

## Novel glucose-lowering drugs for non-alcoholic fatty liver disease

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### Abstract

#### BACKGROUND

The efficacy of novel glucose-lowering drugs in treating non-alcoholic fatty liver disease (NAFLD) is unknown.

#### AIM

To evaluate the efficacy of glucose-lowering drugs dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors in treating NAFLD and to perform a comparison between these treatments.

#### METHODS

Electronic databases were systematically searched. The inclusion criteria were: Randomized controlled trials comparing DPP-4 inhibitors, GLP-1 RAs, or SGLT2 inhibitors against placebo or other active glucose-lowering drugs in NAFLD patients, with outcomes of changes in liver enzyme [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] from baseline.

#### RESULTS

Nineteen studies were finally included in this meta-analysis. Compared with placebo or other active glucose-lowering drug treatment, treatment with DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors all led to a significant decrease in ALT change and AST change from baseline. The difference between the DPP-4 inhibitor and SGLT2 inhibitor groups in ALT change was significant in favor of

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DPP-4 inhibitor treatment ( $P < 0.05$ ). The trends of reduction in magnetic resonance imaging proton density fat fraction and visceral fat area changes were also observed in all the novel glucose-lowering agent treatment groups.

## CONCLUSION

Treatment with DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors resulted in improvements in serum ALT and AST levels and body fat composition, indicating a beneficial effect in improving liver injury and reducing liver fat in NAFLD patients.

**Key Words:** Non-alcoholic fatty liver disease; Glucose-lowering drug; Meta-analysis; Dipeptidyl peptidase-4 inhibitor; Sodium-glucose cotransporter 2 inhibitor; Glucagon-like peptide-1 receptor agonist

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**Core Tip:** The efficacy of novel glucose-lowering drugs in treating non-alcoholic fatty liver disease is unknown. The results of this meta-analysis showed that treatment with dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium-glucose cotransporter 2 inhibitors resulted in improvements in serum alanine aminotransferase and aspartate aminotransferase levels, indicating a beneficial effect in the improvement of liver injury.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of liver disease worldwide. The prevalence of NAFLD has increased rapidly over the past two decades. Approximately 24% of the adult population are reported suffering from NAFLD worldwide<sup>[1]</sup>. NAFLD is characterized by the presence of > 5% hepatic fat accumulation without alcohol abuse, virus infection, autoimmunity, or other secondary causes of liver disease<sup>[2]</sup>, leading to inflammation and subsequent disruption of hepatic function<sup>[3]</sup>. There is growing evidence that NAFLD is not limited to liver-related morbidity and mortality, but also known to be a multisystem disease. NAFLD increases the risk of type 2 diabetes mellitus (T2DM), chronic kidney disease, heart failure, cancer, and cardiovascular disease<sup>[4]</sup>.

Nowadays, the effective treatment for NAFLD is limited. Lifestyle modification is the standard management, including calorie restriction, body weight control, and adequate physical activity<sup>[5]</sup>. Based on the common pathophysiological pathways shared by T2DM and NAFLD including insulin resistance, lipotoxicity, inflammation, and oxidative stress<sup>[6]</sup>, pharmacotherapies treating T2DM might be effective for NAFLD.

Incretin-based therapies and sodium-glucose cotransporter 2 (SGLT2) inhibitors are novel classes of glucose-lowering drugs used in the management of T2DM. Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent the degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide, while GLP-1 receptor agonists (GLP-1 RAs) directly mimic the action of GLP-1<sup>[7-9]</sup>. By improving insulin resistance and inflammation, and decreasing dietary fat, incretin-based therapies might offer potential benefits in treating NAFLD<sup>[10]</sup>. SGLT2 inhibitors are a class of novel glucose-lowering drugs by stimulating glucose excretion in the urine. SGLT2 inhibitors not only improve hyperglycemia, but also obesity, oxidative stress, and inflammation<sup>[11-13]</sup>.

Although accumulated evidence suggests that these novel glucose-lowering drugs are promising in the treatment of NAFLD and nonalcoholic steatohepatitis (NASH)<sup>[14-16]</sup>, there is conflicting evidence and no convincing consensus on their long-

term efficacy and outcome. In addition, there have been few head-to-head clinical trials comparing these novel glucose-lowering drugs directly. In this context, we carried out this meta-analysis to further evaluate the efficacy of novel glucose-lowering drugs in treating NAFLD and to perform a comparison between these treatments.

## MATERIALS AND METHODS

### Data sources and searches

The inclusion criteria for this meta-analysis were: (1) Randomized controlled trials conducted in patients with NAFLD; (2) Studies comparing DPP-4 inhibitors, GLP-1 RAs, or SGLT2 inhibitors against placebo or other active glucose-lowering drugs; and (3) The primary outcome was the change of liver enzyme [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] from baseline. The secondary outcomes were the changes of magnetic resonance imaging proton density fat fraction (MRI-PDFF), visceral fat area (VFA), body weight, body mass index (BMI), and/or glycated hemoglobin A1c (HbA1c) from baseline. Case reports, animal studies, and case-control studies were excluded. The study selection followed the Preferred Reporting Items for systematic reviews and meta-analyses flow diagram<sup>[17]</sup>.

