Systematic Review and Meta-Analysis

Medicine

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Liraglutide on type 2 diabetes mellitus with nonalcoholic fatty liver disease

A systematic review and meta-analysis of 16 RCTs

Yan Zhao, Master[a], Wenli Zhao, PhD[b,c], Huaien Bu, PhD[d], Maeda Toshiyoshi, Master[e], Ye Zhao, MD, PhD, MBA[f,*]

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity of type 2 diabetes mellitus (T2DM). Our aim is to investigate the effects of liraglutide on T2DM with NAFLD.

Methods: Relevant articles published from the earliest publication to March 2022 were selected from several databases. The Cochrane Collaboration's RevMan software was used for the analysis.

Results: Sixteen studies are selected for this meta-analysis, which includes totally 634 patients in the treatment group and 630 patients in the control group. As a result, 14 studies show that fasting plasma glucose levels of the experimental group are lower than that of the control group; 15 studies show that glycosylated hemoglobin A1c levels of the experimental group are lower than that of the control group; 13 studies show that triglyceride levels of the experimental group are lower than that of the control group; twelve studies show that total cholesterol levels of the experimental group are lower than that of the control group; 10 studies show that alanine aminotransferase levels of the experimental group is lower than that of the control group; 10 studies show that no significant difference in changes in aspartate transaminase between 2 groups; 13 studies show that low density lipoprotein cholesterol levels of the experimental group is lower than that of the control group; 9 studies show that no significant difference in changes in high density lipoprotein cholesterol between 2 groups; 7 studies mentioned adverse effects and the difference is significant.

Conclusion: Liraglutide is potentially curative for T2DM with NAFLD.

Abbreviations: AEs = adverse effects, ALT = alanine aminotransferase, AST = aspartate transaminase, CI = confidence intervals, DM = diabetes mellitus, FFAs = free fatty acids, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin A1c, GK = glucokinase, GLP-1 = glucagon-like peptide-1, HDL-C = high density lipoprotein cholesterol, IR = insulin resistance, LDL-C = low density lipoprotein cholesterol, MD = mean difference, NAFLD = nonalcoholic fatty liver disease, PPAR = peroxisome proliferator-activated receptor, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglyceride, WANFANG = Wanfang Data Knowledge Service Platform databases.

Keywords: diabetes mellitus, liraglutide, meta-analysis, nonalcoholic fatty liver disease, systematic review

1. Introduction

Diabetes mellitus (DM) is a kind of metabolic disease, a disorder of lipid metabolism is especially manifested. In 2019, International Diabetes Federation reported that global DM patients' amount reaches 463 million, and may increase to 700 million by the end of 2045.[1] According to the standard of the American Diabetes Association, DM can be divided into 4 categories: type 1 DM, type 2 diabetes mellitus (T2DM), gestational DM and special type DM.[2] The patients amount of T2DM is the largest, which contributes greater than 90% of all DMs. The number increases sharply in countries of low-income and middle-income.[3] T2DM is manifested as a disorder of glucose metabolism which is caused by genetic and/or environmental factors. An impaired insulin regulation is the first pathophysiological characteristic of T2DM. Then the following dysfunction of islets β-Cells usually cause a decreased insulin secretion.[4] Obesity is a T2DM risk factor. Due to the body

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[a] Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin, China, [b] Department of Public Health, International College, Krirk University, Bangkok, Thailand, [c] Liver Center, Saga University Hospital, Saga University, Saga, Japan, [d] School of Health Science and Engineering, Tianjin University of Traditional Chinese Medicine, Tianjin, China, [e] International Education College, Shandong University of Traditional Chinese Medicine, Jinan, China, [f] Department of Public Health, International College, Krirk University, Bangkok, Thailand.

** Correspondence: Ye Zhao, Department of Public Health, International College, Krirk University, Bangkok 10220, Thailand (e-mail: zhao.ye@staff.krirk.ac.th).*

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fat accumulation, insulin resistance (IR) and hyperinsulinemia form. Then the tissues' glucose utilization and tolerance decrease, and T2DM emerges finally.[5] IR is a core pathophysiological mechanism for both obesity and T2DM. Adipose tissue remodels and adipokines release from mast adipocytes when the fat deposits. It leads to the IR and T2DM.[6] Excessive fat deposition transmits a significant negative signal, which prevents the stored fat from generating energy. Fat accumulation worsens the insulin sensitivity. Peroxisome proliferator-activated receptor (PPAR) γ expresses a large number of genes, especially adiponectin, which is related to lipid mobilization and energy production through mitochondria.[7] In inflammatory adipose tissue, the down-regulation of adiponectin is mainly affected by inactivation of PPAR γ transcription factor. Inhibitory phosphorylation is on the Serine 273.[8,9] Since PPAR γ regulates the expression of mitochondrial bioenergetics genes involved in fat mobilization, its inactivity could cause IR majorly.[10] The sustained hyperglycemia damages islet β cells. It can down-regulate some islet β cell genes, including the pancreaticoduodenal homologous box gene 1, the insulin promoter element 3β binding protein 1, glucose transporter 2, and glucokinase (GK) etc.; it up-regulates the CCAAT/enhancer binding protein β mRNA and cAMP response element regulators (CREM and ICER).[11] Hyperglycemia also can decrease the binding activity of insulin promoter element 3β binding protein 1 to the C1 box of insulin gene promoter.[12] Free fatty acid (FFA) inhibits the expression of acetyl coenzyme A carboxylase gene, decreases the contents of glucose transporter 2, GK and malonyl coenzyme A on the surface of β cells. It can impair glucose transport and activation, and reduce glucose stimulated insulin secretion.[13] In addition, FFAs inhibits the activity of K^+-adenosine triphosphate (ATP) channel, hinders the opening of voltage dependent L-type Ca^{2+} channel. As a result, it directly reduces the secretion of insulin and the conversion of proinsulin into insulin. Long term high free fatty acidemia up-regulate the uncoupling protein 2 gene, reduce the intracellular ATP synthesis, decrease the ATP/adenosine diphosphate ratio, and decrease the glucose stimulated insulin secretion.[14] Impaired β cell function is a necessary condition for the pathogenesis of T2DM. IR is a promoting factor and also plays an important role in T2DM.[15] Under the development of the biochemical examination, more T2DM combined with nonalcoholic fatty liver disease (NAFLD) is detected gradually.[16] NAFLD is a metabolic hepatocyte injury, excluding alcohol, related to the abnormal metabolism of glucose and lipid. NAFLD includes NAFL, nonalcoholic steatohepatitis, and nonalcoholic steatocirrhosis.[17] It is shown that more than 76% of T2DM patients have NAFLD.[16] Some studies show that confirmed NAFLD, the prevalence of NAFLD in T2DM patients also reaches 69.4% to 78%.[18,19] T2DM may be the risk factors of NAFLD And NAFLD itself may be also a risk factor for T2DM and its complications.[20] The causes of T2DM complicated with NAFLD may be: an imbalance of fat metabolism comes from insufficient insulin secretion, lacking hypolipidemic effect, high free fatty acidemia, and over-synthesized fat in hepatocyte[21]; FFA can further induce fatty infiltration in hepatocytes[22]; and a storage of FFA in hepatocytes causes damage to lysosomes, mitochondria, cytoplasm, then triggers inflammatory reaction, and eventually induces hepatocyte degeneration to necrosis.[23] Lipid metabolism disorder and obesity are predisposing factors of T2DM with NAFLD, and IR is the key pathogenesis.

