, 10 T2DM patients with biopsy-con-

firmed NASH (hepatic fibrosis stage 1–3) received canagliflozin 100 mg for 12 weeks. The primary end point was change in serum ALT level. The change in ALT from baseline to week 12 was -23.9 IU/L. There were also significant improvements in AST and fibrosis-4 index. A different tendency in ALT-change between the stage 1 and stage 2/3 groups was found; the degree of ALT-lowering was greater in the stage 1 group, representing the early stages of NASH, than in the stage 2/3 group.

A 24-week trial by Cusi et al.²¹ showed that treatment with canagliflozin 300 mg decreased intrahepatic triglyceride measured by proton-magnetic resonance spectroscopy compared to placebo (-6.9% vs. -3.8% , respectively), and the reduction was strongly correlated with extent of weight loss.

In a prospective, open-label, uncontrolled, pilot study of 35 patients with NAFLD receiving canagliflozin 100 mg for 6 months, canagliflozin significantly reduced the serum levels of ALT, AST, ferritin, and fibrosis-4 index.²²

Ipragliflozin

Komiya et al.²³ found that treatment with ipragliflozin significantly improved serum ALT level irrespective of the change in body weight in 25 patients with T2DM diagnosed with NAFLD by ultrasonography. Ito et al.²⁴ compared the efficacy of ipragliflozin 50 mg versus pioglitazone 15–30 mg in patients with NAFLD and T2DM. The authors found that ipragliflozin showed equivalent beneficial effects with pioglitazone on NAFLD during the 24-week trial period. Ipragliflozin ameliorated hepatic steatosis, which was evaluated using the liver-to-spleen ratio on CT, and reduced serum aminotransferase level. Additionally, a case report described the amelioration of liver biopsy-proven histological findings in a patient with NASH and T2DM after administration of ipragliflozin.²⁵

POSSIBLE MECHANISM OF ACTION OF SGLT2 INHIBITORS ON NAFLD

Although the mechanisms by which SGLT2 inhibitors exert their beneficial effects (reduced liver fat and improved liver enzymes, inflammation, and/or fibrosis) remain to be elucidated, the following possible explanations have been presented.

Weight- or visceral fat-dependent effects (related to reduction of body weight or visceral fat)

Glycosuria by SGLT2 inhibitors is associated with weight loss, mainly fat mass loss.¹⁴ According to a previous meta-analysis, weight loss above 5% improved hepatic steatosis, and losses above 7% also improved histological features of NAFLD.²⁶ Weight loss and improvement of insulin resistance by SGLT2 inhibitors may ameliorate liver steatosis.^{11,18} SGLT2 inhibitors can improve insulin resistance and lipotoxicity and thereby decrease hepatocyte apoptosis and inflammation.

Improvement of glucose control

SGLT2 inhibitors promote glycosuria, which decreases blood glucose level and ameliorates insulin resistance. Glycemic control downregulates carbohydrate responsive element-binding protein, a transcription factor responsible for activating fatty acid synthesis.²⁷ Amelioration of insulin resistance by glucose control results in downregulation of sterol regulatory element-binding protein 1c, a transcription factor related to lipid production and blockage of de novo lipogenesis.²⁸

Weight- and glucose-independent effects

Several studies showed that improvement of steatosis was largely independent of changes in body weight, visceral fat mass, or glycosuria.^{7,16,23} SGLT2 inhibitors seem to have a beneficial effect on NAFLD/NASH through weight- and glucose-independent mechanisms, such as reduction in inflammatory markers, decrease in oxidative stress, decrease in lipogenesis, and increase in oxidation of free fatty acids (FFAs).²⁹

Inhibition of de novo lipogenesis in the liver

Previous studies using a rat/mice model of NAFLD/NASH with diabetes demonstrated that both decrease of de novo lipogenesis and increase of fatty acid β -oxidation play a role in improvement of hepatic steatosis by SGLT2 inhibitors.^{9,23}

