Effects of sodium–glucose cotransporter 2 inhibitors on non-alcoholic fatty liver disease in patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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Keywords
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ABSTRACT

Aims/Introduction: Non-alcoholic fatty liver disease (NAFLD) is increasingly common in patients with type 2 diabetes mellitus. Currently, some studies have found that sodium–glucose cotransporter 2 (SGLT2) inhibitors, a new hypoglycemic drug, can improve non-alcoholic fatty liver in addition to its hypoglycemic effect. Thus, we undertook a meta-analysis of randomized controlled trials to evaluate the efficacy of SGLT2 inhibitors on the treatment of NAFLD.

Materials and Methods: PubMed, Embase and the Cochrane Library were searched for randomized controlled trials of SGLT2 inhibitors in patients with NAFLD and type 2 diabetes mellitus up to 1 October 2019. Differences were expressed as weight mean difference (WMD) with 95% confidence interval (CI) for continuous outcomes. The I² statistic was applied to evaluate the heterogeneity of studies.

Results: A total of six trials including 309 patients were selected into our meta-analysis. SGLT2 inhibitors could reduce alanine aminotransferase (WMD −11.05 IU/L, 95% CI −19.85, −2.25, P = 0.01) and magnetic resonance imaging proton density fat fraction (WMD −2.07%, 95% CI −3.86, −0.28, P = 0.02). However, SGLT2 inhibitors did not reduce aspartate aminotransferase (WMD −1.11 IU/L, 95% CI −2.39, 0.17, P = 0.09). In addition, secondary outcomes, such as bodyweight and visceral fat area, were also reduced (WMD −1.62 kg, 95% CI −2.02, −1.23, P < 0.00001; WMD −19.98 cm², 95% CI −27.18, −12.79, P < 0.00001, respectively).

Conclusions: SGLT2 inhibitors can significantly decrease alanine aminotransferase and liver fat, accompanied with weight loss, which might have a positive effect on fatty liver in patients with type 2 diabetes mellitus. The limitation is that the sample size of the studies was small. Therefore, more large randomized controlled trials specified on NAFLD are required to evaluate these results.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been the cause of great public focus worldwide, and is estimated to affect 75% of patients with type 2 diabetes mellitus. According to some studies, up to 30% of patients with NAFLD progress to non-alcoholic steatohepatitis (NASH), and further to liver cirrhosis and hepatocellular carcinoma. Some studies have confirmed that there is a clear and close association between type 2 diabetes mellitus and NAFLD or NASH. Furthermore, the prevalence of NAFLD often accompanies various complications, such as cardiovascular adverse events, in patients with type 2 diabetes mellitus, which is detrimental to the prognosis of those patients. Therefore, effective therapy for NAFLD is important for patients with type 2 diabetes mellitus. Nowadays, although we have evidence that pioglitazone, an insulin sensitizer, can improve the function of the liver when it plays a hypoglycemic role, but its side effects are not ignored.
effect, it also has side-effects, such as the increase of subcutaneous fat tissue and bodyweight gain with edema. Sodium–glucose cotransporter 2 (SGLT2) inhibitor is a novel and potent oral hypoglycemic agent used to treat type 2 diabetes mellitus, which can increase urinary glucose excretion, thereby lowering the blood glucose level and bodyweight. Some previous studies showed that the effect on weight loss of SGLT2 inhibitors was useful for the alleviation of NAFLD. Komiya et al. also found SGLT2 inhibitors can significantly reduce bodyweight in NAFLD patients. In addition, more recently, a multi-institutional cohort study suggested that the administration of SGLT2 inhibitors to patients with type 2 diabetes mellitus could improve serum alanine aminotransferase (ALT) levels in clinical practice, particularly for patients with especially high ALT levels. However, there are no specific statistics on the degree of reduction of ALT by SGLT2 inhibitors. Therefore, we carried out a meta-analysis on the effects of several common SGLT2 inhibitors on ALT, liver fat and bodyweight.