More treatments for T2DM are developed, such as antidiabetic drugs, metabolic surgery, intestinal microecological agents, gene therapy and so on. Glucagon-like peptide-1 (GLP-1) analogues include exenatide, liraglutide, albiglutide and dulaglutide.[24] There are also some other targets, for instance sodium glucose co-transporter 2 inhibitors, dopamine receptor agonists, GK agonist. Compared with above, however, NAFLD has no approved drug. Metformin, vitamin E and ursodeoxycholic acid are indirectly used in NAFLD for anti-IR, anti-oxidative stress and cell protection therapy.[25] Drugs with farnesoid X-activated receptor agonist activity, such as albencholic acid, have been approved for the treatment of patients with primary cholangitis and have been shown to be particularly useful in improving insulin sensitivity in NAFLD patients with type 2 diabetes.[26] Statins can effectively reduce blood lipid levels, significantly reduce the risk of cardiovascular accidents and severe liver complications in patients with NAFLD.[27] The lifestyle of diet and exercise may reduce the NAFLD risk of obese patients by decreasing the level of Alanine aminotransferase (ALT).[28] Gradual weight loss should be emphasized, because a sudden reduction might lead to severe steatosis, and bring the risk of liver failure and inflammation.[29]

As an analogue of human GLP-1, liraglutide is wildly used in the T2DM clinical treatment. It has 97% structural homology with endogenous human GLP-1.[30] It is found that liraglutide can promote a weight loss and improve the IR, prevent the liver lipid deposition and decelerate the hepatic steatosis.[31] However, the positive effect of liraglutide on T2DM with NAFLD remains unclear. Conflicting findings about the efficacy and safety of liraglutide limit decision-making.[32] Therefore, we performed a meta-analysis to investigate the efficacy and safety of liraglutide in the treatment of T2DM patients with NAFLD.

2. Methods

2.1. Research strategy

We searched the National Library of Medicine (PubMed), Cochrane Library, Web of Science (WOS), China National Knowledge Infrastructure (CNKI) and WANFANG databases from the first publication to March 2022. Liraglutide, T2DM and NAFLD were used as keywords. According to the unique requirements of each individual database, the search is performed by combining medical subject words and text words.

2.2. Inclusive criteria

The inclusion criteria are randomized controlled clinical trials. The experimental group is treated with liraglutide alone or on the basis of conventional treatments (including the use of metformin to lower blood sugar), and the control group is treated with other conventional drugs without liraglutide for T2DM with NAFLD. Outcome indicators were fasting plasma glucose (FPG), glycosylated hemoglobin A1c (HbA1c), ALT, aspartate transaminase (AST), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). The included studies did not consider language and publication limitations.

2.3. Exclusion criteria

Studies with at least one of the following criteria were excluded: repetitive articles; animal research or cell research; studies including type 1 diabetic or non-diabetic patients; and a trial in which the information provided is insufficient to make a judgment.

2.4. Quality evaluation and data extraction

The methodological quality is evaluated based on the Cochrane systematic review manual. The main evaluation criteria of the included studies follows references to the prior work about vitamin C.[33] We scored each domain as "Low," "High" or "Unclear" risk of bias.

2.5. Statistical analysis

Revman 5.3 software provided by Cochrane Collaboration Network was used for meta-analysis. The risk ratio was used for dichotomous variable, while the mean difference (MD) and the standardized mean difference were adopted for continuous variables as effect size. If there is no heterogeneity among the studies that is a P value greater than .10 or I^2 less than 50%. It is explained that the heterogeneity of the research is small, and the fixed effect model is used to analyze. A P value less than .10 or I^2 greater than 50% suggested that there is obvious heterogeneity among the included studies, and the random effect model is used to combine the effect volume. The bias of the study is analyzed by funnel plot.

3. Results

3.1. Study selection

A total of 158 studies were identified after the initial search of the electronic databases. Of these, 60 duplicate studies were excluded. According to the inclusion criteria, 82 unqualified trials were excluded. Finally, 16 eligible articles are included in the meta-analysis. We use the Supplementary PRISMA CHECKLIST to help reporting the quality of the study. The study selection procedure is outlined in Figure 1.

3.2. Study characteristics and quality

The detailed characteristics of all eligible trials are presented in **Table 1** and the quality of the study evaluation is shown in Table 2.

3.3. Meta-analysis of outcome

3.3.1. FPG. Fourteen articles were included and the results are shown in Figure 2. A total of 1133 cases of T2DM complicated with NAFLD are included in this assessment (554 in the experimental group and 579 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.98$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the FPG level of the experimental group was lower than that of the control group ($Z = 4.47$, $P < .00001$, MD = −1.37, 95% confidence intervals [CI]: −1.97 to −0.77).

3.3.2. HbA1c. Fifteen articles were included and the results are shown in Figure 3. A total of 1236 cases of T2DM complicated with NAFLD are included in this assessment (605 in the experimental group and 631 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.98$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the HbA1c level of the experimental group was lower than that of the control group ($Z = 3.68$, $P = .0002$, MD = −0.90, 95% CI: −1.38 to −0.42).

3.3.3. TG. Thirteen articles were included and the results are shown in Figure 4. A total of 1137 cases of T2DM complicated with NAFLD are included in this assessment (556 in the experimental group and 581 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.97$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the TG level of the experimental group was lower than

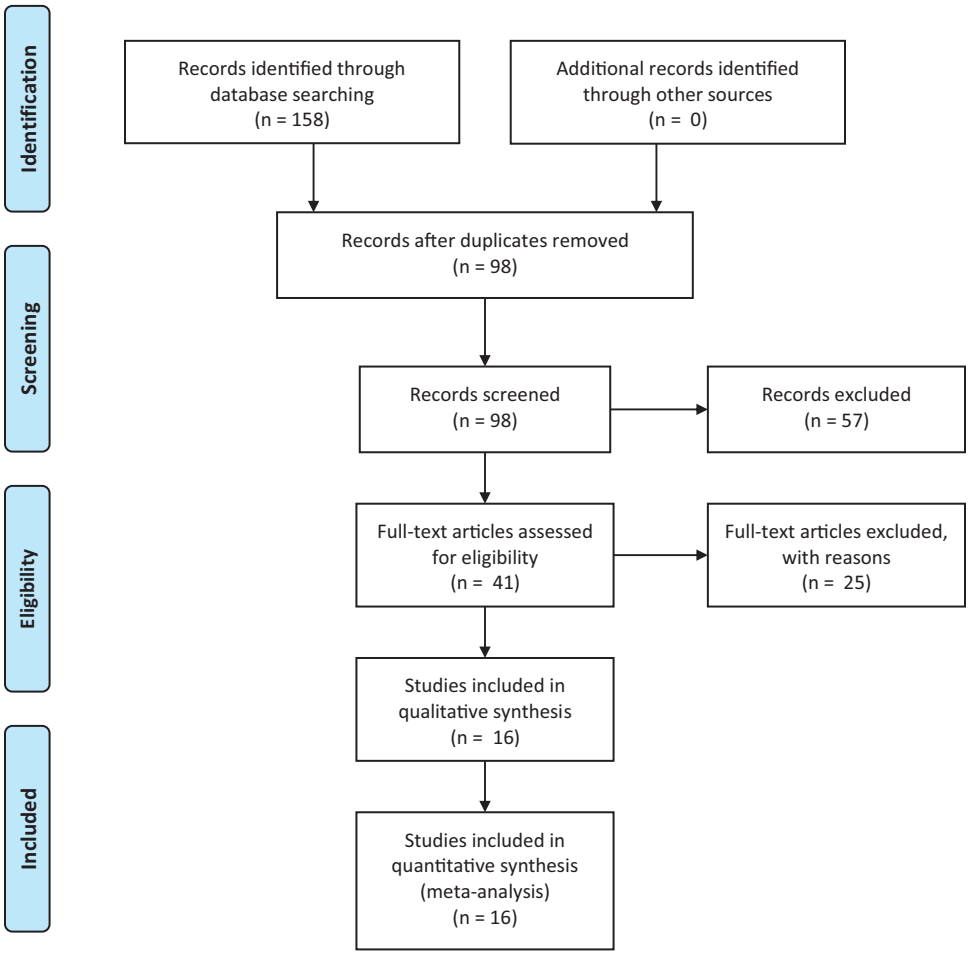

Figure 1. PRISMA 2009 flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1

Basic information included in the literature.