Glucagon effect

In addition to its effects on glucose metabolism, glucagon is also known to contribute to lipid metabolism. Glucagon action is important for multiple pathways regulating lipid metabolism and

leading to decreased lipogenesis.³⁰ Decreased glucagon action was associated with development of fatty liver, and exogenous glucagon administration reduced fatty liver in human and animal studies.^{31,32} In addition, improvement in glucagon-to-insulin ratio (GI ratio) or use of SGLT2 inhibitors can ultimately increase ketogenesis in the liver.³³ Ketogenesis can protect against steatosis.³⁴

The above-mentioned studies by Bajaj et al.¹² and Choi et al.¹⁵ showed that SGLT2 inhibitors were associated with considerably greater reduction in ALT than incretin therapies, independent of weight and glycosuria change. SGLT2 inhibitors induce increased plasma glucagon level; although the precise mechanism is yet known, glycosuria's glucose lowering effect may contribute. Hansen et al.³⁵ and Ferrannini et al.³⁶ explained that the opposing effects of SGLT2 inhibitors and incretin agents on the GI ratio may explain the different impacts of the two drugs on NAFLD. SGLT2 inhibitors cause glucagon stimulation, leading to an increase in GI ratio, whereas incretin agents give rise to glucagon suppression and insulin stimulation, resulting in a decrease in GI ratio. In our previous study, we also observed that a lower GI ratio was significantly associated with NAFLD in patients with T2DM.³⁷ Therefore, these contrasting glucagon effects may be considered as a possible mechanism in the differential hepatic effects of SGLT2 inhibitors and incretin agents. Future randomized prospective studies are needed to investigate the mechanistic link regarding GI ratio and NAFLD in patients with NAFLD and T2DM.

GLP-1R AGONISTS

Accumulating data support the beneficial effect of GLP-1RAs on NAFLD.^{38,39} Patients who had elevated ALT level were treated with various GLP-1RAs and showed subsequent improvement of ALT.⁴⁰⁻⁴² In addition, improved liver enzymes, experimental animal studies, and some clinical studies have revealed that GLP-1RAs can improve liver histology and fibrosis in patients with NAFLD/NASH and even in those with lean NASH.^{43,44}

Liraglutide

A meta-analysis of 26-week, phase-III, RCT T2DM trials, which included the "Liraglutide Effect and Action in Diabetes (LEAD)" program, showed that liraglutide 1.8 mg significantly improved liv-

er enzymes. In addition, the LEAD-2 sub-study showed that liraglutide 1.8 mg showed a tendency toward improving hepatic steatosis versus placebo by evaluation with liver-to-spleen attenuation ratio on CT.⁴²

The effect of liraglutide on liver histology was first evaluated in the Liraglutide Efficacy and Action in NASH (LEAN) trial, which compared 48 weeks of liraglutide 1.8 mg versus placebo in 52 patients with biopsy-confirmed NASH (17 subjects had T2DM).⁸ Dissipation of hepatocyte ballooning without impairment of fibrosis (a resolution of NASH) was the primary end point and was obtained in 39% of the liraglutide group versus 9% of the placebo group. Liraglutide significantly improved steatosis, NAFLD activity score, and hepatocyte ballooning without significant differences in lobular inflammation. The authors hypothesized that the positive effects of liraglutide on NASH resulted from a combination of direct hepatic effect and weight loss.

Nineteen Japanese patients with ALT level above normal received liraglutide 0.9 mg/day for 24 weeks to evaluate its effect on biopsy-confirmed NASH with glucose intolerance (LEAN-J study).⁴⁵ Liraglutide treatment significantly improved body mass index, visceral fat, aminotransferases, and glucose abnormalities. Repeated liver biopsy was performed in 10 subjects who continued liraglutide treatment for 96 weeks, and six subjects showed improvement of histological inflammation.

The study by Petit et al.⁴⁶ demonstrated that 6 months of treatment with liraglutide 1.2 mg in 68 patients with uncontrolled T2DM was associated with a 31% reduction in liver fat content as measured with proton magnetic resonance spectroscopy (Lir-NAFLD). The effect was predominantly caused by body weight loss.