METHODS
Search strategy and study selection
We searched PubMed, Embase and the Cochrane Library for relevant articles up to 1 October 2019, with no language restriction. Search terms were MeSH terms and entry terms. For example, for the PubMed database, we searched (“Sodium–Glucose Transporter 2 Inhibitors” [MeSH] OR SGLT2 Inhibitors OR SGLT-2 Inhibitors OR SGLT 2 Inhibitors OR Gliflozins OR Dapagliflozin OR Empagliflozin OR Ipragliflozin OR Ertagliflozin OR Canagliflozin OR Luseogliflozin OR Sotagliflozin) AND (“Nonalcoholic Fatty Liver Disease” [MeSH] OR NAFLD OR Fatty Liver OR Nonalcoholic Steatohepatitis OR Nonalcoholic Steatohepatitis OR NASH). The eligible searches were limited to randomized controlled trials (RCTs). Two independent reviewers (BD Xing, BZ Dong) independently screened the titles and abstracts of all records, and full texts of potentially eligible studies. Any disagreements were resolved by consensus with a third reviewer (WS Lv). The following inclusive selection criteria were applied. First, populations were patients (aged 20–75 years) with type 2 diabetes mellitus and NAFLD. The glycated hemoglobin (HbA1c) was of 6.0–12.0%. The inclusion criteria for NAFLD were as follows: (i) fatty liver based on imaging examination (ultrasound or computed tomography); (ii) alcohol intake not exceeding 140 g/week in women and 210 g/week in men; and (iii) exclusion of other causes of liver disease (e.g., viral, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and Wilson’s disease). Second, the treatment intervention was SGLT2 inhibitors (regardless of which type). Third, the primary outcome was the change of liver enzyme (ALT and aspartate aminotransferase [AST]) and magnetic resonance imaging proton density fat fraction (MRI-PDFF) from baseline. The secondary outcomes were the change of visceral fat area (VFA), bodyweight and HbA1c from baseline. Fourth, the study design was RCT. We excluded case reports, animal experiments, conference abstracts, reviews, subgroup analysis and editorials.

Data extraction and quality assessment
Two independent reviewers (YH Zhao and BZ Dong) extracted the following information from the eligible articles: study characteristics (first author, year of publication, sample size, intervention [type and dose of SGLT2 inhibitor], the medicine of the comparison group, follow-up time), and patients’ baseline (age, type 2 diabetes mellitus duration, HbA1c, body mass index) and clinical outcomes (ALT, AST, MRI-PDFF, VFA, bodyweight and HbA1c). At present, MRI-PDFF, based on MRI, is a most accurate indicator to measure liver fat. VFA was measured through abdominal computed tomography.

The quality of RCTs was assessed by the Cochrane risk-of-bias tool, including: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) blinding of outcome data (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); and (vii) other bias: some bias has a great relationship with outcome, but not in the aforementioned items. The judgment for each entry involves answering a question, with “yes” indicating low risk of bias, “no” indicating high risk of bias and unclear indicating a lack of information or uncertainty about the possibility of bias. The quality evaluation was carried out and checked independently by two researchers (BD Xing and YH Zhao). If there is any disagreement, we negotiated with the third researcher (Y Zhou).

Ethical approval
This study complied with the Declaration of Helsinki. Given the study was a meta-analysis, no prior ethical approval was required.

Statistical analysis
Differences were expressed as weight mean difference (WMD) with 95% confidence interval (CI) for continuous outcomes. The I^2 statistic was applied to evaluate the heterogeneity of studies. Studies with an I^2 statistic of 25–50% were considered to have low heterogeneity, those with an I^2 of 50–75% were considered to have moderate heterogeneity and those with an I^2 of >75% were considered to have high heterogeneity. A random effects model was applied regardless of heterogeneity. According to the characteristics of the studies, we further carried out subgroup analyses or sensitivity analyses to explain the reason for heterogeneity as soon as possible. All statistical analyses were carried out with Review Manager version 5.3 (The Cochrane Collaboration, The Nodic Cochrane Center, Copenhagen, Denmark).

RESULTS
Selection results
A total of 408 articles were selected by preliminary search, with 118 articles being duplications. A total of 244 records were eliminated based on the titles and abstracts. Following the full text of
the remaining 46 articles, seven articles were excluded because they were not RCTs, five articles were removed because they were conference abstracts, 21 articles had uncompleted outcomes and six articles were duplications with the same samples. The remaining seven articles met out inclusion criteria. However, one study had too many participants (>1,000) compared with the other six articles, which might affect the final results, so we excluded it. Finally, six studies including 309 participants were eligible for the meta-analysis. The selection process is shown in Figure 1.