Author	Year	Age	M/F	Duration (wk)	Treatment		Control		Evaluation
					Cases	Measures cases	Measures	Indicator	
Bouchi[34]	2017	T: 57 ± 16 C: 60 ± 22	8/9	36	8	Liraglutide 0.9 mg/d	9	Insulin	Weight, TG, HbA1c, LDL-C, HDL-C
Dong[35]	2020	T: 70.25 ± 7.23 C: 70.61 ± 7.40	35/27	12	31	Liraglutide 1.8 mg/d + Metformin 2 g/d	31	Metformin 2 g/d	FPG, TG, TC, ALT, AST, LDL-C, HbA1c, adverse reactions
Feng[36]	2019	T: 46.80 ± 1.80 C: 46.30 ± 2.30	40/18	24	29	Liraglutide 1.8 mg/d	29	Metformin 2 g/d	FPG, HbA1c, ALT, AST, TG, LDL-C, HDL-C
Feng[37]	2017	T: 46.79 ± 1.80 C: 48.07 ± 2.34	41/17	24	29	Liraglutide 1.8 mg/d	29	Gliclazide 120 mg/d	Weight, BMI, ALT, AST, FPG, HbA1c, TG, LDL-C, HDL-C
Gao[38]	2020	T: 53.84 ± 10.32 C: 54.27 ± 10.28	78/68	12	72	Liraglutide 1.2 mg/d	72	Metformin 1 g/d	FPG, HbA1c, HOMA-IR, TG, TC, LDL-C
Geng[39]	2020	T: 59.77 ± 4.31 C: 59.81 ± 4.52	55/25	12	40	Liraglutide 1.8 mg/d+RT	40	RT	FPG, HbA1c, TC, LDL-C, HDL-C
Guo[40]	2020	T: 53.10 ± 6.30 C: 52.60 ± 3.90	36/25	26	31	Liraglutide 1.8 mg/d	30	Placebo	ALT, AST, TG, TC, BMI, LDL-C, HDL-C, weight, HbA1c, FPG, HOMA-IR, adverse reactions
Lin[41]	2019	T: 49.12 ± 5.76 C: 48.69 ± 5.24	35/25	16	30	Liraglutide 1.8 mg/d+RT	30	RT	ALT, AST, GGT, BMI, FPG, HbA1c, TG, TC, LDL-C, HDL-C, HOMA-IR, adverse reactions
Liu[42]	2018	T: 52.30 ± 11.30 C: 51.80 ± 11.10	63/57	12	60	Liraglutide 1.8 mg/d+RT	60	RT	TC, TG, LDL-C, FPG, HbA1c
Tian[43]	2018	T: 58.50 ± 7.60 C: 56.40 ± 8.40	74/53	12	52	Liraglutide 1.2 mg/d	75	Metformin 1.5 g/d	ALT, AST, TG, TC, LDL, HDL, FPG, HbA1c, weight, BMI, HOMA-IR, adverse reactions
Wang[44]	2020	T: 52.71 ± 6.60 C: 52.58 ± 6.43	41/31	12	36	Liraglutide 1.8 mg/d + Metformin 2 g/d	36	Metformin 2 g/d	FPG, TG, TC, LDL-C, HbA1c
Yan[45]	2019	T: 43.10 ± 9.70 C: 45.70 ± 9.20	38/13	26	24	Liraglutide 1.8 mg/d	27	Sitagliptin 100 mg/d	FPG, HbA1c, weight, BMI, ALT, AST, TG, TC, LDL-C, HDL-C, adverse reactions
Zhang[46]	2018	T: 55.50 ± 1.10 C: 54.50 ± 1.20	57/37	24	47	Liraglutide 1.8 mg/d	47	Insulin	FPG, HbA1c, weight, BMI, ALT, AST, TG, TC
Zhang[47]	2019	52 ± 10	45/35	24	40	Liraglutide 1.8 mg/d	40	Metformin 2 g/d	ALT, AST, TG, TC, BMI, FPG, HbA1c, LDL-C, HDL-C
Zhang[48]	2020	T: 50.20 ± 11.50 C: 51.50 ± 12.10	28/32	24	30	Liraglutide 1.2 mg/d	30	Pioglitazone 30 mg/d	FPG, HbA1c, ALT, AST, GGT, HOMA-IR, adverse reactions
Zhu[49]	2021	T: 56.91 ± 7.37 C: 56.85 ± 7.34	85/65	8	75	Liraglutide 1.8 mg/d	75	Metformin1 g/d	FPG, HbA1c, TG, TC, LDL-C, adverse reactions

ALT = alanine aminotransferase, AST = aspartate transaminase, BMI = body mass index, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin A1c, HDL-C = high density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment for insulin resistance, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol, TG = triglyceride.

that of the control group ($Z = 4.39$, $P < .0001$, MD = −0.66, 95% CI: −0.96 to −0.37).

3.3.4. TC. Twelve articles were included and the results are shown in Figure 5. A total of 1101 cases of T2DM complicated with NAFLD are included in this assessment (538 in the experimental group and 563 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.96$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the TC level of the experimental group was lower than that of the control group ($Z = 3.44$, $P = .0006$, MD = −1.00, 95% CI: −1.56 to −0.43).

3.3.5. ALT level. Ten articles were included and the results are shown in Figure 6. A total of 711 cases of T2DM complicated with NAFLD are included in this assessment (343 in the experimental group and 368 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.91$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the ALT level of the experimental group was lower than that of the control group ($Z = 3.67$, $P = .0002$, MD = −0.99, 95% CI: −1.51 to −0.46).

3.3.6. AST level. Ten articles were included and the results are shown in Figure 7. A total of 711 cases of T2DM complicated with NAFLD are included in this assessment (343 in the experimental group and 368 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.93$), so the random effect model is used. The results show that the difference is no significant.

3.3.7. LDL-C level. Thirteen articles were included and the results are shown in Figure 8. A total of 1056 cases of T2DM complicated with NAFLD are included in this assessment (527 in the experimental group and 529 in the control group). And there was a large heterogeneity ($P < .00001$, $I^2 = 0.96$), so the random effect model is used. The results show that the difference is significant. The meta-analysis showed that the LDL-C level of the experimental group was lower than that of the control group ($Z = 2.23$, $P = .03$, MD = −0.28, 95% CI: −0.52 to −0.03).

Table 2

Quality evaluation of included literatures.