### Study selection

Two investigators (ZDF and XLC) independently conducted systematic searches of the databases MEDLINE, Cochrane central register of controlled trials, and Embase for studies up to May 30, 2020 according to the Cochrane handbook for systematic reviews for meta-analysis. The following terms were searched: Dipeptidyl peptidase 4 inhibitor, DPP-4 inhibitor, DPP-IV inhibitor, sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, dutogliptin, teneligliptin, anagliptin, evogliptin, retagliptin, omarigliptin, glucagon-like peptide-1 receptor agonist, GLP-1 receptor agonist, GLP-1 RA, GLP1RA, liraglutide, semaglutide, albiglutide, lixisenatide, taspoglutide, exenatide, dulaglutide, sodium-glucose cotransporter 2 inhibitor, SGLT2 inhibitor, SGLT-2 inhibitor, empagliflozin, dapagliflozin, canagliflozin, luseogliflozin, ipragliflozin, tofogliflozin, sotagliflozin, ertugliflozin, nonalcoholic fatty liver disease, NAFLD, fatty liver, NASH, nonalcoholic steatohepatitides, NASH, NAFLD, non-alcoholic steatohepatitis, and non-alcoholic steatohepatitides. To identify additional relevant data of eligible published trials, we also searched ClinicalTrial.gov.

### Data extraction and quality assessment

Two independent reviewers (ZDF and XLC) extracted data from each publication, including sources of publication, title, year, first author, study design, baseline characteristics of study population (sample size, age, assessment of diagnosis, body weight, BMI, and HbA1c), treatment allocation, duration of treatment, and changes of ALT, AST, MRI-PDFF, VFA, body weight, BMI, and HbA1c from baseline. If the above relevant data was not reported in the published trial, the registry report of ClinicalTrials.gov was further extracted.

The quality of all included studies was assessed using the Cochrane risk of bias tool. The following aspects were included: Selection bias, performance bias, detection bias, attrition bias, reporting bias, and others.

### Statistical analysis

The continuous outcomes in this meta-analysis were evaluated by computing the weighted mean differences (WMDs) and 95% confidence intervals (CIs). The  $I^2$  statistic was analyzed to assess the heterogeneity. If  $I^2 > 50\%$  and the  $P$  value of the  $\chi^2 < 0.10$ , representing statistical heterogeneity across studies, the random-effects model was used. The fixed-effects model was used with low levels of heterogeneity. Publication bias was assessed *via* visual inspection of funnel plot. All analyses were conducted with Review Manager, version 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark). Meta-regression analyses were conducted with STATA statistical software package (Version 13.1, Stata Corp, College Station, TX, United States). A  $P$  value  $< 0.05$  was considered statistically significant.

## RESULTS

### Characteristics of enrolled studies

After literature search, 19 studies were included in the meta-analysis (Table 1). Among these 19 studies, 7 compared DPP-4 inhibitors with placebo or other active glucose-lowering drugs<sup>[18-24]</sup>, 8 compared GLP-1 RAs with placebo or other active glucose-lowering drugs<sup>[24-31]</sup>, and 5 compared SGLT2 inhibitors with placebo or other active glucose-lowering drugs<sup>[32-36]</sup>. The process of study selection is presented in Figure 1. The risks of bias of the included studies are presented in Supplementary Figure 1.

### Changes in ALT and AST

Overall, compared with placebo or other active glucose-lowering drug treatment, DPP-4 inhibitor treatment led to a significant decrease in ALT (WMD = -9.48 IU/L, 95%CI: -15.61 to -3.36 IU/L,  $P < 0.01$ ) and AST from baseline (WMD = -8.36 IU/L, 95%CI: -14.86 to -1.85 IU/L,  $P = 0.01$ ) in NAFLD patients (Figure 2A and B). Compared with placebo or other active glucose-lowering drug treatment, GLP-1 RA treatment led to a significant decrease in ALT (WMD = -8.73 IU/L, 95%CI: -13.29 to -4.18 IU/L,  $P < 0.01$ ) and AST from baseline (WMD = -2.65 IU/L, 95%CI: -5.14 to -0.16 IU/L,  $P = 0.04$ ) (Figure 2C and D). Compared with placebo or other active glucose-lowering drug treatment, SGLT2 inhibitor treatment also led to a significant decrease in ALT (WMD = -3.44 IU/L, 95%CI: -5.08 to -1.81 IU/L,  $P < 0.01$ ) and AST from baseline (WMD = -1.47 IU/L, 95%CI: -2.65 to -0.30 IU/L,  $P = 0.01$ ) (Figure 2E and F).

When DPP-4 inhibitor treatment was compared with SGLT2 inhibitor treatment, the difference between groups in AST change was significant in favor of DPP-4 inhibitors treatment ( $P = 0.04$ ). When GLP-1 RA treatment was compared with SGLT2 inhibitor treatment, the difference between groups in ALT change and AST change was not significant ( $P > 0.05$ ). While comparisons between DPP-4 inhibitor treatment and GLP-1 RA treatment also indicated no significant difference between groups in ALT or AST change relative to baseline ( $P > 0.05$ ).