In contrast, negative findings have been reported. In an RCT by Tang et al.,⁴⁷ liraglutide treatment showed no significant change on liver fat (magnetic resonance spectroscopy-PDF, liver volume, and total liver fat index). In the LEAD-2 sub-study, liver-to-spleen attenuation ratio on CT was assessed after combination treatment with liraglutide and metformin.⁴⁸ There was a non-significant trend toward reduction in liver steatosis in only 23 patients treated with a higher dose of 1.8 mg of liraglutide. The liraglutide 1.2 mg treatment group did not show a change of ratio, and the 0.6 mg liraglutide treatment group showed a slightly decreasing ratio. Regarding

the possible reason for the negative finding of GLP-1RA on NAFLD, Tang et al.⁴⁷ explained that GLP-1 analogs induce a decrease in glucagon secretion and a postprandial increase in insulin secretion in the portal circulation, favoring lipogenesis with subsequent lack of beneficial effect of liraglutide on hepatic steatosis.⁴⁵

Exenatide

In a study by Kenny et al.,⁴⁴ eight T2DM patients with biopsy-confirmed NAFLD were treated with 5–10 µg exenatide for 28 weeks. Liver histology was evaluated using NAFLD activity score, and there was no overall significant improvement in liver histology. However, three of eight subjects met the primary end point of improved liver histology.

Sixty newly diagnosed T2DM patients with obesity, NAFLD, and elevated liver enzymes were included in the study by Shao et al.⁴⁹ The patients were randomly divided into two groups: the “exenatide group” treated with both exenatide and insulin glargine and the “intensive insulin group” treated with insulin glargine and aspart for 12 weeks. Following treatment, the levels of ALT, AST, and γGT in the exenatide group were significantly lower than the levels in the intensive insulin group. The ALT, AST, and γGT changes correlated with mean body weight changes. Moreover, the resolution rate of fatty liver was significantly higher in the exenatide group (93.3%) than in the intensive insulin group (66.7%).

Dulaglutide

Seko et al.⁵⁰ retrospectively evaluated 15 T2DM patients with biopsy-confirmed NAFLD who received once-weekly dulaglutide 0.75 mg for 12 weeks. FibroScan and body composition were evaluated before and after treatment in only five patients. Transaminase activities were significantly decreased after dulaglutide treatment. In addition, liver stiffness measured by FibroScan and total body fat mass also decreased after treatment.

Lixisenatide

No RCTs on lixisenatide for NAFLD have been published, but there are some trials on lixisenatide for overweight patients with mildly elevated liver enzymes. A previous meta-analysis by Gluud et al.⁵¹ reported the impact of lixisenatide on elevated liver enzymes in patients with T2DM. The meta-analysis was comprised of 12

RCTs for lixisenatide versus placebo and three RCTs with active comparison groups (liraglutide, exenatide, or sitagliptin). Lixisenatide increased the proportion of patients with normalized ALT. Because few RCT studies that include lixisenatide and dulaglutide have been performed, their impact on NAFLD is relatively less established.

Semaglutide

A phase IIb RCT is currently underway to investigate the efficacy and safety of semaglutide for 72 weeks of treatment in patients with NASH. The primary outcome is resolution of NASH without worsening of fibrosis. The trial is due to finish in July 2019 (ClinicalTrials.gov identifier: NCT02970942).

POSSIBLE MECHANISMS OF ACTION OF GLP-1RAs ON NAFLD

Weight loss and glycemic control

Certainly, GLP-1RAs cause significant weight loss in patients with T2DM.⁵² Studies that demonstrated a significant decrease in liver fat content after treatment with GLP-1RAs also showed a significant correlation among weight reduction, glycemic control, and decreased liver fat.^{39,53,54} In the Lira-NAFLD study, the reduction in liver fat content obtained after treatment with liraglutide for 6 months was significantly correlated with body weight reduction, even after multivariate adjustment.⁴⁶ Similar results were also obtained in the 26-week exenatide treatment study by Dutour et al.⁵³

Direct action on hepatic cells

A previous *in vitro* study suggested that GLP-1RAs may act directly on human hepatocytes via a G-protein-coupled receptor, resulting in a direct effect on reduction of hepatic steatosis.⁵⁴ However, there are different opinions regarding the presence of GLP-1RAs in human hepatocytes, and this has not yet been determined.