**Basic characteristics and quality assessment**

The characteristics of the included six studies\(^{14-19}\) are shown in Table 1. In all the studies, the interventions of the experiment groups were dapagliflozin (two studies), empagliflozin (one study), luseogliflozin (one study) and ipragliflozin (two studies), respectively. In addition, in terms of the control group, one study used metformin, one study used pioglitazone, three studies used standard hypoglycemic treatment (according to local guidelines) and one study used a placebo in the background of basic hypoglycemic medicine (mainly metformin and sulfonlureas). Basic hypoglycemic drugs were used throughout the study to control blood glucose. It must be noted that other studies did not involve thiazolidinediones, except for the control group, which was pioglitazone. Glucagon-like peptide-1 receptor agonist, an incretin-based hypoglycemic drug that had a great effect on lowering blood glucose and reducing weight, was not included in any of the studies. We can see the baseline of outcomes in Table 2. In addition, we evaluated the bias of these studies using the Cochrane risk bias assessment tool. Four studies\(^{14,16,17,19}\) were open-label, with the selective and performance bias being high or unclear. Four studies\(^{14,16,17,9}\) had no participants drop out, whereas the other two studies\(^{15,18}\) had participants who were lost to follow up. As for the remaining bias, most of the studies were low risk and the details are shown in Figure S1.

**Outcome meta-analysis**

**ALT and AST**

Five studies evaluated the effects of SGLT2 inhibitors on ALT. Overall analysis showed that SGLT2 inhibitors could significantly decrease ALT level (ALT WMD \(-11.05\) IU/L, 95% CI \(-19.85, -2.25\), \(P = 0.01\); Figure 2a). However, a heterogeneity test showed that the \(I^2\) of ALT was 73%, suggesting that it had a moderate heterogeneity. We also carried out an analysis for AST level, which showed that SGLT2 inhibitors had no statistical difference on AST reduction (WMD \(-8.11\) IU/L, 95% CI \(-19.18, 2.97\), \(P = 0.17\); Figure 2b). The \(I^2\) was 0%, showing that the result was stable.

**Imaging examination: MRI-PDFF and VFA**

Although just two studies used the indicator of MRI-PDFF, both of them showed SGLT2 inhibitors could reduce it (WMD \(-2.07\)%, 95% CI \(-3.86, -0.28\), \(P = 0.02\)). The agents of these two studies were dapagliflozin and empagliflozin. In addition, a heterogeneity test showed \(I^2\) was 10%, suggesting that the result had a very low heterogeneity (Figure 2c). Furthermore, VFA was observed in four studies, the results suggesting that SGLT2 inhibitors could obviously decrease VFA (WMD \(-19.98\) cm\(^2\), 95% CI \(-27.18, -12.79\), \(P < 0.0001\); Figure 2d), with a low heterogeneity of results. The \(I^2\) was 37%.

**Bodyweight**

There were five studies that reported the effect of SGLT2 inhibitors on bodyweight. In contrast with the control group, SGLT2 inhibitors could evidently reduce bodyweight (WMD \(-1.42\) kg, 95% CI \(-1.64, -1.21\), \(P < 0.00001\); Figure 2e). Furthermore, a heterogeneity test showed that the result had a low heterogeneity, with \(I^2 = 31\%\).

**HbA1c**

All studies evaluated the indicator of HbA1c. The results showed that SGLT2 inhibitors, compared with other oral antidiabetic drugs (OADs), had no statistical difference on HbA1c reduction (WMD \(-0.41\)%, 95% CI \(-1.16, 0.12\), \(P = 0.13\); Figure 3). However, the result had high heterogeneity, with \(I^2 = 93\%\). Some studies included other effective hypoglycemic agents, which might affect the final outcome, resulting in high heterogeneity as well. Furthermore, in the present meta-analysis, we mainly observed the effect of liver enzyme and liver fat of SGLT2 inhibitors, so we did not carry out further tests for heterogeneity of HbA1c.

**Subgroup analyses and sensitivity analyses**

Because of its obvious heterogeneity, we made a subgroup analysis for ALT by comparing SGLT2 inhibitor type, control groups, sample size and follow-up time. Based on the differences of the control groups, we carried out further subgroup analysis. We found that SGLT2 inhibitors significantly reduced ALT level compared with standard hypoglycemic treatment (ALT: WMD \(-17.62\) IU/L, 95% CI \(-29.69, -5.54\), \(P = 0.004\)), whereas the reduction of ALT level was lower, compared with pioglitazone (ALT: WMD \(-2.5\) IU/L, 95% CI \(-4.29, -0.71\), \(P = 0.006\)). However, compared with metformin, there was no statistical difference of SGLT2 inhibitors on the reduction of ALT (WMD \(-9.13\) IU/L, 95% CI \(-19.18, 0.92\), \(P = 0.08\)). The difference between groups showed statistically significance (\(\chi^2 = 7.36\), \(P = 0.003\), \(I^2 = 72.8\%\); Figure 4). In addition, stratified by SGLT2 inhibitor type, sample size and follow-up time, we found no statistically significant difference between groups, which were \(P = 0.96\), 0.67 and 0.14, respectively (Figures S2–S4).