### Changes in body weight and BMI

The absolute body weight change relative to baseline after DPP-4 inhibitor treatment was -1.20 kg (95%CI: -1.44 to -0.95 kg,  $P < 0.01$ ) when compared with placebo or other active glucose-lowering drug treatment, while the absolute BMI change relative to baseline showed no significant difference. When GLP-1 RA treatment was compared with placebo or other active glucose-lowering drug treatment, the difference between groups in body weight and BMI were both significant (WMD = -3.61 kg, 95%CI: -5.74 to -1.48 kg,  $P < 0.01$ ; WMD = -1.46 kg/m<sup>2</sup>, 95%CI: -2.23 to -0.69 kg/m<sup>2</sup>,  $P < 0.01$ , respectively). When SGLT2 inhibitor treatment was compared with placebo or other active glucose-lowering drug treatment, the difference between groups in body weight and BMI were both significant (WMD = -2.53 kg, 95%CI: -3.35 to -1.71 kg,  $P < 0.01$ ; WMD = -1.72 kg/m<sup>2</sup>, 95%CI: -2.68 to -0.75 kg/m<sup>2</sup>,  $P < 0.01$ , respectively) (Table 2).

The body weight change from baseline and BMI change from baseline were significantly greater with GLP-1 RA treatment and SGLT2 inhibitor treatment when compared with DPP-4 inhibitor treatment ( $P < 0.05$ ). No significant difference was observed in the change of body weight or BMI from baseline between the GLP-1 RA treatment and SGLT2 inhibitor treatment groups ( $P > 0.05$ ).

### Change in HbA1c

The majority of the included studies evaluated the change in HbA1c from baseline. The results showed that DPP-4 inhibitor treatment, compared with placebo or other active glucose-lowering drug treatment, had a significant reduction in HbA1c level from baseline (WMD = -0.425%, 95%CI: -0.58% to -0.25%,  $P < 0.01$ ). While GLP-1 RA and SGLT2 inhibitor treatment showed no statistical difference in HbA1c reductions (WMD = -0.29, 95%CI: -0.85% to 0.26%,  $P < 0.30$ ; WMD = -0.36, 95%CI: -0.80% to 0.08%,  $P = 0.11$ , respectively) (Table 3). Subgroup analyses only comprising studies that evaluated the studied drugs against placebo showed that HbA1c levels decreased significantly in the DPP-4 inhibitor, GLP-1 RA, and SGLT2 inhibitor treatment groups (Table 3). The difference of HbA1c change from baseline between all these three treatment groups was not significant ( $P > 0.05$ ).

### Changes in MRI-PDFF and VFA

Two studies provided information on MRI-PDFF change in the comparison between the DPP-4 inhibitor and control groups. The results showed no significant reduction in MRI-PDFF, with a WMD of -2.31% (95%CI: -4.92% to 0.29%,  $P = 0.08$ ). The only one

Table 1 Summary of included studies

Ref.	Study duration	Population	Assessment of NAFLD	Intervention	No. of participants
Alam <i>et al</i> <sup>[18]</sup> , 2018	52 wk	NAFLD	Biopsy	Sitagliptin 100 mg QD + lifestyle modification	20
				Lifestyle modification	20
Cui <i>et al</i> <sup>[19]</sup> , 2017	24 wk	NAFLD with prediabetes or early diabetes	MRI	Sitagliptin 100 mg QD	25
				PBO	25
Hussain <i>et al</i> <sup>[20]</sup> , 2016	12 wk	NAFLD + dyslipidemia	Ultrasound	Vildagliptin 50 mg Bid	29
				PBO	29
Macauley <i>et al</i> <sup>[21]</sup> , 2015	6 mo	T2DM with hepatic steatosis	Imaging (CT or ultrasound)	Vildagliptin 50 mg Bid	22
				PBO	22
Joy <i>et al</i> <sup>[22]</sup> , 2017	24 wk	NASH	Biopsy	Sitagliptin 100 mg QD	6
				PBO	6
Li <i>et al</i> <sup>[23]</sup> , 2019	24 wk	T2DM with NAFLD	Imaging or biopsy	Saxagliptin 5 mg QD	31
				Glimepiride 2 mg QD	33
				Glimepiride 2 mg QD + polyenephosphatidylcholine 456 mg TID	31
Yan <i>et al</i> <sup>[24]</sup> , 2019	26 wk	T2DM with NAFLD	MRI	Liraglutide 1.8 mg + metformin	24
				Sitagliptin + metformin	27
				Glargine 0.2 IU/Kg/d + metformin	24
Armstrong <i>et al</i> <sup>[25]</sup> , 2016	48 wk	T2DM with NASH	Biopsy	Liraglutide 1.8 mg QD	26
				PBO	26
Cusi <i>et al</i> <sup>[26]</sup> , 2018	6 mo	T2DM with NAFLD/NASH	Laboratory liver tests	Duraglutide 1.5 mg QW	971
				PBO	528
Fan <i>et al</i> <sup>[27]</sup> , 2013	12 wk	T2DM with NAFLD	Ultrasound	Exenatide	49
				Metformin	68
Feng <i>et al</i> <sup>[28]</sup> , 2017	24 wk	T2DM with NAFLD	Ultrasound	Metformin 1000 mg Bid	29
				Gliclazide 120 mg/d	29
				Liraglutide 1.8 mg QD	29
Khoo <i>et al</i> <sup>[29]</sup> , 2017	26 wk	NAFLD	MRI	Liraglutide 3.0 mg QD	12
				Diet and exercise	12
Shao <i>et al</i> <sup>[30]</sup> , 2014	12 wk	T2DM with NAFLD	Ultrasound	Exenatide 10 µg bid + glargine	30
				Intensive insulin therapy	30
Tian <i>et al</i> <sup>[31]</sup> , 2018	12 wk	T2DM with NAFLD	Ultrasound	Liraglutide 0.6-1.2 mg QD	52
				Metformin 1000-1500 mg/d	75
Eriksson <i>et al</i> <sup>[32]</sup> , 2018	12 wk	T2DM with NAFLD	MRI	Dapagliflozin 10 mg QD	21
				PBO	21
				Dapagliflozin 10 mg QD + OM-3CA	22

