Clinical efficacy of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: A meta-analysis

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ARTICLE INFO

ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved to treat type 2 diabetes mellitus (T2DM), which have been considered at the same treatment pattern point as basal insulin (BI). Thus, comprehensively comparing these drugs is conducive to informing the treatment decisions. In this context, this work was developed to evaluate the clinical efficacy and safety of GLP-1 RAs by comparing them with basal insulin. GLP-1 RAs were compared with basal insulin in adults with T2DM with inadequate oral anti-hyperglycemic drug control by searching related literature from MEDLINE, EMBASE, CENTRAL, and PubMed databases, which were published from established the datasets to October 2022. Data on hemoglobin A1c, body weight, and blood glucose were extracted and analyzed. The MD values of HbA1C, weight, and fasting blood glucose (FBG) change were -0.02, -1.37, and -1.68, respectively. Meanwhile, the OR of the hypoglycemia ratio was 0.33. In conclusion, GLP-1 RAs exhibited a great effect on blood glucose and weight control and a better effect on FBG control.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease, which is featured insulin resistance and increased blood glucose due to reduced insulin release (1). The incidence of T2DM has been increasing these years. It is reported by the Global Diabetes Alliance (IDF) that the number of diabetes cases worldwide is expected to soar to 642 million by the end of 2040. Cardiovascular disease (CVD) is the largest reason for death and increased health care costs for people with diabetes. Studies have shown that people with T2DM have a 2 - to 5-fold increased risk of CVD. Abnormal blood pressure is common in T2DM patients (2). According to statistics, in patients with hypertension worldwide, about 74% of patients will increase the risk of CVD and death due to various complications. The UK Prospective Patient Monitoring Unit (UKPDS) conducted a prospective study of 1,148 patients with T2DM with acute hypertensive symptoms over an 8-year period. This scientific study points out that long-term monitoring of blood pressure lowering levels can improve the likelihood of mortality and complications in diabetic patients (3). In addition, the study revealed that people with the same symptoms of diabetes and acute hypertension are nearly four times more likely to progress into CVD than healthy people in similar age stages. Two large foreign studies, Action to Control Cardiovascular Risk in Diabetes - Blood Pressure (ACCORD-BP) and Systolic Blood Pressure Intervention Trial (SPRINT), showed that improving blood pressure can reduce the incidence of cardiovascular events, while other Chinese scholars' studies also reached the same conclusion. Therefore, the reasonable intervention of T2DM blood pressure is a necessary measure to prevent CVDs (4-6).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are insulin-stimulating resistance drugs. It is a class of hypoglycemic drugs different from insulin resistance. It is usually administered by subcutaneous injection. In recent years, GLP-1 RA has become increasingly common in T2DM therapy (7). GLP-1 is mainly composed of and produced by L bacteria in the ileum and colon, and improves insulin secretion through a glucose-concentration-dependent method to stabilize blood glucose in the body (8,9). According to the protein composition of the drug, GLP-1RA can be divided into two types: one is a new protein composition based on exendin-4. In the artificial preparation, the sequence of amino acids had low homology with human GLP-1. The other is composed of human GLP-1, and after partial modification and processing of the chemical protein of human GLP-1, it has a high consistency with the amino acid sequence of human GLP-1 (10). Pancreatic GLP-1RA, as an emerging drug for lowering blood glucose, has its unique glucose concentration dependence. It can promote insulin genetic transcription, insulin production and interpretation, and even promote the proliferation and division of pancreatic beta cells, so as to achieve safe and effective control of blood glucose. At present, the human GLP-1 RA listed internationally includes the following 7 types: exenatide, lixisenatide, benaretalide, liraglutide, albiglutide, dulaglutide, and semaglutide. According to drug action time, GLP-1 RA can be divided into short-acting preparations and sustainable development preparations, and exenatide can be classified into short-acting preparations and sustai-

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nable development preparations (11). There are currently four major large clinical trials looking at its cardiovascular safety. Some studies have shown cardiovascular benefits, such as liraglutide, but some studies have shown no clear cardiovascular benefits, such as exenatide (12). Whether GLP-1 RA can improve blood pressure to benefit the cardiovascular system, and whether drugs differ with different structural and temporal effects, is not yet known. Therefore, this paper will comprehensively evaluate the clinical effect of a new hypoglycemic drug, glucagon GLP-1 RA, in patients with T2DM through meta-analysis technology, so as to provide evidence-based evidence for clinical use.