Included	Random	Allocation	Double blind	Evaluation of	Data	Selective	others
Studies	Allocation	Concealment	Method	Blindness	Integrity	Report	
Bouchi 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear
Dong 2020	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Feng 2019	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear
Feng 2017	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Low risk
Gao 2020	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Geng 2020	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Guo 2020	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Lin 2019	Low risk	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear
Liu 2018	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Tian 2018	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Wang 2020	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Yan 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Zhang 2018	Low risk	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Zhang 2019	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Zhang 2020	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Zhu 2021	Low risk	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear

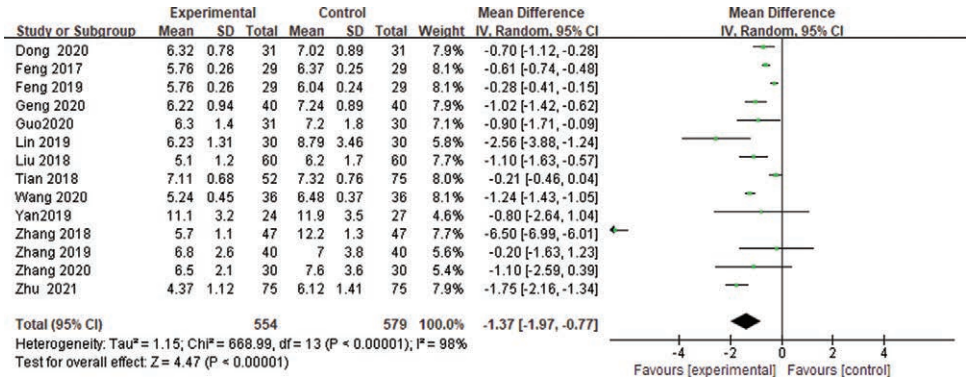

Figure 2. The experimental group compared with the control group in FPG changes after treatment. CI = confidence interval, FPG = fasting plasma glucose, SD = standard deviation.

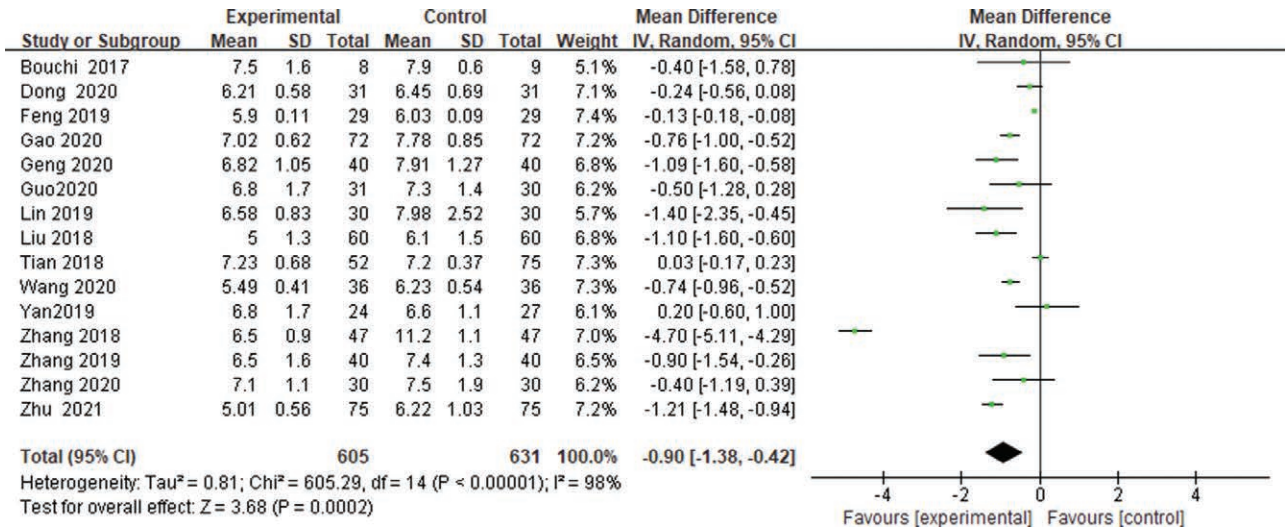

Figure 3. The experimental group compared with the control group in HbA1c changes after treatment. CI = confidence interval, HbA1c = glycosylated hemoglobin A1c, SD = standard deviation.

3.3.8. HDL-C level. Nine articles were included and the results are shown in Figure 9. A total of 525 cases of T2DM complicated with NAFLD are included in this assessment (261 in the experimental group and 264 in the control group). And

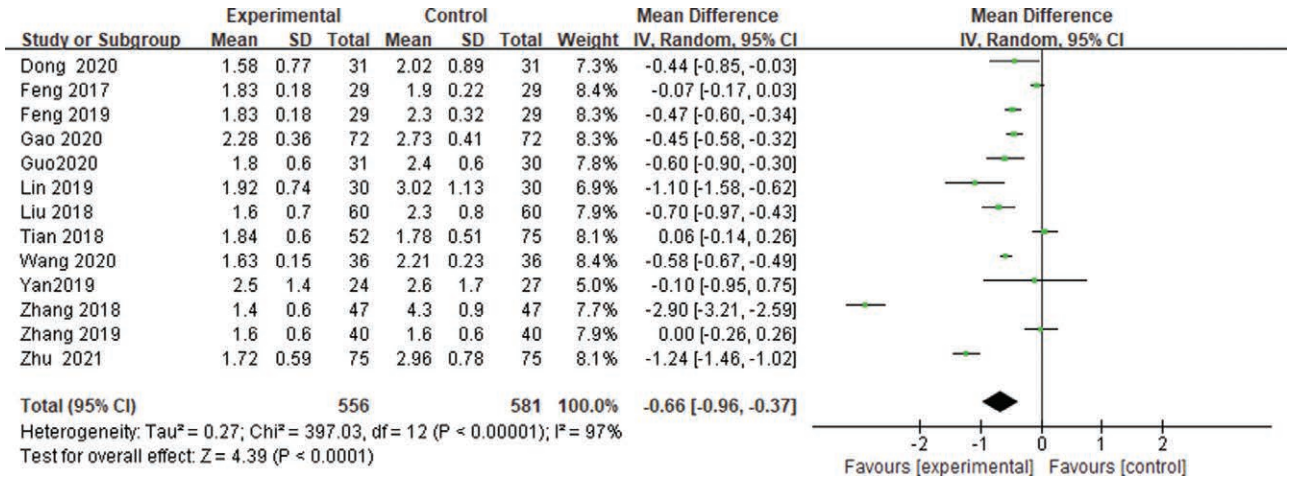

Figure 4. The experimental group compared with the control group in TG changes after treatment. CI = confidence interval, SD = standard deviation, TG = triglyceride.

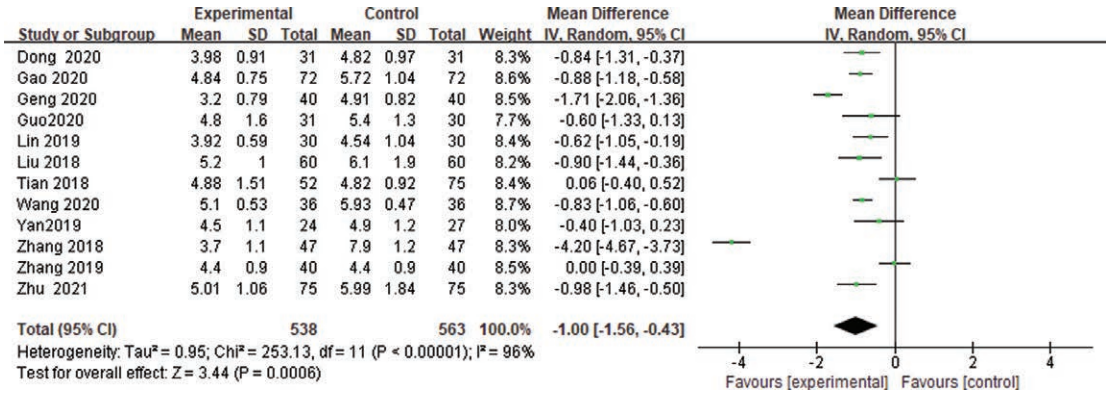

Figure 5. The experimental group compared with the control group in TC changes after treatment. CI = confidence interval, SD = standard deviation, TC = total cholesterol.