Ito <i>et al</i> <sup>[33]</sup> , 2017	24 wk	T2DM with NAFLD	Clinical laboratory tests or imaging	OM-3CA 4 g	20
				Ipragliflozin 50 mg QD	32
				Pioglitazone 15–30 mg QD	34
Kuchay <i>et al</i> <sup>[34]</sup> , 2018	20 wk	T2DM with NAFLD	MRI	Empagliflozin 10 mg QD	22
				Control	20
Shibuya <i>et al</i> <sup>[35]</sup> , 2018	6 mo	T2DM with NAFLD	Imaging (CT or ultrasound)	Luseogliflozin 2.5 mg QD	16
				Metformin 1500 mg QD	16
Shimizu <i>et al</i> <sup>[36]</sup> , 2018	24 wk	T2DM with NAFLD	Transient elastography	Dapagliflozin 5 mg QD	33
				Control	24

NAFLD: Non-alcoholic fatty liver disease; MRI: Magnetic resonance imaging; T2DM: Type 2 diabetes mellitus; NASH: Nonalcoholic steatohepatitis; CT: Computed tomography.

**Table 2 Comparison of body weight and body mass index changes from baseline in different treatment groups**

	Studies	Participants	WMD	95%CI		P value
Body weight change						
DPP-4 inhibitors	4	140/138	-1.20	-1.44	-0.95	< 0.0001
GLP-1 RAs	8	1222/821	-3.61	-5.74	-1.48	0.0009
SGLT2 inhibitors	5	146/135	-2.53	-3.35	-1.71	< 0.0001
BMI change						
DPP-4 inhibitors	5	144/146	-0.59	-1.80	0.61	0.33
GLP-1 RAs	7	251/293	-1.46	-2.23	-0.69	0.0002
SGLT2 inhibitors	4	114/101	-1.72	-2.68	-0.75	0.0005

WMD: Weighted mean difference; CI: Confidence interval; DPP-4: Dipeptidyl peptidase-4; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; SGLT2: Sodium-glucose cotransporter 2; BMI: Body mass index.

**Table 3 Comparison of hemoglobin A1c change from baseline in different treatment groups**

	Studies	Participants	WMD	95%CI		P value
HbA1c change						
DPP-4 inhibitors	6	166/166	-0.42	-0.58	-0.25	< 0.0001
GLP-1 RAs	7	1210/809	-0.29	-0.85	0.26	0.30
SGLT2 inhibitors	5	146/135	-0.36	-0.80	0.08	0.11
HbA1c change (placebo-controlled studies only)						
DPP-4 inhibitors	5	102/102	-0.38	-0.71	-0.05	0.02
GLP-1 RAs	3	1009/566	-0.88	-1.56	-0.19	0.01
SGLT2 inhibitors	1	21/21	-0.50	-0.84	-0.16	0.004

HbA1c: Hemoglobin A1c; WMD: Weighted mean difference; CI: Confidence interval; DPP-4: Dipeptidyl peptidase-4; GLP-1 RA: Glucagon-like peptide-1 receptor agonists; SGLT2: Sodium-glucose cotransporter 2.

study used the indicator of MRI-PDFF in the comparison between the GLP-1 RA and control groups showed a significant -3.20% reduction (95%CI: -5.98% to -0.42%,  $P = 0.02$ ). MRI-PDFF was observed in two studies with SGLT2 inhibitor treatment, and the results suggested that SGLT2 inhibitor treatment decreased MRI-PDFF with marginal significance in the comparison with the control group (WMD = -1.18%, 95%CI: -2.38% to 0.03%,  $P = 0.06$ ) (Table 4). The difference of MRI-PDFF change from baseline between all these three treatment groups was not significant ( $P > 0.05$ ).

One study comprising sitagliptin and liraglutide arms reported the effect of VFA change in the comparison with glargine insulin treatment. The results of this study indicated that both sitagliptin and liraglutide could obviously decrease VFA (WMD -23.10 cm<sup>2</sup>, 95%CI: -38.84 to -7.36 cm<sup>2</sup>,  $P = 0.004$ ; WMD -30.40 cm<sup>2</sup>, 95%CI: -46.86 to -13.94 cm<sup>2</sup>,  $P < 0.001$ ; respectively). Although only two studies used the indicator of VFA in the included studies comparing the SGLT2 inhibitor and control groups, both of which showed that SGLT2 inhibitors could reduce it (WMD -23.48 cm<sup>2</sup>, 95%CI: -25.85 to -21.12 cm<sup>2</sup>,  $P < 0.001$ ) (Table 4). The difference of VFA change from baseline between all these three treatment groups was not significant ( $P > 0.05$ ).