Materials and Methods

Literature retrieval

Computerized searches were performed on Pubmed, MEDLINE, EMBASE, and Cochrane Central databases of controlled trials. "GLP-1 RA", "new hypoglycemic drugs", "type 2 diabetes mellitus", "exenatide", "lixisenatide", "benaretalide", "liraglutide", "albiglutide", "dulaglutide", and "semaglutide" were undertaken the test terms to search the relevant literature published during establishment of the above datasets to October 2022. A separate search strategy was designed for each database. Each search strategy was defined as the free text for T2DM and GLP-1 RA, MeSH, and EMTREE terms, and randomized controlled trial (RCTS) study design filters in MEDLINE and EMBASE.

Criteria based on which the literature was excluded or included

The RCTS were enrolled according to predefined eligibility criteria using the population, intervention, control, outcome, and study design (PICOS) framework, as shown in Table 1.

Trials in newly treated T2DM patients, or only those with comorbidities were excluded. Two evaluators determined whether the RCTS meet the inclusion criteria in an independent way. Each evaluator first reviewed the title and abstract, and then full texts in the case of not determined eligibility after the title and abstract review. Diffe-

rences between reviewers were friendly discussed for an agreed solution or adjudication from another reviewer.

Data extraction

Literature screening and data extraction were conducted independently by 2 professionals using unified Microsoft Excel, who was also responsible for cross-checking the final results. If you have a disagreement, it could be discussed. The main data extracted included: (I) title, first author, publication period, etc.; (II) brief introductions of objects: number, age, etc.; (III) key elements of bias risk assessment (BRA): random method, blind method, allocation hiding, etc.; and (IV) concerned outcome indicators and outcome measurement data, etc.

Literature quality evaluation

With the RevMan 5.3, the included studies were evaluated with reference to the RCT-bias risk assessment methods under the Cochrane Manual of Systematic Review 5.3. The specific assessment content was listed in Table 2. According to the possibility of bias, it can be evaluated as low, medium, high, and unknown risks. If the evaluation was inconsistent, the two researchers could discuss it together or the third researcher can intervene.

Statistical methods

Baseline patient characteristics and outcomes at the end of the study were reported as mean ± SD or count (percentage). The combined mean and SD mean of all studies in subgroups using short - and long-acting GLP-1 RA were calculated with their corresponding standard equations, respectively. Results under the meta-analysis were reported as differences between baseline and end of the study and GLP-1 RA+ basal insulin treatment versus basal insulin + placebo and their 95% confidence intervals (CIs). The inverse variance method of successive endings and the Mantel-Haenszel method of classified endings were used. A statistical test for heterogeneity was conducted to understand the consistency of the results. The main heterogeneity measure adopted in the assessment was the I^2 value.

Table 1. Criteria based on which the literature can be enrolled.

No.	Specific requirements
1	Adults with T2DM with inadequate OADs control
2	Most subjects were treated with US-approved GLP-1 RA doses
3	Basal insulin with at least one oral antidiabetic drug (OAD) in the control group
4	The RCT lasted ≥ 16 weeks

Table 2. Specific evaluation contents of literature.

No.	Item	Specific requirements
1	Random allocation method	Whether the method for generating randomly assigned sequences was described in detail
2	Allocation hiding	Whether to describe in detail the method of hiding the random assignment sequence to determine whether the allocation of interventions was predictable before the outcome of the experiment
3	Blind method	Whether subjects, researchers, and outcome raters were blinded to the assigned interventions
4	Incomplete outcome data	Each of the primary outcome data was evaluated for the complete description and for incomplete outcome data that was properly processed
5	Selective reporting	Whether all outcomes of pre-determined primary outcome measures were fully reported
6	Other bias	Whether there were other factors that cause high risk of bias in the experiment

Results

Search results and introduction of literature

317 literatures were obtained by searching the database, 36 of which were repeatedly published, 27 of which were unqualified and 45 of which were eliminated because of other reasonable causes, and 209 articles were left after the first stage of searching and screening. 97 articles were determined as unqualified ones based on the reading results of their abstracts and titles. After further checking, another 43 articles were removed because they were unqualified in the type (such as research reports and reviews), and 69 remained. After the full texts of them were read one by one, another 27 literatures were eliminated due to incorrect types, 30 ones were not enrolled because they exhibited incomplete or unavailable data, and 2 articles were excluded because their focuses were not humans, and finally 10 articles were included in the meta-analysis (13-22). Figure 1 showed how to retrieve the literature.