Beneficial effects on lipid metabolism

The mechanism of action of GLP-1RAs in NAFLD/NASH cannot be entirely explained by weight loss and improvements in metabolic profile. Indeed, an experimental rodent study and *in vitro* studies have shown that GLP-1RA treatment decreases hepatic fat

by modulating fatty acid oxidation and de novo lipogenesis.⁵⁵⁻⁵⁷ A sub-study of LEAN demonstrated that treatment with 1.8 mg liraglutide for 12 weeks improved hepatic insulin sensitivity (suppression of endogenous hepatic glucose production) and increased adipose tissue insulin sensitivity, thereby enhancing the action of insulin to suppress lipolysis, which leads to reduced lipotoxic products and inflammatory cytokines.⁵⁸ In addition, liraglutide reduced hepatic de novo lipogenesis in primary human hepatocytes. GLP-1RAs may also resolve NASH and improve liver fibrosis through suppression of oxidative stress and inflammation in the liver.⁵⁹

CONCLUSION

Recent studies have shown that SGLT2 inhibitors and GLP-1RAs have beneficial effects on NAFLD and NASH in patients with T2DM. Accumulating evidence suggests that SGLT2 inhibitors and GLP-1RAs may be a promising treatment modality and can be recommended as a specific therapy for NAFLD/NASH patients with T2DM (Tables 1 and 2). The two classes of hypoglycemic agents have common mechanisms, including body weight or fat tissue reduction, glycemic control and reduction in inflammatory markers, decreased lipogenesis, and increase in FFA oxidation as well as decrease in oxidative stress (Fig. 1).

On the other hand, the actions of SGLT2 inhibitors and GLP-1RAs on lipid metabolism in regard to glucagon are contradictory. Whereas SGLT2 inhibitors lead to glucagon stimulation, GLP-1RAs lead to glucagon suppression (Fig. 1). It is still not clear whether these two opposing glucagon effects on lipid metabolism have different effects on NAFLD.

Based on these various mechanisms, Athyros et al.⁶⁰ suggested that treatment with a combination of SGLT2 inhibitors with GLP-1RAs has a scientific basis in patients with NAFLD, because the two drug classes show complimentary effects (effects on glucagon, gluconeogenesis, and appetite showing relatively opposing effects), which may produce additive effects (weight and glucose control effects) and finally NAFLD improvement.⁶¹ This hypothesis needs to be proven in large RCTs. In addition, well-designed observational studies in real clinical practice can provide valuable information.

Table 1. Studies assessing the effects of SGLT2 inhibitors in patients with NAFLD and T2DM