### **Association between changes in transaminase, body fat composition, and weight loss**

Meta-regression analyses indicated that the weight change difference was not associated with the difference of ALT, AST, MRI-PDFF, and VFA between antidiabetes drugs and controls (Table 5).

## **DISCUSSION**

In the present meta-analysis, we found that compared with placebo or other active glucose-lowering agents, pooling of results from the included studies revealed significant improvements in serum ALT and AST levels following treatment with the novel agents (DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors) in NAFLD patients. VFA and MRI-PDFF are quantitative biomarkers that can accurately estimate liver fat content. Although there were just four studies, all of them showed that novel glucose-lowering agents could decrease VFA. Furthermore, the trends of reduction in MRI-PDFF changes were also observed in all the novel glucose-lowering agent treatment groups. Therefore, all these novel glucose-lowering agents showed a beneficial effect in improving liver injury and reducing liver fat in NAFLD patients.

Apart from the proven effect on glucose control, GLP-1 RAs have several metabolic functions, including decreasing insulin resistance and lipotoxicity, enhancing liver glucose uptake, and improving peripheral insulin sensitivity<sup>[37]</sup>. DPP-4 inhibitors act on the enzyme DPP-4, which are expected to prolong the action of GLP-1. SGLT2 inhibitors also appear to have a beneficial hepatic effect in patients with NAFLD and T2DM<sup>[38]</sup>. The incretin-based therapies and SGLT2 inhibitors act in numerous potential ways in the pathogenesis of NAFLD: (1) Weight loss is a recognized predictor of reductions in liver fat<sup>[39]</sup>. The amount of weight loss is considered to be a determinant of histologic improvements in liver injury<sup>[40]</sup>. Clearly, the evidence that GLP-1 RAs and SGLT2 inhibitors lead to significant weight loss has been proven in many clinical trials conducted in various populations, although through different mechanisms. In the current meta-analysis, significant reductions in BMI and body weight were also observed in NAFLD patients treated with GLP-1 RAs and SGLT2 inhibitors; (2) Improvement of inflammation and oxidation: DPP-4 inhibitors were shown to affect inflammatory pathways in animal models of NASH, including reduced expression of proinflammatory mediators and attenuation of endoplasmic reticulum stress and hepatocyte apoptosis<sup>[41,42]</sup>. In an animal model of non-obese NASH, GLP-1 RAs were shown to inhibit hepatic inflammation through inhibition of hepatic free fatty acid influx and oxidative stress<sup>[43]</sup>. In addition, GLP-1 RAs can act directly on Kupffer cell function to reduce the influx of macrophages to the liver<sup>[44]</sup>. SGLT2 inhibitor treatments were also shown to attenuate the development of NASH through anti-inflammatory and oxidation effects in rodent models<sup>[11,45]</sup>; (3) Hyperglycaemia plays an important role in the process of liver lipogenesis by activating the key modulator-carbohydrate-responsive element-binding protein transcriptional factor<sup>[46]</sup>. Therefore, improvement in glycaemic control observed in the current meta-analysis might also contribute to the amelioration of NAFLD; and (4) The above effects help to ameliorate the condition of insulin resistance, which is a common and key feature of NAFLD that contributes to its pathogenesis<sup>[47]</sup>. All these effects provide the possibility for the treatment of NAFLD with incretin-based therapies and SGLT2 inhibitors.

**Table 4 Comparison of magnetic resonance imaging proton density fat fraction and visceral fat area change from baseline in different treatment groups**

	Studies	Participants	WMD	95%CI		P value
MRI-PDFF change						
DPP-4 inhibitors	2	52/49	-2.31	-4.92	0.29	0.08
GLP-1 RAs	1	24/24	-3.20	-5.98	-0.42	0.02
SGLT2 inhibitors	2	65/61	-1.18	-2.38	0.03	0.06
VFA change						
DPP-4 inhibitors	1	27/24	-23.10	-38.84	-7.36	0.004
GLP-1 RAs	1	24/24	-30.40	-46.86	-13.94	0.0003
SGLT2 inhibitors	2	48/50	-23.48	-25.85	-21.12	< 0.0001

MRI-PDFF: Magnetic resonance imaging proton density fat fraction; VAF: Visceral fat area; WMD: Weighted mean difference; CI: Confidence interval; DPP-4: Dipeptidyl peptidase-4; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; SGLT2: Sodium-glucose cotransporter 2.

**Table 5 Meta-regression analyses of association between weight change difference and difference of alanine aminotransferase, aspartate aminotransferase, magnetic resonance imaging proton density fat fraction, and visceral fat area between antidiabetes drugs and controls ( $\beta$  coefficient value, P value, and 95%CI are shown)**

	$\beta$	P value	95%CI
ALT	0.064	0.267	-0.053-0.181
AST	0.020	0.735	-0.104-0.144
MRI-PDFF	0.308	0.701	-2.678-3.294
VFA	1.776	0.343	-11.723-15.275

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRI-PDFF: Magnetic resonance imaging proton density fat fraction; VFA: Visceral fat area.