The brief literature information was extracted further. It was found that among the 10 included literatures, 7 randomized controlled trials reported changes in HbA1c baseline and weight baseline, and 5 reported episodes of low blood glucose and changes in FBG. Table 3 listed the brief introduction of the enrolled literatures.

BRA results

The enrolled 10 literatures were subject to quality evaluation here, and the results suggested that 6 literatures were rated at grade A (60.00%), 3 literatures rated at grade B (30.00%), and 1 literature rated at grade C (10.00%). Figure 2 and Figure 3 demonstrated the chart for BRA and the summary chart of BRA.

HbA1C change

MD was undertaken as an indicator of clinical outcome, as displayed in Figure 4. The MD value analyzed for HbA1C changes in 7 literatures was -0.02, 95% CI was (-0.04, -0.01), I^2 = 18.20%, and P = 0.00. MD values exhibited that HbA1C variation had low heterogeneity among study groups. Among them, the lowest and highest MD values were -0.24 and 0.15, respectively, with 95% CIs of (-0.38, -0.10) and (0.02, 0.28), respectively.

The effectiveness of treatment was analyzed comprehensively. Figure 5 exhibited the heterogeneity test diagram of HbA1C changes. The heterogeneity and potential abnormal value of various studies were evaluated. Figure 6 presented the funnel plot of HbA1C changes, and the risk of bias in each literature was small. The above results demonstrate that sm-440, a novel GLP-1RA, is convenient
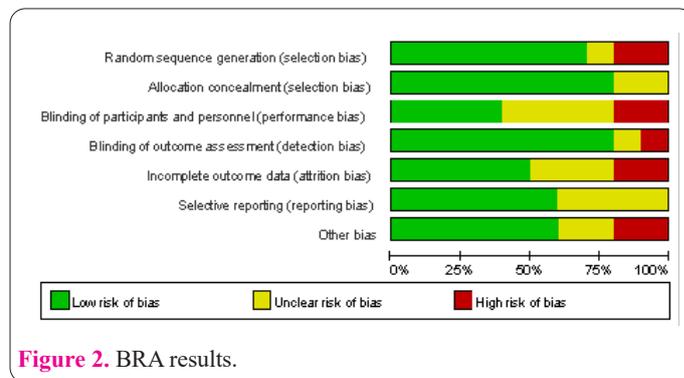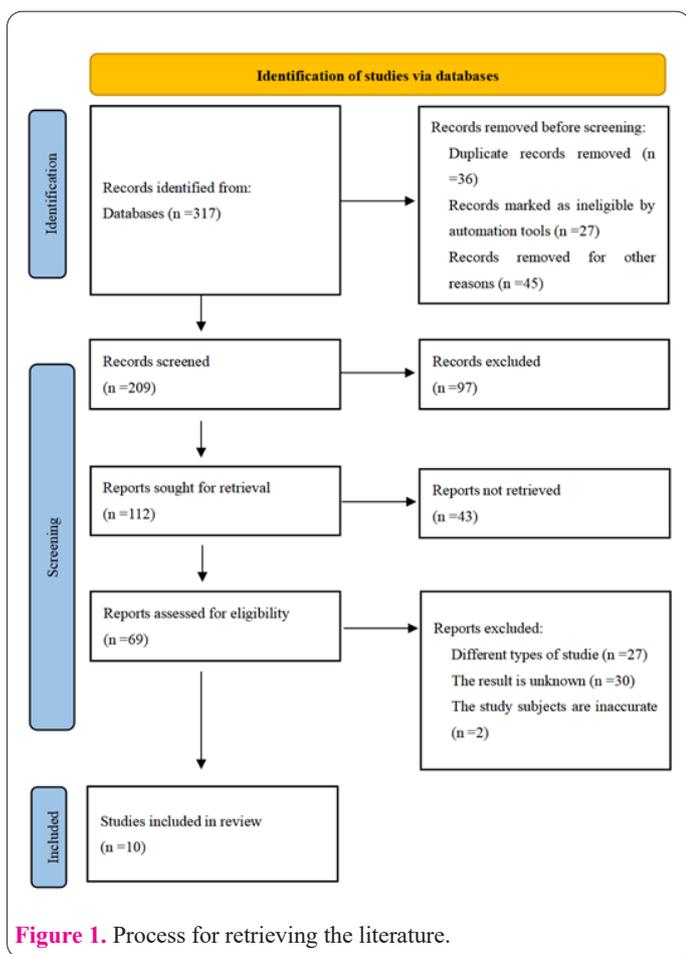

Figure 1. Process for retrieving the literature.