We also carried out a sensitivity analysis to test for heterogeneity. By deleting the literature one by one, we found that Ito’s study might be the source of heterogeneity. After deleting this article, heterogeneity changed from 73 to 37%, and the \(P\)-value decreased significantly (from 0.01 to 0.001), which might be related to the control group taking pioglitazone. Other outcomes, such as AST, VFA and bodyweight, showed low heterogeneity, so we did not carry out further tests.
Publication bias
As the number of studies we included was <10, we did not carry out a test of publication bias.

DISCUSSION
The main aim of the present meta-analysis was to evaluate the effect of SGLT2 inhibitors on NAFLD by the change of liver enzyme and liver fat volume. In this meta-analysis, we found that compared with other OADs, SGLT2 inhibitors can significantly decrease ALT (−11.05 IU/L). Although pioglitazone has been shown to have a great effect on the improvement of liver function, SGLT2 inhibitors resulted in an additional ALT reduction of 2.5 IU compared with pioglitazone in that study. SGLT2 inhibitors can also reduce AST (−1.11 IU/L); however, the reduction is slight and shows no statistical difference, considering the reason might be that AST is not a very specific indicator of fat liver.

Figure 1 | Flow chart of literature selection. RCTs, randomized controlled trials.
and is susceptible to other factors. The above results are consistent with the results of a large study we excluded (because of too many participants)\(^2\). The study included the EMPA-REG OUTCOME trial (\(n = 7,020\)), pooled data from four 24-week placebo-controlled trials (\(n = 2,477\)) and a trial of empagliflozin versus glimepiride over a period of 104 weeks (\(n = 1,545\)), showing highly consistent results that empagliflozin could reduce aminotransferases in individuals with type 2 diabetes mellitus, with the reductions of ALT being more than AST. Furthermore, it is worth mentioning that although there were just two articles, both of them showed that SGLT2 inhibitors can decrease liver fat content by 2.07%, as measured by MRI-PDFF. MRI-PDFF is a quantitative MRI-based biomarker that can accurately estimate liver fat content and evaluate the treatment response in NASH clinical trials\(^3\). Therefore, the reduction of MRI-PDFF illustrates that SGLT2 inhibitors have a beneficial effect on reducing liver fat, which shows a guiding significance for the application of SGLT2 inhibitors on NAFLD in the future. In addition, in the analysis, we found that SGLT2 inhibitors show great superiority to the other OAD so with respect to VFA (\(-19.98 \text{ cm}^2\)) and bodyweight (\(-1.62 \text{ kg}\)), which can also demonstrate that SGLT2 inhibitors are helpful to improve NAFLD. However, in our meta-analysis, SGLT2 inhibitors did not show a greater effect on the reduction of HbA1c than other OADs. We suspect it might have a relationship to study itself, because background glucose-lowering therapy is different in some studies. In addition, it might indicate that the decrease of ALT and MRI-PDFF have nothing to do with whether HbA1c reduces or not. In other words, the improvement of NAFLD by SGLT2 inhibitors might be independent of the hypoglycemic effect.

### Table 1 | Basic characteristic of included six studies

| Author     | Year published | Sample (F) | Age (years) | Intervention | Duration (years) | Follow-up time |
|------------|----------------|------------|-------------|--------------|------------------|----------------|
| Ito D      | 2017           | 66 (34)    | 58.2 (10.9) | Ipragliflozin: 50 mg | 9.1 (5.8) | 24 weeks |
| Aso Y      | 2019           | 57 (23)    | 55.0 (8.6)  | Standard hypoglycemic treatment + dapagliflozin 5 mg | 9.6 (45) | 12 weeks |
| Bando Y    | 2017           | 62 (22)    | NR          | Continued hypoglycemic treatment + ipragliflozin 50 mg | NR     | 20 weeks |
| Kuchay MS  | 2018           | 50 (20)    | 65.3 (6.23) | Standard hypoglycemic treatment + empagliflozin 10 mg | NR     | 20 weeks |
| Eriksson JM| 2018           | 42 (9)     | 65.3 (6.23) | Dapagliflozin: 10 mg | NR     | 12 weeks |
| Shibuya    | 2017           | 32 (14)    | 56.5 (11.68)| Luseogliflozin: 5 mg | NR     | 6 months |

Data are the mean (standard deviation). F, female; NR, not reported.