In this meta-analysis, we also tried to figure out the difference of these novel drugs' effects on NAFLD. To the best of our knowledge, there is no head-to-head study comparing their effect. The serum ALT is a specific indicator of hepatic inflammation, which is recommended as a means of monitoring disease improvement<sup>[48]</sup>. The indirect comparison result from our meta-analysis suggested that GLP-1 RAs can better improve serum ALT level when compared with SGLT2 inhibitors. Regarding VFA and MRI-PDFF, no significance difference was observed between these treatment groups. As mentioned above, the incretin-based therapies and SGLT2 inhibitors shared several targets in the pathogenesis of NAFLD. However, GLP-1 RAs and SGLT2 inhibitors also possess additive benefits, respectively. Ketogenesis plays an important role in the pathogenesis of NAFLD. It has been found that SGLT2 inhibitors could enhance ketone body metabolism by upregulating transporters and ketogenic enzymes in the liver<sup>[49]</sup>. Besides, the benefits of GLP-1 RAs in amelioration of lipotoxicity were observed in several clinical trials<sup>[25,50]</sup>. In addition, it is worth noting that heterogeneity existed between different treatment groups. Therefore, we should explain the results with caution, and it is still hard to judge which treatment is more effective. Individualized treatment options for patients with different characteristics might be more appropriate. More head-to-head studies are needed to further illuminate the underlying difference between these treatments.

As a meta-analysis, this study has several potential limitations. First, as mentioned above, this meta-analysis included studies with different treatment durations, baseline characteristics, and predefined outcomes, which might result in bias. Second, the numbers of participants with available reports of VFA and MRI-PDFF were limited, which might weaken the statistical power. Third, the diagnostic criteria for NAFLD were different, leading to heterogeneity across studies. Additionally, the included trials were relatively short in duration compared to the timescale of progression of NAFLD. As we know, the histological progression or resolution is recognized as the