Figure 2. BRA results.

Table 3. Brief information on the enrolled literatures.

Author	Year	GLP-1 RA	Target dose of GLP-1 RA	Cases	
				Experimental	Control
Araki (13)	2015	Dulaglutide/Glargine	Free	181	180
Barnett (14)	2007	Exenatide/Glargine	Free	68	70
Bunck (15)	2009	Exenatide/Glargine	Free	36	33
Giorgino (16)	2015	Dulaglutide	Free	273	262
Guja (17)	2018	Exenatide	Free	231	230
Pozzilli (18)	2017	Dulaglutide	Free	150	150
Rosenstock (19)	2016	Lixisenatide	Fixed (iGlarLixi)	233	466
Seino (20)	2012	Lixisenatide	Free	154	157
Weissman (21)	2014	Albiglutide/Glargine	Free	496	239
Yang (22)	2018	Lixisenatide	Free	224	224

and effective for the change of HbA1C in patients with T2DM.

Figure 6. Funnel plot of HbA1C change analysis.
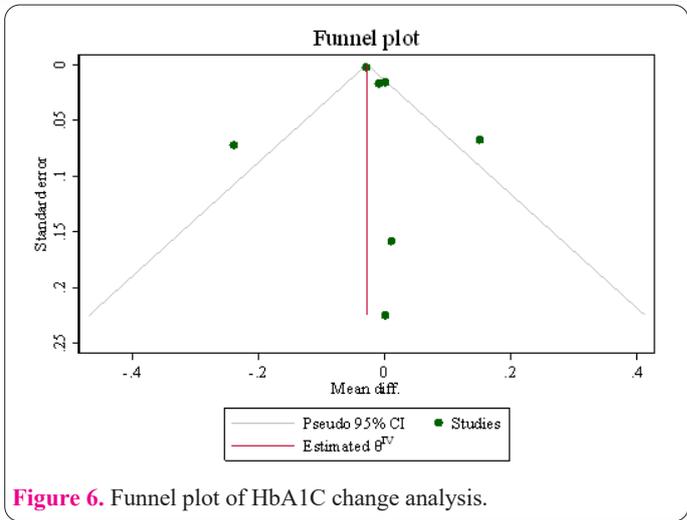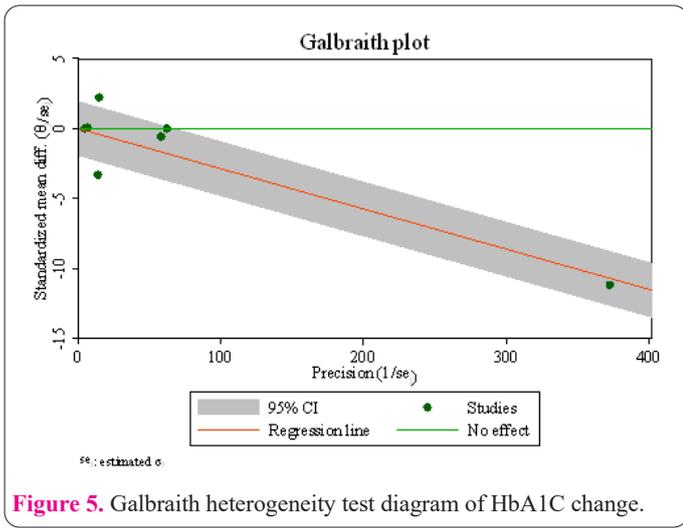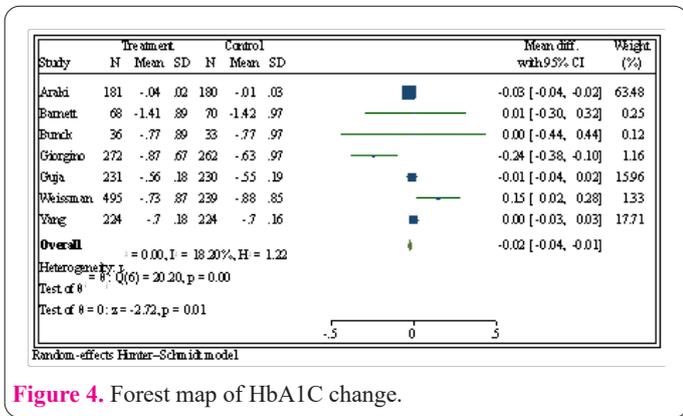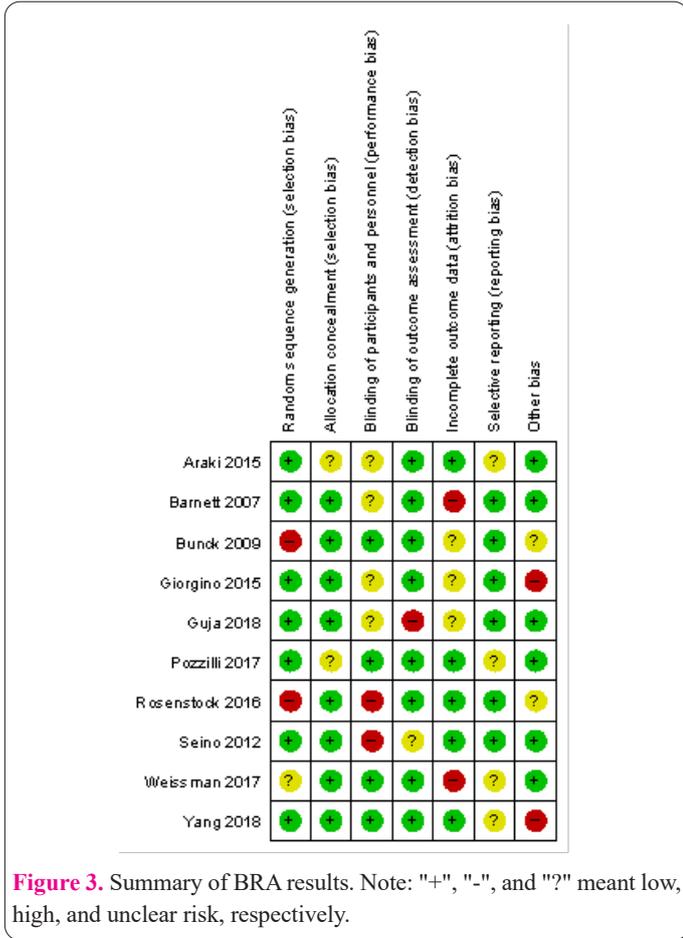
Weight changes

