European Review for Medical and Pharmacological Sciences 2024; 28: 3073-3084

Network meta-analysis of the risk of dyspepsia and anorexia in patients with type 2 diabetes mellitus induced by glucagon-like peptide 1 receptor agonist hypoglycemic drugs

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Abstract. – OBJECTIVE: The aim of this study was to investigate and evaluate the risk of dyspepsia and anorexia in patients with type 2 diabetes mellitus (T2DM) induced by glucagon-like peptide 1 receptor agonist (GLP-1 RA) hypoglycemic drugs.

MATERIALS AND METHODS: We searched papers in PubMed, Web of Science, Cochrane Library, Google Scholar, CNKI, Wanfang, Embase and VIP databases, and the retrieval time limit was set from the establishment of the database to May 2023. Randomized Controlled Trials (RCTs) were collected in which the subjects were T2DM patients, the intervention was GLP-1RA compared with placebo or traditional hypoglycemic drugs, and the outcome indicators included dyspepsia and anorexia. A meta-analysis and a network meta-analysis were performed.

RESULTS: The results of the traditional meta-analysis showed that the risk of dyspepsia and anorexia of total GLP-1 RA was 3.01 and 2.56 times that of placebo, respectively. All types of GLP-1RA were compared with placebo and the results also showed a trend towards increased risk of digestive system adverse events (DSAEs). Among all interventions included, liraglutide was the one with the highest risk of dyspepsia in patients with T2DM, and dulaglutide was the one with the highest risk of anorexia.

CONCLUSIONS: The results of the two meta-analyses are consistent, and both clearly show that GLP-1RA can increase the risk of dyspepsia and anorexia in T2DM patients.

Key Words:
Type 2 diabetes mellitus, Dyspepsia, Anorexia, GLP-1RA, Meta-analysis.

Introduction

With economic development and lifestyle changes, the incidence of metabolic diseases such as obesity, hyperlipidemia, and diabetes is increasing year by year, especially diabetes. With the progression of the disease, the function of pancreatic β-cells is damaged until apoptosis, which seriously endangers human health.

According to the IDF Global Diabetes Map (9th Edition)[1] published on the official website of the International Diabetes (DM) Federation (IDF) in 2021, The number of patients with diabetes mellitus (DM) worldwide has significantly increased compared to the past. In 2021, the global prevalence of DM in adults (20-79 years old) reached 10.5%, with a total of 537 million cases, an increase of 74 million cases compared with 2019, and it is pointed out that there are an estimated 447,000 adult DM patients who have not been diagnosed. The new version of IDF map data[2] shows that from 2021 to 2045, the number of DM patients in China will increase from 140 million to 174 million. The global prevalence of DM remains high and is still on the rise. Solving the problem of hyperglycemia in many patients is currently a major challenge[3].

Although the existing oral diabetes drugs can control blood glucose, there is a risk of hypoglycemia and many side effects, and the etiology of diabetes cannot be reversed. It has no obvious effect on the growth, differentiation, and proliferation of islet β cells. Therefore, finding safe hypoglycemic drugs that can reverse the etiology is a current research hotspot. Glucagon-like peptide-1 (GLP-1) is an endogenous active polypeptide secreted by small intestinal L cells, which promotes insulin secretion in a glucose-dependent manner and has the effect of lowering blood glucose[4,5]. Compared with oral diabetes treatment drugs, GLP-1 has outstanding advantages: it has a good effect on controlling blood glucose, can avoid the occurrence of hypoglycemia, protects

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the function of islet β cells and promotes their proliferation, slows down gastric emptying, and suppresses appetite, etc[6].