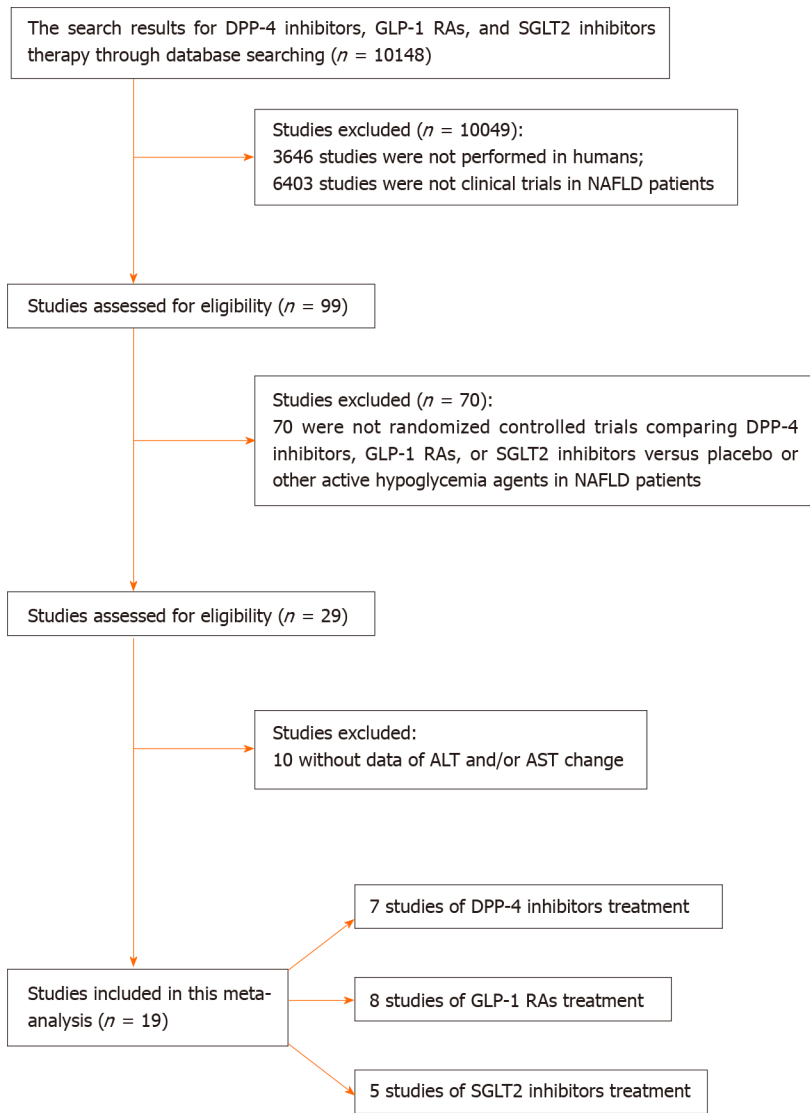


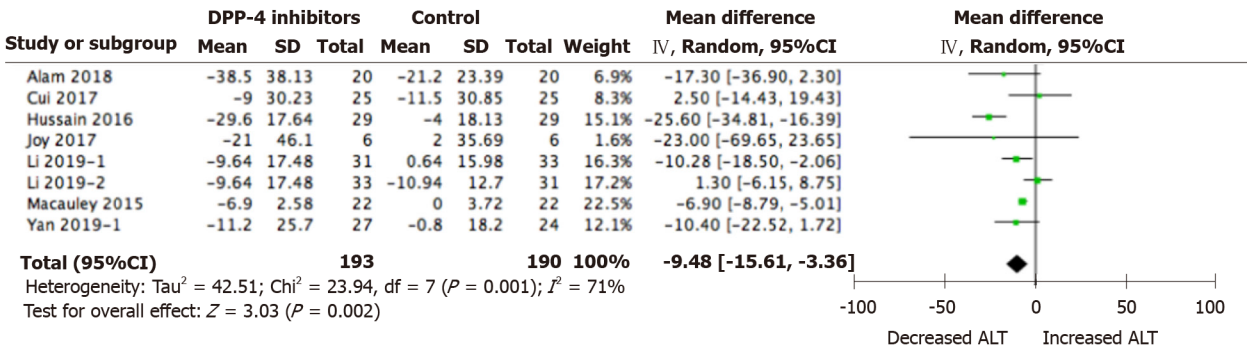
Figure 1 Flow chart of included studies.

"gold standard" of disease evaluation. However, a search of the previous literature showed that controlled trials with histological outcomes were limited. In this context, we used the indirect quantified measures (changes in ALT and AST levels) as the primary outcome measures.

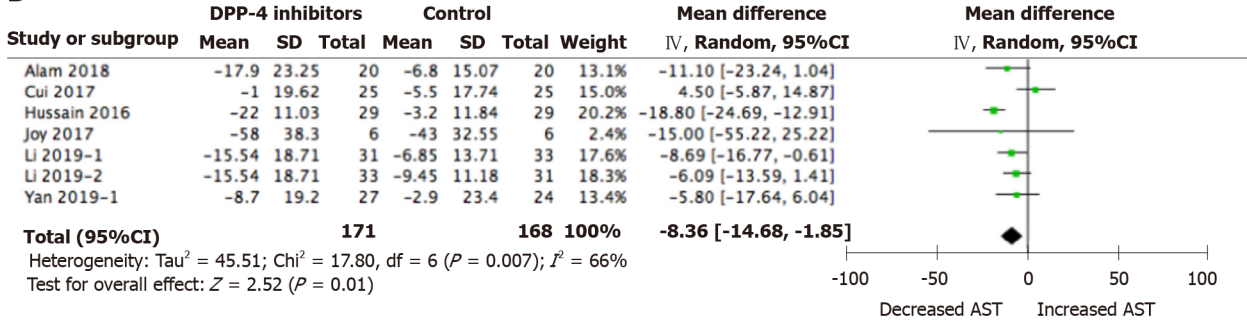
## CONCLUSION

According to this study, treatment with DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors resulted in improvements in serum ALT and AST levels and body fat composition, indicating that all these novel glucose-lowering agents have a beneficial effect in improving liver injury and reducing liver fat in NAFLD patients.