Taking MD as an indicator of clinical outcome, the MD of weight change in 7 literatures was -1.37, with a 95% CI of (-1.98, -0.76), I² = 97.80%, and *P* = 0.00 (Figure 7). MD values presented a high heterogeneity among study groups, and further heterogeneity tests were needed. The lowest MD value was -3.66, with a 95% CI of (-4.03, -3.29), and the highest MD value was -0.35, with a 95% CI of (-0.51, -0.20).

The weight changes were comprehensively analyzed in this work (as illustrated in figure below). Figure 8 exhibited the heterogeneity test chart of weight changes. Heterogeneity and potential abnormal value of various studies were evaluated, which suggested that the heterogeneity
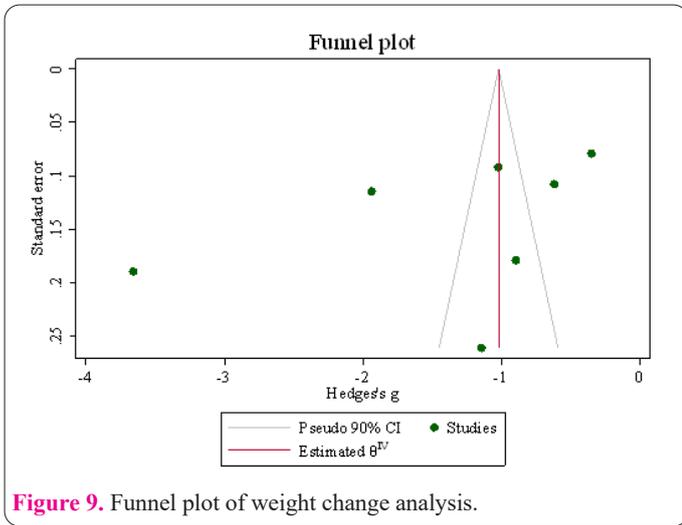

Figure 3. Summary of BRA results. Note: "+", "-", and "?" meant low, high, and unclear risk, respectively.

Figure 4. Forest map of HbA1C change.

Figure 7. Forest map of weight change analysis.

Figure 5. Galbraith heterogeneity test diagram of HbA1C change.