| Drug | Author (year) | Trial design | Dosage/ duration | Definition of NAFLD | Body weight | Liver enzyme | Imaging modality for liver fat content | Histology |
|---------------|---|---|---------------------|---|-------------|--------------|---|---|
| Dapagliflozin | Shimizu et al. (2019) ⁷ | RCT, dapagliflozin (n = 33) or the standard treatment without SGLT2 inhibitors group (n = 24) | 5 mg/24 wk | Elevated ALT level and fatty liver on US | Reduced | Improved | Transient elastography (FibroScan) | Not assessed |
| | Bajaj et al. (2018) ¹² | Canadian diabetes register, canagliflozin and dapagliflozin vs. liraglutide, sitagliptin | Mean, 4.8 mo | Not defined NAFLD | Reduced | Improved | Not assessed | Not assessed |
| Empagliflozin | Eriksson et al. (2018) ¹³ | RCT, dapagliflozin (n = 21), omega-3 carboxylic acids (n = 20), a combination of both (n = 22), or placebo (n = 21) | 10 mg/12 wk | MRI-derived PDFF > 5.5% | Reduced | Improved | MRI-derived PDFF | Not assessed |
| | Tobita et al. (2017) ¹⁴ | Nonrandomized, single-arm, 11 patients with liver biopsy-confirmed NASH | 5 mg/24 wk | Percutaneous liver biopsy | Reduced | Improved | Not assessed | Not assessed |
| Empagliflozin | Choi et al. (2018) ¹⁵ | Retrospective, metformin+dapagliflozin (n = 50) vs. metformin+DPP4i (n = 52) | Not definite | Fatty liver on US | Reduced | Improved | Not assessed | Not assessed |
| | Sattar et al. (2018) ¹⁶ | EMPA-REG OUTCOME trial (n = 7,020), pooled data from four 24-week placebo-controlled trials (n = 2,477) and a trial of empagliflozin vs. glimepiride over 104 wk (n = 1,545) | 10 mg/20 wk | MRI-derived PDFF > 6% | Reduced | Improved | Liver fat by MRI-derived PDFF | Not assessed |
| Canagliflozin | Kuchay et al. (2018) ¹⁷ | RCT, empagliflozin vs. standard treatment without empagliflozin | 10 mg/20 wk | MRI-derived PDFF > 6% | Reduced | Improved | Liver fat by MRI-derived PDFF | Not assessed |
| | Leiter et al. (2016) ¹⁸ | Two 52-week, active-controlled studies of canagliflozin 300 mg vs. sitagliptin 100 mg (n = 1,488) and four 26-week, placebo-controlled studies of canagliflozin 100 mg and 300 mg (n = 2,313) | 100 mg/12 mo | Not defined | Reduced | Improved | Not assessed | Not assessed |
| Canagliflozin | Inoue et al. (2018) ¹⁹ | Prospective, nonrandomized, single-arm, canagliflozin (n = 20) | 100 mg/12 mo | By abdominal echography | Reduced | Improved | Hepatic fat fraction by MRI | Not assessed |
| | Seko et al. (2018) ²⁰ | Single-arm, exploratory study, canagliflozin (n = 10) | 100 mg/12 wk | Biopsy-proven NASH (hepatic fibrosis stage 1–3) | Reduced | Improved | Controlled attenuation parameter by transient elastography | Not assessed |
| Canagliflozin | Cusi et al. (2018) ²¹ | RCT, canagliflozin (n = 26) vs. placebo (n = 30) | 300 mg/24 wk | Not defined | Reduced | Improved | Intrahepatic triglyceride content by liver proton MR spectroscopy | Not assessed |
| | Itani and Ishihara (2018) ²² | Prospective, uncontrolled pilot study, canagliflozin (n = 35) | 100 mg/24 wk | By abdominal US | Reduced | Improved | Not assessed | Not assessed |
| Ipragliflozin | Komiya et al. (2016) ²³ | Single-arm study, ipragliflozin (n = 25) | 50 mg/24 wk | By abdominal US | Reduced | Improved | Not assessed | Not assessed |
| | Ito et al. (2017) ²⁴ | RCT, ipragliflozin (n = 32) vs. pioglitazone (n = 34) | 50 mg/24 wk | Hepatic dysfunction and hepatic steatosis on imaging studies (CT or US) | Reduced | Improved | L/S ratio on CT | Not assessed |
| Ipragliflozin | Takeda et al. (2017) ²⁵ | Case report | 4 mo | Biopsy-proven NASH | Reduced | Improved | Fat deposits by US and CT | Marked improvement in steatosis, inflammation, and ballooning |

SGLT2, sodium-glucose cotransporter 2; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; RCT, randomized controlled trial; ALT, alanine aminotransferase; US, ultrasonography; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; NASH, non-alcoholic steatohepatitis; DPP4i, dipeptidyl peptidase-4 inhibitor; L/S ratio, liver-to-spleen attenuation ratio.