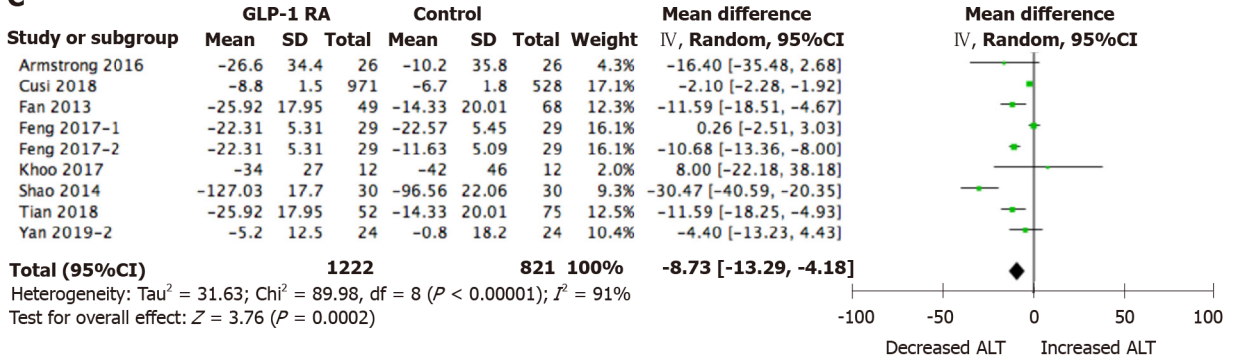
**A**



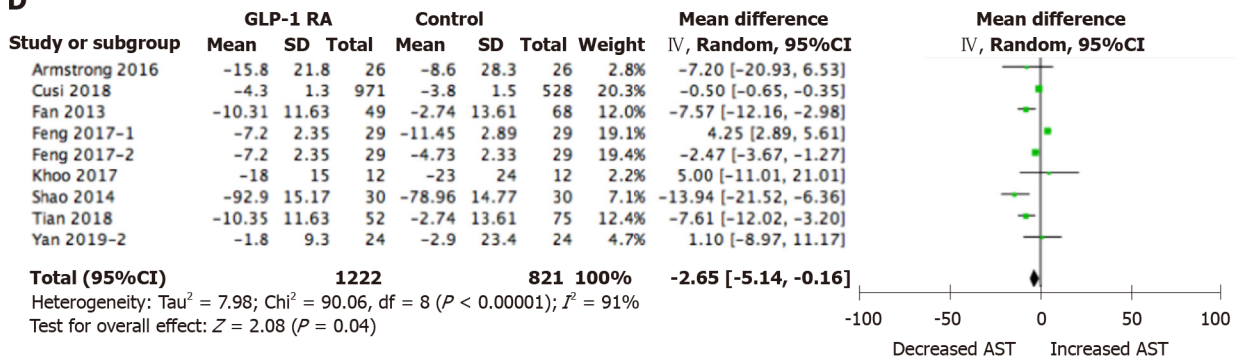
**B**

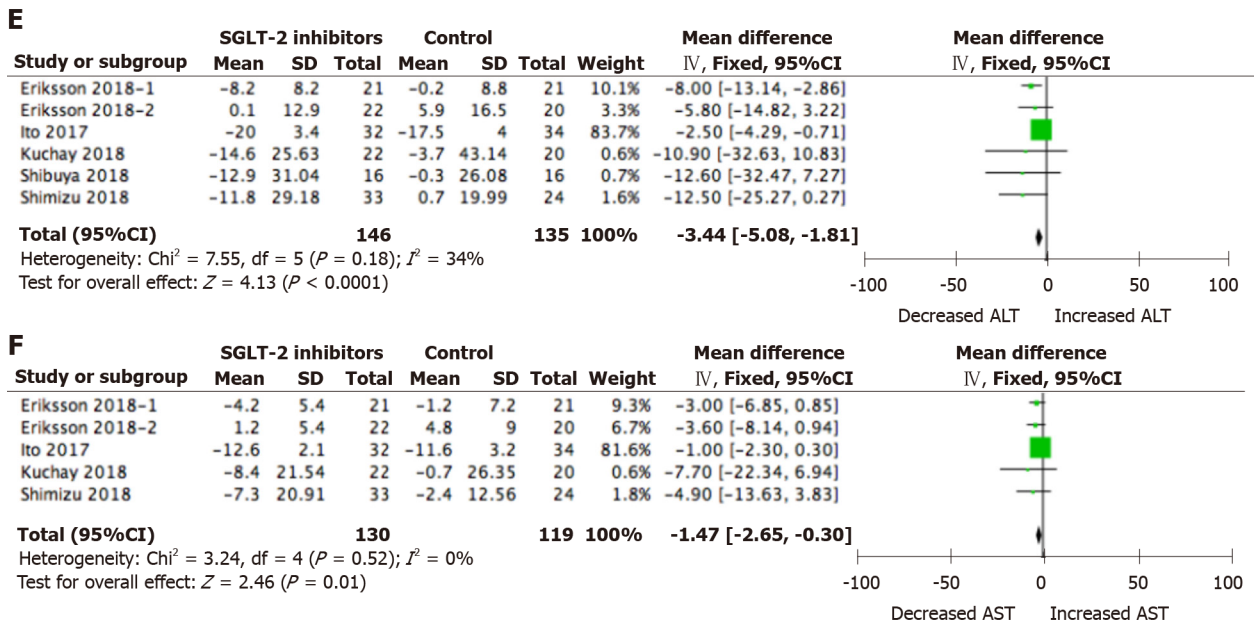


**C**



**D**





**Figure 2 Alanine aminotransferase and aspartate aminotransferase changes from baseline in non-alcoholic fatty liver disease patients treated with novel glucose-lowering drugs.** A: Alanine aminotransferase (ALT) changes with dipeptidyl peptidase-4 inhibitor treatment; B: Aspartate aminotransferase (AST) changes with dipeptidyl peptidase-4 inhibitor treatment; C: ALT changes with glucagon-like peptide-1 receptor agonist treatment; D: AST changes with glucagon-like peptide-1 receptor agonist treatment; E: ALT changes with sodium-glucose cotransporter 2 inhibitor treatment; F: AST changes with sodium-glucose cotransporter 2 inhibitor treatment.

## ARTICLE HIGHLIGHTS

### Research background

The efficacy of novel glucose-lowering drugs in treating non-alcoholic fatty liver disease (NAFLD) is unknown.

### Research motivation

Although accumulated evidence suggests that these novel glucose-lowering drugs are promising in the treatment of NAFLD and nonalcoholic steatohepatitis, there is conflicting evidence and no convincing consensus on their long-term efficacy and outcome. In addition, there have been few head-to-head clinical trials comparing these novel glucose-lowering drugs directly.

### Research objectives

We carried out this meta-analysis to evaluate the efficacy of novel glucose-lowering drugs in treating NAFLD.

### Research methods

Electronic databases were systematically searched. The inclusion criteria were: Randomized controlled trials comparing dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), or sodium-glucose cotransporter 2 (SGLT2) inhibitors against placebo or other active glucose-lowering drugs in NAFLD patients, with outcomes of changes in liver enzyme [alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)] from baseline.

### Research results

Treatment with DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors resulted in improvements in serum ALT and AST levels. The trends of reduction in magnetic resonance imaging proton density fat fraction and visceral fat area changes were also observed in the DPP-4 inhibitor, GLP-1 RA, and SGLT2 inhibitor treatment groups.

### Research conclusions

Treatment with DPP-4 inhibitors, GLP-1 RAs, and SGLT2 inhibitors resulted in improvements in serum ALT and AST levels and body fat composition, indicating a

beneficial effect in improving liver injury and reducing liver fat in NAFLD patients.

### Research perspectives

In this meta-analysis, we made a comprehensive evaluation of the efficacy of novel glucose-lowering drugs in treating NAFLD.

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