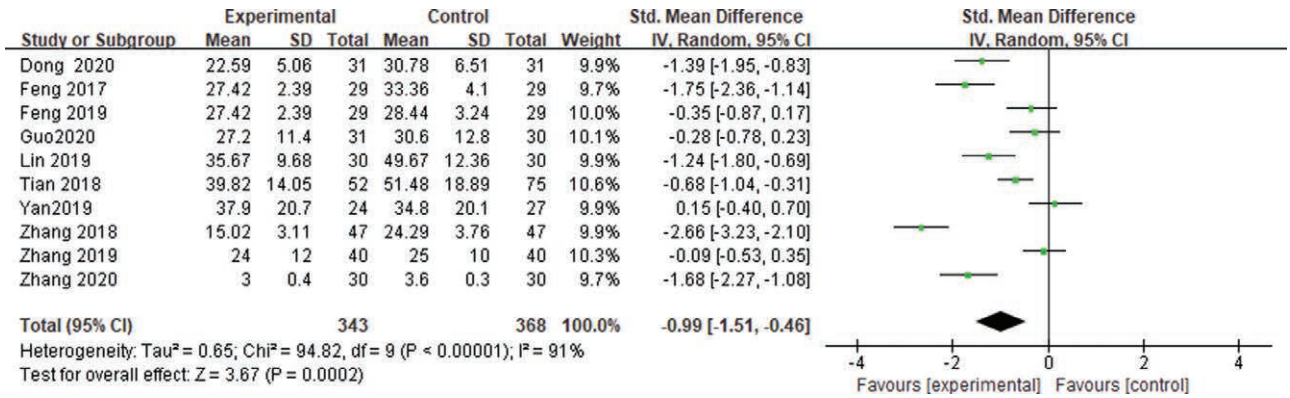

Figure 6. The experimental group compared with the control group in ALT changes after treatment. ALT = alanine aminotransferase, CI = confidence interval, SD = standard deviation.

there was a large heterogeneity ($P < .00001$, $I^2 = 0.97$), so the random effect model is used. The results show that the difference is no significant.

3.3.9. Adverse effects. Seven articles were included and the results are shown in Figure 10. A total of 571 cases of T2DM complicated with NAFLD are included in this assessment (273 in the experimental group and 298 in the control group). And there was a small heterogeneity ($P = .36$, $I^2 = 0.09$), so the fixed effect model is used. The results show that the difference is significant. The meta-analysis showed that adverse effects of the experimental group was higher than that of the control group ($Z = 3.81$, $P = .0001$, risk ratio = 2.53, 95% CI: 1.57–4.07).

3.3.10. Publication bias. As shown in Figure 11, based on the HbA1c level, funnel plot is applied to evaluate the publication biases of all 16 studies. The results showed that publication bias is small.

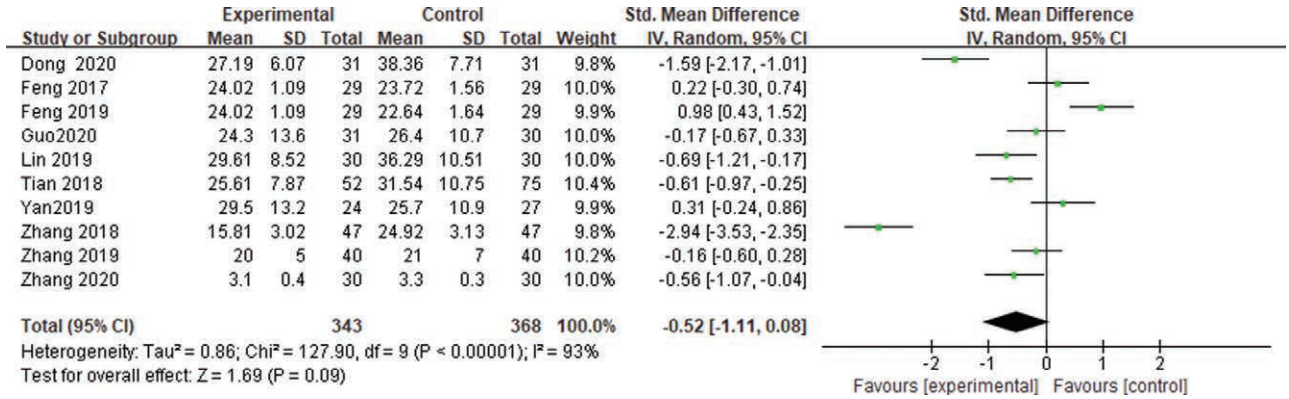

Figure 7. The experimental group compared with the control group in AST changes after treatment. AST = aspartate transaminase, CI = confidence interval, SD = standard deviation.

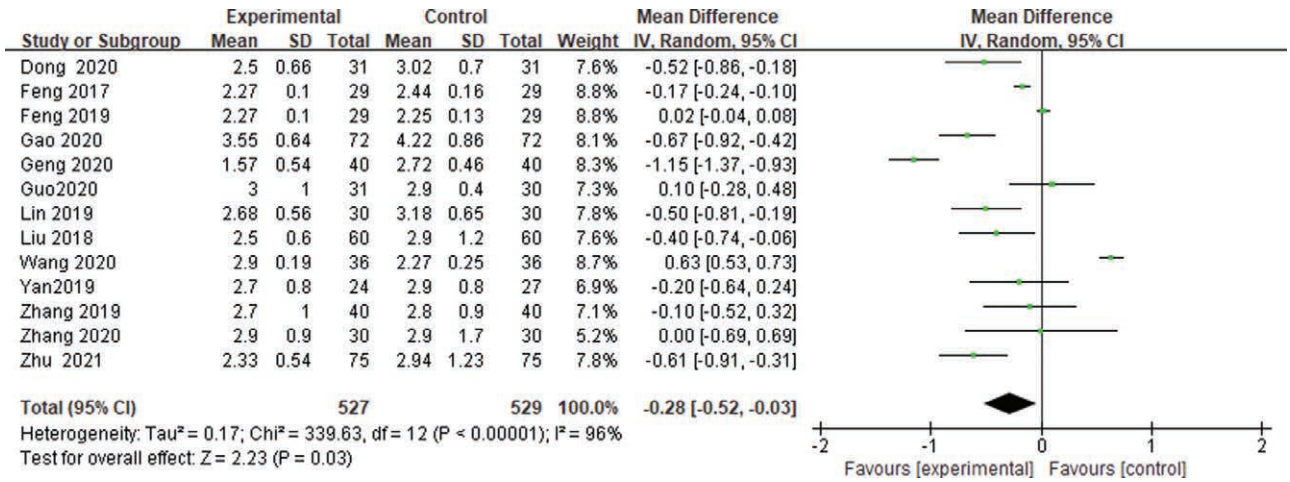

Figure 8. The experimental group compared with the control group in LDL-C changes after treatment. CI = confidence interval, LDL-C = low density lipoprotein cholesterol, SD = standard deviation.