### Table 2 | Baseline characteristic of participants in the six included studies

| Author     | BMI | Weight (kg) | HbA1c (%) |
|------------|-----|-------------|-----------|
| Ito D      | 30.7 (5.0) | 29.9 (6.2) | 79.6 (17.9) | 76.7 (15.2) | 8.5 (1.5) | 8.3 (1.4) |
| Aso Y      | 27.6 (4.7) | 28.3 (3.5) | 73.9 (16.1) | 76.4 (13.9) | 8.37 (1.48) | 7.7 (1.24) |
| Bando Y    | 27.8 (3.9) | 27.3 (3.1) | 80.8 (13.0) | 81.1 (13.0) | 8.1 (1.0) | 8.2 (1.1) |
| Kuchay MS  | 30.0 (3.8) | 29.4 (3.1) | NR | NR | 9.0 (1.0) | 9.1 (1.4) |
| Eriksson JM| 30.5 (2.8) | 30.3 (3.1) | 90.2 (8.7) | 93.0 (12.2) | 7.38 (0.56) | 7.44 (0.80) |
| Shibuya    | 27.6 (2.03) | 28.03 (5.77) | 76.27 (18.2) | 75.4 (19.1) | 7.3 (0.65) | 7.6 (0.57) |

Data are the mean (standard deviation). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NR, not reported; VFA, visceral fat areas.
Figure 2 | (a) Forest plots showing alanine aminotransferase level comparisons between sodium–glucose cotransporter 2 (SGLT2) inhibitors and the control group. (b) Forest plots showing aspartate aminotransferase level comparisons between SGLT2 inhibitors and the control group. (c) Forest plots showing magnetic resonance imaging proton density fat fraction comparisons between SGLT2 inhibitors and the control group. (d) Forest plots showing visceral fat areas comparisons between SGLT2 inhibitors and the control group. (e) Forest plots showing bodyweight comparisons between SGLT2 inhibitors and the control group. CI, confidence interval; SD, standard deviation.
The possible mechanisms of SGLT2 inhibitors to improve NAFLD are as follows. First, decreasing inflammatory markers and oxidation stress. The increase in fatty acid oxidation instead of carbohydrate oxidation could also play a role in the reduction of hepatic fat accumulation and might also suppress hepatic inflammation. SGLT2 inhibitors have shown that they can reduce inflammatory markers, accelerate lipolysis, reduce glucose oxidation, decrease oxidative stress and increase oxidation of free fatty acids, which are quite important in the improvement of NAFLD. In addition, a recent study showed that canagliflozin has a beneficial effect on NAFLD by upregulating zinc-α2-glycoprotein levels, reducing hepatic inflammatory cytokines and lowering oxidative stress in the liver. Therefore, the reduction of liver inflammatory factors and oxidation by SGLT2 inhibitors might be one mechanism to improve NAFLD. Second, weight loss. SGLT2 inhibitors can cause energy loss through increasing urine glucose excretion, thereby reducing visceral adiposity and bodyweight.

This energy loss might promote β-oxidation in the liver and visceral adiposity, as well as induce liver fat metabolism. In NAFLD therapy, bodyweight loss through lifestyle intervention is considered a basic and effective therapy, suggesting that weight loss accompanying visceral fat is beneficial for improving NAFLD. Third, improving glucose control. Carbohydrate response element-binding protein is a transcription factor in the liver that can cause excessive carbohydrate conversion to fat for long-term storage. SGLT2 inhibitors can promote glycogenesis, which decreases blood glucose level. Glycemic control has a significant role in down-regulate carbohydrate response element-binding protein, which is helpful to reduce liver fat. Fourth, improving insulin resistance. The main pathological condition in NAFLD patients is insulin resistance. Several studies showed that improving insulin resistance and sensitivity reduces the extent of fatty liver disease, and might prevent the second-step in hepatocyte injury caused by...
Ketogenesis can dispose of much of the fat entering the liver, which ultimately improve NAFLD. A recent study suggested that SGLT2 inhibitors might promote glucagon secretion by regulating SGLT1 in islet α-cells; however, the specific mechanism is not clear. Sixth, ketone body metabolism. Ketogenesis can dispose of much of the fat entering the liver, and dysfunction in this pathway could potentially contribute to NAFLD pathogenesis. Cotter’s findings suggest that ketogenesis might prevent fatty liver injury and hepatic steatosis through regulating hepatic acetyl coenzyme A metabolism, glucose metabolism and tricarboxylic acid cycle function. The latest research shows that SGLT2 inhibitors could increase ketone body metabolism by upregulating ketogenic enzymes and transporters in the liver, which might be a significant part of the improvement of NAFLD.