Figure 8. Galbraith heterogeneity test diagram of weight change analysis.
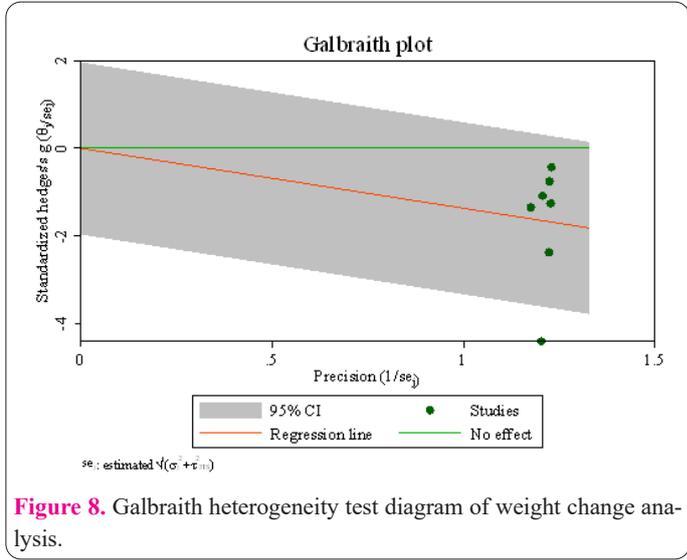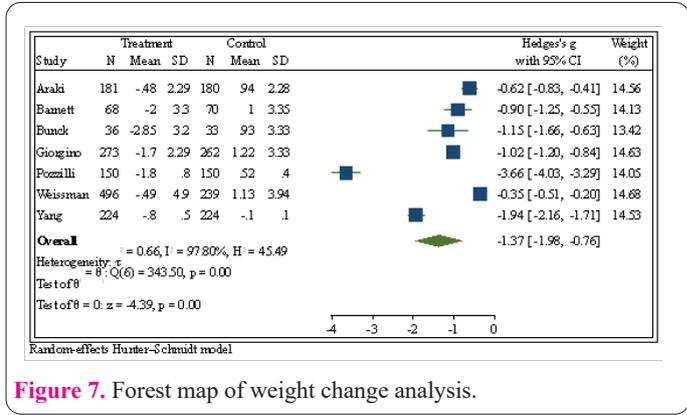
Figure 9. Funnel plot of weight change analysis.

Figure 11. Labbe heterogeneity test for blood glucose with low OR value.

of each study was small and had high accuracy. Figure 9 gave the funnel plot of weight changes. Thus, the literature enrolled here exhibited a small BRA. Such results fully confirm that sm-440, a novel GLP-1RA, is effective in weight change in patients with T2DM.

Blood glucose with low OR value

Taking OR as an indicator of clinical outcome, the OR of low blood glucose in 5 literatures was 0.33 (Figure 10), with a 95% CI of (-0.47, 1.14), I^2 = 92.57%, and P = 0.00. OR values presented that the blood glucose with low OR exhibited a high heterogeneity among study groups, and further heterogeneity tests were necessary. Among them, the lowest and highest OR values were -0.89 and 1.50, respectively, and their corresponding 95% CI values were (-1.38, -0.40) and (0.94, 2.07), respectively.

The blood glucose with low OR was analyzed comprehensively and detailed. Figure 11 and Figure 12 showed the heterogeneity test of blood glucose with low OR. The heterogeneity and potential anomalous value of various studies were assessed, and the heterogeneity of each study was small, with high accuracy. Therefore, it is further confirmed that sm-440, as a novel GLP-1RA, is effective in low blood glucose ratios in T2DM patients.

FBG analysis

Taking MD as an indicator of clinical outcome, the MD of FBG in 5 literatures was -1.68, with a 95% CI of (-3.41, 0.07), a I^2 of 99.51%, and a P value of 0.00. The specific data were given in Figure 13. MD values showed high heterogeneity of FBG among study groups, and further heterogeneity test was needed. Among them, the lowest and the highest MD values were -4.46 and 1.81, respectively, with 95% CIs of (-4.81, -4.12) and (1.57, 2.06), respecti-