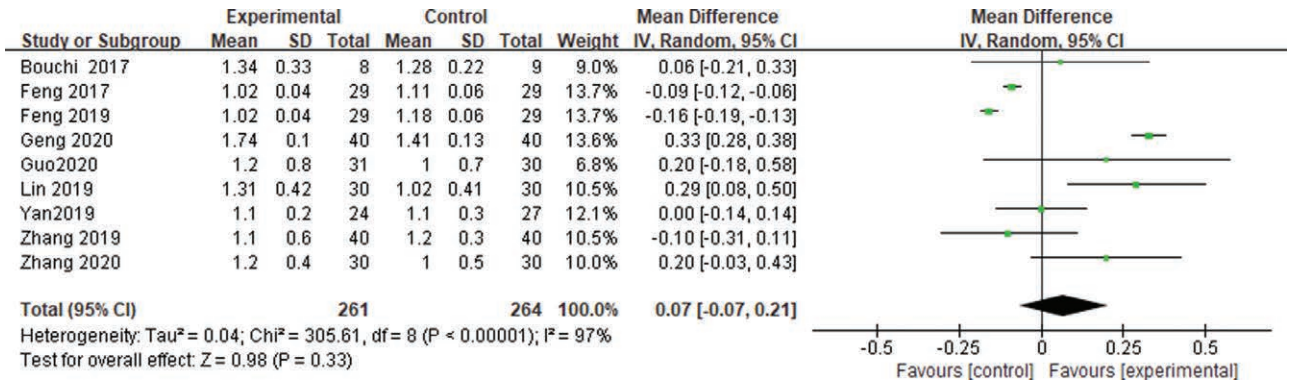

Figure 9. The experimental group compared with the control group in HDL-C changes after treatment. CI = confidence interval, HDL-C = high density lipoprotein cholesterol, SD = standard deviation.

4. Discussion

4.1. Efficacy analysis

This study was a meta-analysis to assess the efficacy and safety of the GLP-1 receptor agonist liraglutide on T2DM patients with NAFLD. The results indicated that ALT, LDL-C, TG, TC, FPG, and HbA1c decreased. There is no significant difference in AST and HDL-C. Liraglutide significantly reduced TG, TC, and LDL-C in lipid metabolism indexes. The main reason is that liraglutide can increase the insulin secretion dependent on glucose. It can also effectively control the glucagon, reduce appetite, inhibit gastric emptying, and lose weight. So, it can play a role in improving IR and controlling blood lipid level.[50] The reason of the FPG decreasing is that liraglutide can inhibit islets α cells secreting glucagon, reduce hepatocyte gluconeogenesis, decrease hepatocyte glycogen releasing and lower the fasting blood-glucose.[51] HbA1c is a medium and long-term indicator of blood glucose level. Liraglutide, an analogue binding to the

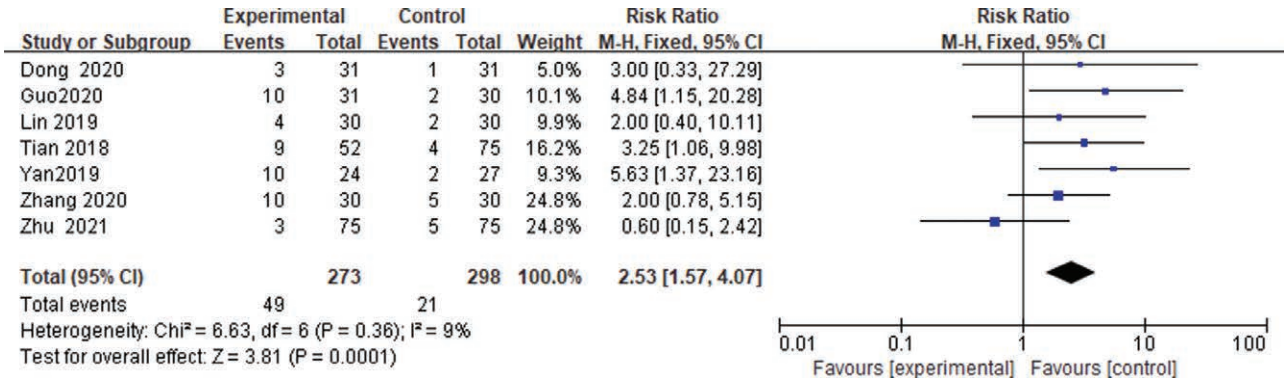

Figure 10. Adverse effect. CI = confidence interval.

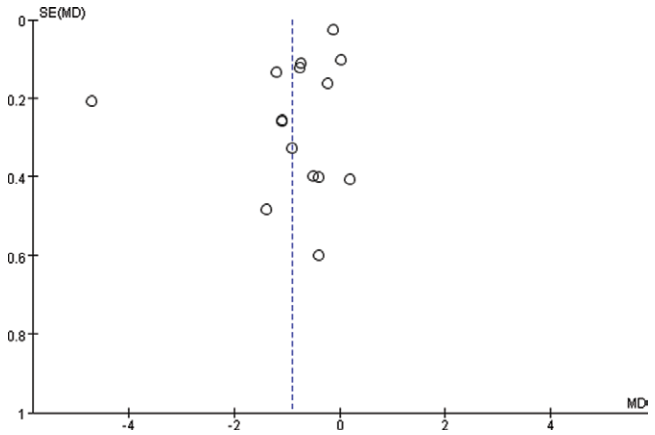

Figure 11. Funnel plot. MD = mean difference, SE = standard error.

GLP-1 receptor, can inhibit the growth of pancreatic islets β cell proliferation and its function regulation. It plays a better regulatory role in T2DM patients based on the function of promoting insulin synthesis and secretion.[52] Liraglutide can improve insulin sensitivity and inhibit IR effectively. It prevents the damage of hepatocyte lipid accumulation by reducing hepatocyte glucose, improving hepatic fibrosis and losing body weight.[53] Adverse effects (AEs) of liraglutide are mainly in gastrointestinal tract. Because liraglutide slows gastric emptying, it may lead the gastric distension to cause nausea and anorexia. These AEs often occur with overdoses. However, AEs usually are mild and/or transient, then can be relieved in time.[52]

4.2. Limitations

The limitations are as follows: the quality of the included articles is different, and not all randomized controlled trials are blinded; the sample size of clinical studies is small, which may affect the results reliability; differences in observation courses, drug doses and patients' qualities may lead a heterogeneity; and there is no negative results included, so it may have some publication bias.