Glucagon-like peptide-1 receptor agonist (GLP-1RA) is currently one of the most important hypoglycemic drugs, which can stimulate insulin secretion and inhibit glucagon secretion. Studies[7] have shown that GLP-1RA can delay the apoptosis of β cells in many ways and improve the ability to store insulin and secrete insulin. GLP-1RA reduces food intake by directly delaying gastrointestinal absorption and stimulating the vague nerve, inhibiting gastrin and feeding. It can also stimulate brown adipose tissue thermogenesis and white adipose tissue browning, increase energy consumption[8] and then help control body mass. GLP-1RA has important implications in the management of type 2 diabetes (T2DM). A recent expert consensus[9,10] suggests that GLP-1RA is the first choice for patients with liver and kidney function-related diseases. Studies[11,12] have shown that GLP-1RA has an antihypertensive effect and mainly reduces systolic blood pressure, but the mechanism of GLP-1RA's antihypertensive effect is still not completely clear, and further research is needed. In the treatment of T2DM, GLP-1RA has more ways to control blood glucose, has an evident hypoglycemic effect, and can maintain a relatively stable blood glucose level. Considering that most T2DM patients have complications such as obesity, cardiovascular disease, chronic kidney disease, and hypertension, GLP-1RA can improve metabolic problems in multiple dimensions, and combined application with oral drugs can improve clinical efficacy. However, there are individual differences in the glycemic response and tolerance of GLP-1RA in clinical application[13], and the reason remains to be explored.

Studies[14] have shown that the blood glucose response of patients to GLP-1RA is quite different (about 50-70% of the blood glucose response rate); some individuals can obtain a significant blood glucose response, but others have no evident improvement in HbA1c. In a Greek clinical study[15] on liraglutide, the glycemic response rate of liraglutide was only 70%. Therefore, based on the existence of a certain degree of GLP-1RA poor blood glucose response, exploring the factors that can predict the subsequent efficacy has become a major research direction. In the three directions of clinical phenotype and disease course, laboratory indicators, and genetic factors, a previous study[16] has found potential predictors of GLP-1RA blood glucose response.

A meta-analysis[17] showed that compared with a placebo, the adverse reactions of GLP-1 RA were mainly manifested in the gastrointestinal tract. At present, there are few randomized controlled trials (RCTs) on the safety comparison between GLP-1RAs and traditional hypoglycemic drugs and between different GLP-1RAs. Moreover, the research results are different due to the differences in sample size, patient course, and observation time[18-20].

However, network meta-analysis mainly uses indirect comparison techniques to evaluate and rank all interventions in the same body of evidence simultaneously comprehensively. The so-called "indirect comparison" refers to the evaluation of the effects of two different interventions that lack direct comparative clinical evidence with the help of other relevant studies that have been carried out.

Dyspepsia and anorexia are the most common digestive system adverse events (DSAE) in patients with T2DM after using GLP-1RA. Therefore, this study aims to conduct a systematic review of the risk of GLP-1RA-induced dyspepsia and anorexia published in domestic professional journals in recent years by searching relevant literature. We used network meta- and traditional meta-analysis methods[21,22] to further understand the impact of all interventions, including GLP-1, RA, and control drugs, on the risk of dyspepsia and anorexia.

Materials and Methods

Literature Search Strategy

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Specific and systematic searches were carried out on PubMed, Embase, Web of Science, Google Scholar, CNKI, Wanfang, and VIP databases; the search terms were: "GLP-1 receptor agonist", "glucagon like peptide", "GLP-1", "glucagon-like peptide-1 agonists" and "LY2189265". The search time limit was set from the establishment of the database to May 2023. The search results were limited to clinical research and were not restricted by language or ethnicity, and manual searches were performed by reading relevant works and summarizing references. Search strategies were adjusted to couple with the relevant regulations in every database.

Literature Inclusion Criteria

Randomized clinical trial (RCT), independently whether single-blind, double-blind, or non-blind. (2) The trial includes a parallel control group; the intervention measures are GLP-1, RA monotherapy and traditional hypoglycemic drugs, placebo, or blank control. (3) The subjects of the study are patients with T2DM. (4) Treatment time is not less than 28 days. (5) Outcome indicators include dyspepsia and anorexia.

Literature Exclusion Criteria

(1) Non-RCT study. (2) Duplicate publications or data duplication. (3) Studies without a control group. (4) Animal experiments. (5) Research methods, results, and conclusions that cannot be explained or do not correspond to each other. (6) Statistical methods and data analysis that have evident errors. (7) Literature on imperfect experimental design. (8) Literature for which data could not be extracted, or data were incomplete. (9) Review animal experiments, special adverse reaction reports, and pharmacology, pharmacokinetics, and other non-clinical research. (10) Patients with severe hepatic and renal insufficiency, etc. (11) The test results and conclusions are clearly inconsistent with the reality. (12) The intervention measures are non-GLP-1RA drugs or the combined application of 2 or more GLP-1RAs. (13) Outcome indicators do not include dyspepsia or anorexia.