The highlight of the present meta-analysis is that it confirms that SGLT2 can improve NAFLD by the reduction of ALT and liver fat, which opens a new door for the treatment of NAFLD in the future, although there were some certain limitations. First, the sample size of included studies was small, which might cause inhomogeneity of results. Therefore, a greater number of large RCTs are required to further validate the present results. Second, the follow-up time was too short to see the long-term effects of SGLT2 inhibitors. Future studies will need to extend the follow-up period to determine whether SGLT2 continues to improve NAFLD. Finally, the present study mainly evaluated whether SGLT2i could improve NAFLD from liver injury markers and liver fat changes, and did not prove whether it was effective in liver histological changes. Further studies are required to evaluate the impact of SGLT2 inhibitors from liver histology.

In summary, SGLT2 inhibitors can significantly reduce liver injury markers and liver fat, along with the effect of weight loss. Furthermore, the effect on improving NAFLD of SGLT2 inhibitors might be independent of hypoglycemic effect. In brief, compared with other OADs, SGLT2 inhibitors have a beneficial effect on improving fatty liver, and are expected to become a new option for the treatment of type 2 diabetes mellitus with NAFLD.

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DISCLOSURE
The authors declare no conflict of interest.

REFERENCES
1. Adams LA, Anstee QM, Tilg H, et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extra-hepatic diseases. Gut 2017; 66: 1138–1153.
2. Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011; 140: 124–131.
3. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology 2009; 129: 113–121.
4. Williamson RM, Price JF, Glancy S, et al. Prevalence and risk factors for hepatic steatosis and nonalcoholic fatty liver disease in people with type 2 diabetes: the Edinburgh type 2 diabetes study. Diabetes Care 2011; 34: 1139–1144.
5. Targher G, Byrne CD, Lonardo A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. J Hepatol 2016; 65: 589–600.
6. Kim KS, Lee BW, Kim YJ, et al. Non-alcoholic fatty liver disease and diabetes: part II: treatment. Diabetes Metab J 2019; 42: 127–143.
7. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006; 355: 2297–2307.
8. Tahara A, Kurosaki E, Yokono M, et al. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. Eur J Pharmacol 2013; 715: 246–255.
9. Yokono M, Takasu T, Hayashizaki Y, et al. SGLT2 selective inhibitor ipragliflozin reduces body fat mass by increasing fatty acid oxidation in high-fat diet-induced obese rats. Eur J Pharmacol 2014; 727: 66–74.
10. Qiang S, Nakatsu Y, Seno Y, et al. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. Diabetol Metab Syndr 2015; 7: 104.
11. Suzuki M, Takeda M, Kito A, et al. Tofogliflozin, a sodium/glucose co-transporter 2 inhibitor, attenuates body weight gain and fat accumulation in diabetic and obese animal models. Nutr Diabetes 2014; 4: e125.
12. Komiya C, Tsuchiya K, Shiba K, et al. Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in type 2 diabetic patients irrespective of body weight reduction. Plos One 2016; 11: e0151511.
13. Shao S, Chang K, Chien R, et al. Effects of sodium glucose co-transporter 2 inhibitors on serum alanine aminotransferase values in type 2 diabetes patients: a multi-institutional cohort study. Diabetes Obes Metab 2020; 22: 128–134.
14. Bando Y, Ogawa A, Ishikura K, et al. The effects of ipragliflozin on the liver-to-spleen attenuation ratio as assessed by computed tomography and on alanine transaminase levels in Japanese patients with type 2 diabetes mellitus. *Diabetol Int* 2017; 8: 218–227.