4.3. Applications prospects

T2DM is a high-risk factor for cardiovascular and cerebrovascular diseases. It may also lead to heart, brain, kidney, eye, liver, vascular and other organ injuries.[54] The prolonged and sustained hyperglycemic state will aggravate or accelerate the liver damage. It causes a gradual development of fatty liver, liver fibrosis and even liver failure.[55] Disorders of glycolipid metabolism, obesity, as well as IR are prevalent in patients with NAFLD.[56] T2DM and NAFLD can affect themselves each other. Liraglutide is currently widely used in the clinic as a long-acting antidiabetic drug. It, in vivo, acts as a GLP-1 analog and promotes insulin secretion to lower blood glucose.[57] Liraglutide also improve hepatic insulin sensitivity, so it can decrease the serum levels of transforming growth factor-β 1 and the liver stiffness. So, it can decrease hepatocyte steatosis and fibrosis.[58]

TC and TG are the most typical indexes of lipid metabolism. Their levels are positively correlated with the degree of abnormal lipid metabolism.[59] HDL-C is a specific molecule with a "*defatting*" effect and ubiquitously reducing in obese diabetic patients.[60] Its content is also inversely correlated with the degree of abnormal lipid metabolism. Patients of the experimental group in this study, after treatment, have lower levels of TC, TG, and LDL-C but higher levels of HDL-C. It indicates that liraglutide may help T2DM patients with NAFLD to optimize their lipid metabolism. It is also one of the intrinsic reasons for liver function optimization.[61] ALT and AST are both indicators of the liver function. They mainly distribute in hepatocytes and present a small fraction in muscle cells. If the liver is damaging or damaged, transaminases in hepatocytes move into the blood. Then ALT and AST levels increase, suggesting a signal for liver disease(s). ALT is more sensitive, which is 100 times in liver tissue than serum. When 1% of hepatocytes becomes necrotic, the ALT will increase by 1-fold. In this study, we analysis both ALT and AST. And it is also demonstrated that liraglutide can improve the liver function of T2DM with NAFLD.[62] HbA1c is a product of the hemoglobin binding to blood glucose. It usually reflects the glycemic situation of patients for nearly 8 to 12 weeks.[63] HbA1c is a better indicator for blood glucose controlling and complications preventing during recent 2 to 3 months.[64] In this study, liraglutide can decrease HbA1c level of T2DM with NAFLD.

To the T2DM patients with NAFLD, liraglutide has both the antidiabetic effect and the lipid-lowering effect. It can inhibit hepatocyte steatosis, attenuate liver damage, and only has a low rate of AEs.

5. Conclusion

Liraglutide is potentially curative for T2DM with NAFLD.
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Author contributions

Conceptualization: Huaien Bu, Ye Zhao.
Data curation: Yan Zhao, Maeda Toshiyoshi.

Formal analysis: Yan Zhao, Wenli Zhao.
Funding acquisition: Ye Zhao.
Investigation: Wenli Zhao.
Methodology: Wenli Zhao, Ye Zhao.
Resources: Yan Zhao, Maeda Toshiyoshi.
Software: Huaien Bu.
Supervision: Huaien Bu, Ye Zhao.
Validation: Maeda Toshiyoshi.
Visualization: Wenli Zhao.
Writing – original draft: Yan Zhao, Maeda Toshiyoshi.
Writing – review & editing: Yan Zhao, Wenli Zhao, Huaien Bu, Ye Zhao.

References

[1] Saeedi P, Petersohn I, Salpea P, et al.; IDF Diabetes Atlas Committee. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.
[2] American Diabetes Association. Standards of medical care in diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S1–232.
[3] International Diabetes Federation. IDF Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019.
[4] Pearson ER. Type 2 diabetes: a multifaceted disease. Diabetologia. 2019;62:1107–12.
[5] Ardissino M, Watson F, Amin R, et al., Imperial Obesity Study Group. Atherosclerotic disease burden after bariatric surgery in patients with obesity and type 2 diabetes. J Diabetes. 2021;13:640–7.
[6] Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol. 2010;314:1–16.
[7] Lee B, Shao J. Adiponectin and lipid metabolism in skeletal muscle. Acta Pharm Sin B. 2012;2:335–40.
[8] Iwaki M, Matsuda M, Maeda N, et al. Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. Diabetes. 2003;52:1655–63.
[9] Choi JH, Banks AS, Estall JL, et al. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. Nature. 2010;466:451–6.
[10] Wang Q, Tang J, Jiang S, et al. Inhibition of PPARγ, adipogenesis and insulin sensitivity by MAGED1. J Endocrinol. 2018;239:167–80.
[11] Choi SE, Lee YJ, Jang HJ, et al. A chemical chaperone 4-PBA ameliorates palmitate-induced inhibition of glucose-stimulated insulin secretion (GSIS). Arch Biochem Biophys. 2008;475:109–14.
[12] Kaneto H, Miyatsuka T, Kawamori D, et al. PDX-1 and MafA play a crucial role in pancreatic beta-cell differentiation and maintenance of mature beta-cell function. Endocr J. 2008;55:235–52.
[13] Xu LJ, Lu FE, Yi P, et al. 8-hydroxy-dihydroberberine ameliorated insulin resistance induced by high FFA and high glucose in 3T3-L1 adipocytes. Yao Xue Xue Bao. 2009;44:1304–8.
[14] Ruiz-Ramírez A, Chávez-Salgado M, Peñeda-Flores JA, et al. High-sucrose diet increases ROS generation, FFA accumulation, UCP2 level, and proton leak in liver mitochondria. Am J Physiol Endocrinol Metab. 2011;301:E1198–207.
[15] Yoshimoto K, Ozawa S, Ishida H. Pathogenic mechanism of type 2 diabetes mellitus from impaired glucose tolerance/borderline type and its reversibility. Nihon Rinsho. 2005;63(Suppl 2):95–9.
[16] Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab. 2015;100:2231–8.
[17] Carr RM, Oranu A, Khungar V. Nonalcoholic fatty liver disease: pathophysiology and management. Gastroenterol Clin North Am. 2016;45:639–52.
[18] Lu H, Zeng L, Liang B, et al. High prevalence of coronary heart disease in type 2 diabetic patients with non-alcoholic fatty liver disease. Arch Med Res. 2009;40:571–5.
[19] Leite NC, Villela-Nogueira CA, Pannain VL, et al. Histopathological stages of nonalcoholic fatty liver disease in type 2 diabetes: prevalences and correlated factors. Liver Int. 2011;31:700–6.
[20] Rhee EJ. Nonalcoholic fatty liver disease and diabetes: an epidemiological perspective. Endocrinol Metab (Seoul). 2019;34:226–33.
[21] Raff EJ, Kakati D, Bloomer JR, et al. Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. J Clin Transl Hepatol. 2015;3:9–16.
[22] Williams KH, Shackel NA, Gorrell MD, et al. Diabetes and nonalcoholic fatty liver disease: a pathogenic duo. Endocr Rev. 2013;34:84–129.
[23] Leite NC, Villela-Nogueira CA, Cardoso CR, et al. Non-alcoholic fatty liver disease and diabetes: from physiopathological interplay to diagnosis and treatment. World J Gastroenterol. 2014;20:8377–92.
[24] Widiarti W, Sukmajaya AC, Nugraha D, et al. Cardioprotective properties of glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus patients: a systematic review. Diabetes Metab Syndr. 2021;15:837–43.
[25] Friedman SL, Neuschwander-Tetri BA, Rinella M, et al. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24:908–22.
[26] Nevens F, Andreone P, Mazzella G, et al.; POISE Study Group. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. N Engl J Med. 2016;375:631–43.
[27] Pockros PJ, Fuchs M, Freilich B, et al. CONTROL: a randomized phase 2 study of obeticholic acid and atorvastatin on lipoproteins in nonalcoholic steatohepatitis patients. Liver Int. 2019;39:2082–93.
[28] Elhence A, Shalimar. Treatment of non-alcoholic fatty liver disease – current perspectives. Indian J Gastroenterol. 2020;39:22–31.
[29] Luyckx FH, Desaive C, Thiry A, et al. Liver abnormalities in severely obese subjects: effect of drastic weight loss after gastroplasty. Int J Obes Relat Metab Disord. 1998;22:222–6.
[30] Garber A, Henry R, Ratner R, et al.; LEAD-3 (Mono) Study Group. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet. 2009;373:473–81.
[31] Tong J, D'Alessio D. Give the receptor a brake: slowing gastric emptying by GLP-1. Diabetes. 2014;63:407–9.
[32] Portillo-Sanchez P, Cusi K. Treatment of nonalco-holic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus. Clin Diabetes Endocrinol. 2016;2:9.
[33] Shuangdi C, Wenli Z, Binjie Z, et al. Clinical effect of intravenous vitamin C on viral myocarditis in children: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019;2019:3082437.
[34] Bouchi R, Nakano Y, Fukuda T, et al. Reduction of visceral fat by liraglutide is associated with ameliorations of hepatic steatosis, albuminuria, and micro-inflammation in type 2 diabetic patients with insulin treatment: a randomized control trial. Endocr J. 2017;64:269–81.
[35] Dong ZH, Xue J, Zhang YN. Effect of Liraglutide on glucose and lipid metabolism of old type 2 diabetes combined with NAFLD patients. Chin J Gerontol. 2020;40:4288–91.
[36] Feng WH, Bi Y, Li P, et al. Effects of liraglutide, metformin and gliclazide on body composition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: a randomized trial. J Diabetes Investig. 2019;10:399–407.
[37] Feng W, Gao C, Bi Y, et al. Randomized trial comparing the effects of gliclazide, liraglutide, and metformin on diabetes with non-alcoholic fatty liver disease. J Diabetes. 2017;9:800–9.
[38] Gao L, Liu HW, Lin L, et al. Effect of Liraglutide on ERS in T2DM and NAFLD patients and its clinic efficacy. Chin Hepatol. 2020;25:972–4.
[39] Geng J. The effect of liraglutide on T2DM with NAFLD patients. Modern Diagnosis Treatment. 2020;31:2395–6.
[40] Guo W, Tian W, Lin L, et al. Liraglutide or insulin glargine treatments improves hepatic fat in obese patients with type 2 diabetes and non-alcoholic fatty liver disease in twenty-six weeks: a randomized placebo-controlled trial. Diabetes Res Clin Pract. 2020;170:108487.
[41] Lin J, Chai ZH, Zeng L, et al. Curative effect of liraglutide on type 2 diabetes mellitus combined with non-alcoholic fatty liver disease. Drug Eval. 2019;16:26–7.
[42] Liu L, Zhang Y. Effect of liraglutide injection on hepatic fat deposition in patients with type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Chin Hepatol. 2018;23:338–40.
[43] Tian F, Zheng Z, Zhang D, et al. Efficacy of liraglutide in treating type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease. Biosci Rep. 2018;38:BSR20181304.
[44] Wang X. Clinical effect of liraglutide in the treatment of type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Henan Med Res. 2020;29:105–7.
[45] Yan J, Yao B, Kuang H, et al. Liraglutide, sitagliptin, and insulin glargine added to metformin. The effect on body weight and intrahepatic lipid in patients with type 2 diabetes mellitus and nonalcoholic fatty liver disease. Hepatology. 2019;69:2414–26.
[46] Zhang Y, Gu DH, Wang XW, et al. Effect of liraglutide on type 2 diabetes with non-alcoholic fatty liver. China Med Pharm. 2018;8:30–2.
[47] Zhang ZW, Yu H. The effect of liraglutide on plasma homocysteine and insulin resistance in patients with type 2 diabetes mellitus and nonalcoholic fatty liver. Chin Remedies Clin. 2019;19:2401–3.