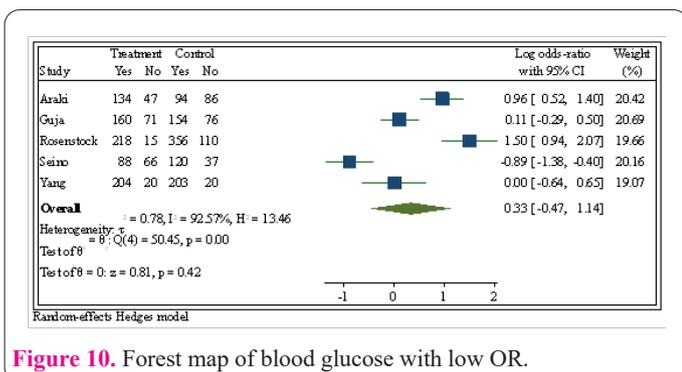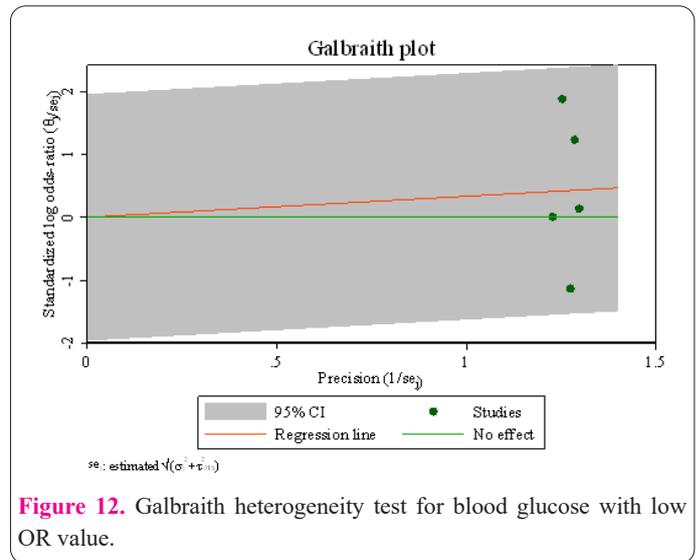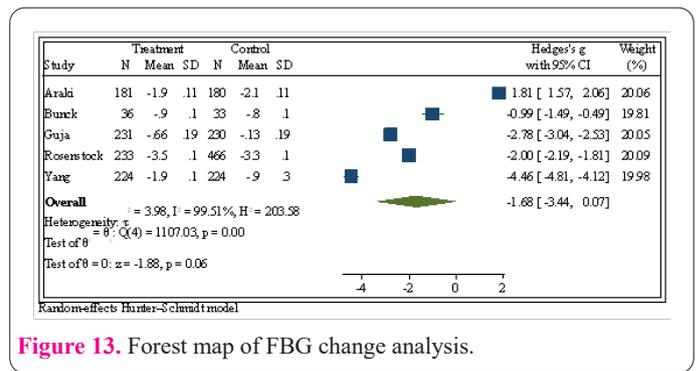**Figure 12.** Galbraith heterogeneity test for blood glucose with low OR value.

Figure 13. Forest map of FBG change analysis.

vely.

FBG was comprehensively analyzed so that the treatment effect could be understood more clearly. Figure 14 showed the heterogeneity test diagram of FBG. Heterogeneity and potential anomalous value of various studies were assessed, and the heterogeneity was small for all literature, with high accuracy. The results here again prove that sm-440, as a novel GLP-1RA, is effective in treating FBG in patients with T2DM.

Reliability analysis

Sensitivity analysis was carried out in this work with various models. Meta-analysis results revealed that the models adopted here exhibited no great change in their
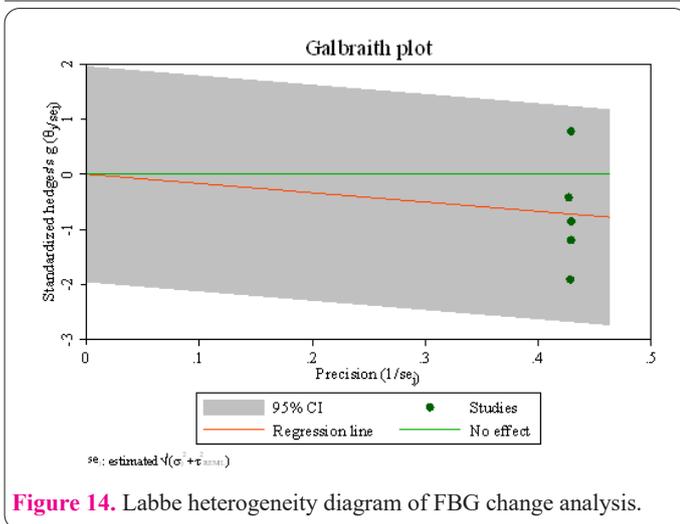

Figure 10. Forest map of blood glucose with low OR.