Table 2. Studies assessing the effect of GLP-1RA in patients with NAFLD and T2DM

| Drug | Author (year) | Trial design | Dosage/duration | Definition of NAFLD | Body weight | Liver enzyme | Imaging modality for liver fat content | Histology |
|--------------|---------------------------------------|---|--|--|-------------|--------------|--|-------------------------------------|
| Liraglutide | Armstrong et al. (2013) ⁴² | Meta-analysis of six phase III RCT, liraglutide vs. active-placebo control | 0.6 mg, 1.2 mg, 1.8 mg | L/S ratio on CT | Reduced | Improved | L/S ratio on CT | Not assessed |
| | LEAN trial team (2016) ⁸ | RCT, liraglutide (n = 26) vs. placebo (n = 26) | 1.8 mg/48 wk | Biopsy-proven NASH | Reduced | Improved | Not assessed | Resolution of NASH |
| | Eguchi et al. (2015) ⁴⁵ | Liraglutide (LEAN-J study), comparison before and after liraglutide treatment | 0.9 mg for 24 wk in 19 subjects and repeated liver biopsy in 10 subjects who continued therapy for 96 wk | Biopsy-proven NASH | Reduced | Improved | Visceral fat area and L/S ratio on CT | Decreased histological inflammation |
| | Petit et al. (2017) ⁴⁶ | Prospective, single center study, liraglutide (n = 68) before and after treatment | 1.2 mg/6 mo | Liver fat content by proton spectroscopy | Reduced | Improved | Liver fat content by proton spectroscopy, visceral fat and subcutaneous fat by MRI | Not assessed |
| Exenatide | Kenny et al. (2010) ⁴⁴ | Open-labeled, prospective case series (n = 8) | 5–10 µg/28 wk | Biopsy-proven NAFLD | Reduced | Improved | Not assessed | No significant improvement overall |
| | Shao et al. (2014) ⁴⁹ | Exenatide group (n = 30) vs. intensive insulin treat group (n = 30) | 5–10 µg/12 wk | By abdominal US | Reduced | Improved | US | Not assessed |
| Dulaglutide | Seko et al. (2017) ⁵⁰ | Retrospective study, dulaglutide (n = 15) before and after treatment | 0.75 mg/12 wk | Biopsy-proven NAFLD | Reduced | Improved | Transient elastography | Not assessed |
| Lixisenatide | Gludd et al. (2014) ⁵¹ | Systematic review, 12 RCTs on lixisenatide vs. placebo or 3 RCTs with active comparators (liraglutide, exenatide, or sitagliptin) | Mean, 29 wk | Elevated liver enzyme | Reduced | Improved | Not assessed | Not assessed |
| Semaglutide | Phase II RCT is ongoing | | | 72 wk | | NASH | | |

GLP-1RA, glucagon-like peptide-1 receptor agonist; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; RCT, randomized controlled trial; L/S ratio, liver-to-spleen attenuation ratio; CT, computed tomography; LEAN, Liraglutide Efficacy and Action in NASH; NASH, non-alcoholic steatohepatitis; MRI, magnetic resonance imaging; US, ultrasonography.

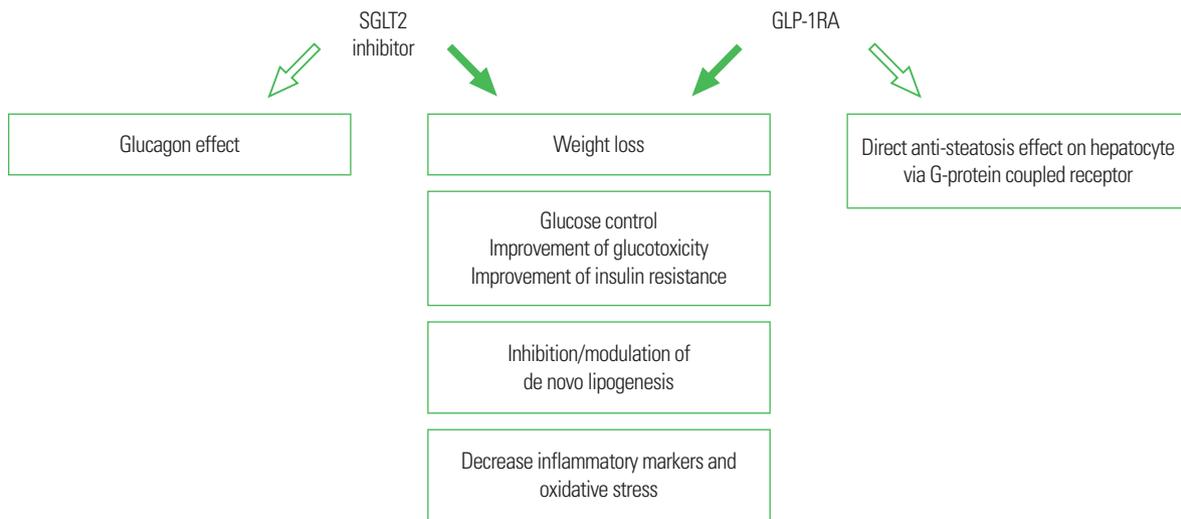


Figure 1. Possible mechanisms of the positive effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) on non-alcoholic fatty liver disease. Hollow arrows indicate uncertain mechanisms.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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