[48] Zhang LY, Qu XN, Sun ZY, et al. Effect of liraglutide therapy on serum fetuin A in patients with type 2 diabetes and non-alcoholic fatty liver disease. Clin Res Hepatol Gastroenterol. 2020;44:674–80.
[49] Zhu YF, Wang T, Qin Y. Effects of liraglutide on glucose and lipid metabolism and liver fat deposition in patients with type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. Drug Eval. 2021;18:254–6.
[50] Taskinen MR, Björnson E, Matikainen N, et al. Effects of liraglutide on the metabolism of triglyceride-rich lipoproteins in type 2 diabetes. Diabetes Obes Metab. 2021;23:1191–201.
[51] Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab. 2002;87:1239–46.
[52] Meier JJ, Rosenstock J, Hincelin-Méry A, et al. Contrasting effects of lixisenatide and liraglutide on postprandial glycemic control, gastric emptying, and safety parameters in patients with type 2 diabetes on optimized insulin glargine with or without metformin: a randomized, open-label trial. Diabetes Care. 2015;38:1263–73.
[53] Cuthbertson DJ, Irwin A, Gardner CJ, et al. Improved glycaemia correlates with liver fat reduction in obese, type 2 diabetes, patients given glucagon-like peptide-1 (GLP-1) receptor agonists. PLoS One. 2012;7:e50117.
[54] Cai X, Ji L. Generalizability of the results of cardiovascular outcome trials of glucagon-like peptide 1 receptor agonists in chinese patients with type 2 diabetes mellitus. Diabetes Ther. 2021;12:1861–70.
[55] Huang J, Li R, Liu N, et al. Liver fibrosis is independently associated with diabetic peripheral neuropathy in type 2 diabetes mellitus. J Diabetes Investig. 2021;12:2019–27.
[56] Arab JP, Díaz LA, Dirchwolf M, et al. Challenges and opportunities to address the public health challenge in Latin America. Ann Hepatol. 2021;24:100359.
[57] Hausenloy DJ, Whittington HJ, Wynne AM, et al. Dipeptidyl peptidase-4 inhibitors and GLP-1 reduce myocardial infarct size in a glucose-dependent manner. Cardiovasc Diabetol. 2013;12:154.
[58] Ben-Shlomo S, Zvibel I, Shnell M, et al. Glucagon-like peptide-1 reduces hepatic lipogenesis via activation of AMP-activated protein kinase. J Hepatol. 2011;54:1214–23.
[59] Sun LL, Zhang SJ, Chen MJ, et al. Relationship between modulator recognition factor 2/AT-rich interaction domain 5B gene variations and type 2 diabetes mellitus or lipid metabolism in a Northern Chinese Population. Chin Med J. 2017;130:1055–61.
[60] Kelany ME, Hakami TM, Omar AH, et al. Combination of sitagliptin and insulin against type 2 diabetes mellitus with neuropathy in rats: neuroprotection and role of oxidative and inflammation stress. Pharmacology. 2016;98:242–50.
[61] Xu M, Zheng XM, Jiang F, et al. MicroRNA-190b regulates lipid metabolism and insulin sensitivity by targeting IGF-1 and ADAMTS9 in non-alcoholic fatty liver disease. J Cell Biochem. 2018;119:5864–74.
[62] Kamm DR, Pyles KD, Sharpe MC, et al. Novel insulin sensitizer MSDC-0602K improves insulinemia and fatty liver disease in mice, alone and in combination with liraglutide. J Biol Chem. 2021;296:100807.
[63] Pasquel FJ, Urrutia MA, Cardona S, et al. Liraglutide hospital discharge trial: a randomized controlled trial comparing the safety and efficacy of liraglutide versus insulin glargine for the management of patients with type 2 diabetes after hospital discharge. Diabetes Obes Metab. 2021;23:1351–60.
[64] Ali AM, Mari A, Martinez R, et al. Improved beta cell glucose sensitivity plays predominant role in the decrease in HbA1c with Cana and Lira in T2DM. J Clin Endocrinol Metab. 2020;105:dgaa494.