Figure 14. Labbe heterogeneity diagram of FBG change analysis.

results, meaning that the enrolled literature presented a good stability.

Discussion

At present, the traditional hypoglycemic program used in the clinic is mainly a guanidine sensitizer; and sulfonylureas and glycinides were the main secreting agents. Glycosidase inhibitors are mainly used as carbon-blocking water absorption agents. Insulin resistance lowering drugs based on gliazone, etc. In addition, various quick-acting, long-acting, and premixed insulin formulations all played a role in controlling blood glucose to varying degrees. However, it does not fundamentally improve insulin resistance and repair insulin function, nor does it intervene in circulatory system diseases such as carotid atherosclerosis (23). It can even be said that due to its pharmacologically related mechanisms, it may even cause side effects such as low blood glucose, increased weight, sodium retention, and even an increased burden on the cardiovascular system. Pancreatic GLP-1RA, as an emerging drug for lowering blood glucose, has its unique glucose concentration dependence (24). It can promote insulin genetic transcription, insulin production and interpretation, and even promote the proliferation and division of pancreatic beta cells, so as to achieve safe and effective control of blood glucose. In addition, it has special effects on the cardiovascular system, reducing weight and visceral fat content, improving lipid distribution, improving myocardial ischemia, and lowering blood pressure. At present, most mammalian experiments have shown that GLP-1 RA can interfere with the progression of atherosclerosis by controlling mononuclear adhesion to endothelial capillaries, controlling the infiltration of macrophages, and delaying the progression of atherosclerosis due to thrombus destruction and intimal thickening (25-27).

So far, the mechanism of GLP-1RA's direct effect on blood pressure remains unclear. Meanwhile, whether GLP-1 RA can improve blood pressure to benefit the cardiovascular system, and whether drugs differ with different structural and temporal effects, is not yet known. It has been confirmed to have effects by activating GLP-1 receptors on capillaries and myocardium, including enhancing endothelial capacity, dilating small cerebral vessels, and diuresis. Mammalian experiments have also shown that Liraglutide can improve the capacity of vascular endothelial cells, increase the level of nitric oxide synthase (e NOS)

in middle vascular endothelial cells, and downregulate the adhesion substance 1(ICAM-1) in median vascular endothelial cells (28). Studies have shown that GLP-1 promotes endothelial function in T2DM patients with coronary heart disease (29). In addition, GLP-1 RA can promote the normal growth of coronary endothelial cells through the activation process of PKA-PI3K/ Akt-eNOS. GLP-1 also enhances capillary dilation. Animal studies have confirmed that GLP-1 improves the functional repair and cardiomyocyte activity of isolated animal myocardium after anoxic reperfusion injury, and dilates the upper capillaries (30). In addition, GLP-1 RA during reperfusion reduced hypoxic injury after anoxic reperfusion and increased c GMP release, upper capillary dilation, and coronary blood flow in wild-type and Glp1r(-/-) type animals. GLP-1 RA may also affect urinary sodium excretion. According to a GLP-1 RCT investigation on water and sodium balance in healthy elderly and obese people, intravenous GLP-1 infusion can improve sodium excretion, thereby reducing H+ secretion and reducing glomerular volume ultrafiltration (31).

When using GLP-1 RA and basal insulin (32), it is important to pay attention to the specific dose combination, because there is a big difference between them. The fixed-dose combination has a specific requirement for the maximum insulin dose to ensure that the GLP-1 RA dose is not too high. At the same time, this requirement is also a criterion for the selection of subjects in this paper (excluding those with higher insulin) (33,34). On the other hand, a subset of patients on the fixed-dose combination may receive less than the prescribed maximum dose. The free dose combination of short-acting and long-acting GLP-1 RA showed significant differences in blood glucose control, which was similar to the conclusion of a previous report (35-40).

Conclusion

It was concluded that GLP-1RAs with basal insulin not only improved overall blood glucose control (HbA1c) but also improved FBG concentration and decreased weight. Of course, this study inevitably has certain defects. The drug concentration in the CRTs included were not uniform. Due to fewer existing RCTs and different outcome indicators, some studies were not enrolled here, and the level of evidence was lowered. Follow-up studies will analyze more indicators and compare the differences between different drug concentrations more comprehensively, so as to offer a more accurate reference for clinical treatment.

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