15. Kuchay MS, Krishan S, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). *Diabetes Care* 2018; 41: 1801–1808.

16. Shibuya T, Fushimi N, et al. Luseogliflozin improves liver fat deposition compared to metformin in type 2 diabetes patients with non-alcoholic fatty liver disease: a prospective randomized controlled pilot study. *Diabetes Obes Metab* 2018; 20: 438–442.

17. Ito D, Shimizu S, et al. Comparison of ipragliflozin and pioglitazone effects on nonalcoholic fatty liver disease in patients with type 2 diabetes: a randomized, 24-week, open-label, active-controlled trial. *Diabetes Care* 2017; 40: 1364–1372.

18. Eriksson JW, Lundkvist P, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomized placebo-controlled study. *Diabetologia* 2018; 61: 1923–1934.

19. Shimizu M, Suzuki K, Aso Y, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2019; 21: 285–292.

20. Sattar N, Fitchett D, Hantel S, et al. Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial. *Diabetologia* 2018; 61: 2155–2163.

21. Noureddin M, Lam J, Peterson MR, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. *Hepatology* 2013; 58: 1930–1940.

22. Mudalair S, Polidori D, et al. Sodium-glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. *Diabetes Care* 2015; 38: 2344–2353.

23. Ferrannini E, Baldi S, Frascerra S, et al. Shift to fatty substrate utilization in response to sodium glucose cotransporter2 inhibition in subjects without diabetes and patients with type 2 diabetes. *Diabetes* 2016; 65: 1190–1195.

24. Kabil SL, Mahmoud NM. Canagliflozin protects against non-alcoholic steatohepatitis in type-2 diabetic rats through zinc alpha-2 glycoprotein up-regulation. *Eur J Pharmacol* 2018; 828: 135–145.

25. Sakai S, Kaku K, Seino Y, et al. Efficacy and safety of the SGLT2 inhibitor luseogliflozin in Japanese patients with type 2 diabetes mellitus stratified according to baseline body mass index: pooled analysis of data from 52-week phase III trials. *Clin Ther* 2016; 38: 843–862.

26. Vilarr Gomeze, Rodriquez de Miranda A, Gra Oramas B, et al. Clinical trial: a nutritional supplement Viusid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2010; 30: 999–1009.

27. Yamashita H, Takenoshita M, Sakurai M, et al. A glucose-responsive transcription factor that regulates carbohydrate metabolism in the liver. *Proc Natl Acad Sci USA* 2001; 98: 9116–9121.

28. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; 362: 1675–1685.

29. Dixon JB, Bhathal PS, Hughes NR, et al. Nonalcoholic fatty liver disease: improvement in liver histological analysis with weight loss. *Hepatology* 2004; 39: 1647–1654.

30. Jojima T, Tomotsune T, Iijima T, et al. Empagliflozin (an SGLT2 inhibitor), alone or in combination with linagliptin (a DPP-4 inhibitor), prevents steatohepatitis in a novel mouse model of non-alcoholic steatohepatitis and diabetes. *Diabetol Metab Syndr* 2016; 8: 45.

31. Habegger KM, Heppner KM, Geary N, et al. The metabolic actions of glucagon revisited. *Nat Rev Endocrinol.* 2010; 6: 689–97.

32. Honda Y, Imajo K, Kato T, et al. The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. *PLoS One* 2016; 11: e0146337.

33. Suga T, Kikuchi O, Kobayashi M, et al. SGLT1 in pancreatic a cells regulates glucagon secretion in mice, possibly explaining the distinct effects of SGLT2 inhibitors on plasma glucagon levels. *Mol Metab* 2019; 19: 1–12.

34. Cotter DD, Erical B, Huang XJ, et al. Ketogenesis prevents diet-induced fatty liver injury and hyperglycemia. *J Clin Invest* 2014; 124: 5175–5190.

35. Kim JH, Lee M, Kim SH, et al. Sodium-glucose cotransporter 2 inhibitors regulate ketone body metabolism via inter-organ crosstalk. *Diabetes Obes Metab* 2019; 21: 801–811.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1** | Quality evaluation chart of included studies.
Figure S2 | Forest plots depicting ALT level comparisons between SGLT2 inhibitors and control group based on the types of SGLT2 inhibitors.

Figure S3 | The comparison of ALT level between SGLT2 inhibitors and control group based on sample size.

Figure S4 | Forest plots depicting ALT level comparisons between SGLT2 inhibitors and control group based on follow-up time.