Literature Screening and Data Extraction

Literature screening

Two researchers, based on the inclusion and exclusion criteria, independently screened the literature, targeting titles and abstracts, including primary screening, secondary screening, and cross-checking to determine possible relevant studies. Firstly, they conducted a preliminary screening by reading and analyzing the titles and abstracts of the articles and eliminating the literature that apparently was not included in the inclusion criteria or duplicate studies. Then, a re-screening was conducted by reading the full text of the papers obtained from the primary screening and then further screening the literature according to the inclusion criteria. Finally, a cross-check of the literature was performed. For documents with incomplete or questionable information, it was necessary to contact the corresponding authors for detailed information. Finally, an evaluation was made on whether to include the literature in the study. If two researchers had different opinions on some articles, they discussed them together until a consensus was reached; if no consensus could be reached, a third researcher participated in the judgment. Finally, the selected documents were included in Excel for the extraction and summary.

Data Extraction

The content of data extraction includes title, first author, year of publication, research type, and observation indicators.

Intervention

The intervention group (GLP-1RA) was compared with the control group [traditional hypoglycemic drugs (insulin, metformin, sulphonates, sialinediones, sitagliptin)] or placebo.

Efficacy Index

1. Dyspepsia
2. Anorexia

Quality Evaluation

Eligible literature was assessed for methodological quality using the Jadad scoring scale, on a scale of 1 to 7, assessing random sequence generation, blinding, allocation concealment, and patient withdrawal or withdrawal. A Jadad score of 4-7 was considered high-quality literature, and 1-3 was considered low-quality literature.

Statistical Analysis

The analyses were pooled using RevMan 5.4 (available at: https://training.cochrane.org/online-learning/core-software/revman) and Stata (Stata Corporation LLC, College Station, TX, USA) statistical software, with odds ratio (OR) and 95% confidence intervals (CI) for continuous data. The heterogeneity index (I^2) was used to evaluate the heterogeneity of the treatment effect. When there was no significant heterogeneity among the studies (I^2<50%), the fixed effect model was used; when there was significant heterogeneity among the studies (I^2≥50%), we used a random effects model. Egger's test was used to assess the potential risk of publication bias, and p>0.05 indicated no publication bias. Sensitivity analysis was performed on factors that may cause heterogeneity and literature with high sensitivity was excluded. A descriptive analysis was performed for articles in which a meta-analysis could not be performed.

Results

Literature Search Results

We systematically retrieved the original literature on T2DM, GLP-1RA and traditional hypoglycemic drugs published in databases such as CNKI, Wanfang, VIP, EMBASE, Web of Science, and PubMed, using subject headings combined with free words for systematic retrieval, and manually retrieved 1,058 studies. 268 animal studies and 37 comments were excluded, and 192 studies were obtained. After reading the full text, 128 studies whose full text could not be obtained and 34 incomplete experimental designs were eliminated, and finally, 9 studies[23-31] were obtained. The literature screening process is shown in Figure 1.

Basic Characteristics and Quality Evaluation of the Included Literature

The demographic characteristics and baseline characteristics of the patients are shown in Table I. The Jadad score of the included literature was 4 to 5, which was high-quality literature, and none of the 9 included studies[23-31] had withdrawal or withdrawal.

Risk of Bias Results

To assess the risk of bias, we used the Cochrane risk assessment tool to conduct an item-by-item evaluation of each included study through the following 6 evaluation criteria:

1) Random sequence generatio;
2) Allocation concealment;
3) Blinding of participants and personnel;
4) Blinding of outcome assessment;
5) Incomplete outcome data;
6) Selective reporting.

Analysis of the results for risk of bias (Figures 2-3) indicated that each of the included studies correctly described the generation of the random sequence and had relatively comprehensive outcome data. As for allocation concealment, only one study[23] did not have a very comprehensive description of performer-participant double blinding, while the rest did.

Efficacy Index Results

Total gastrointestinal adverse reactions

Figure 4 shows that in the 9 studies[23-31], the total gastrointestinal adverse reactions in the experimental group and the control group were 3,874 and 2,416, respectively (RR=2.18, 95% CI 1.88-1.53).

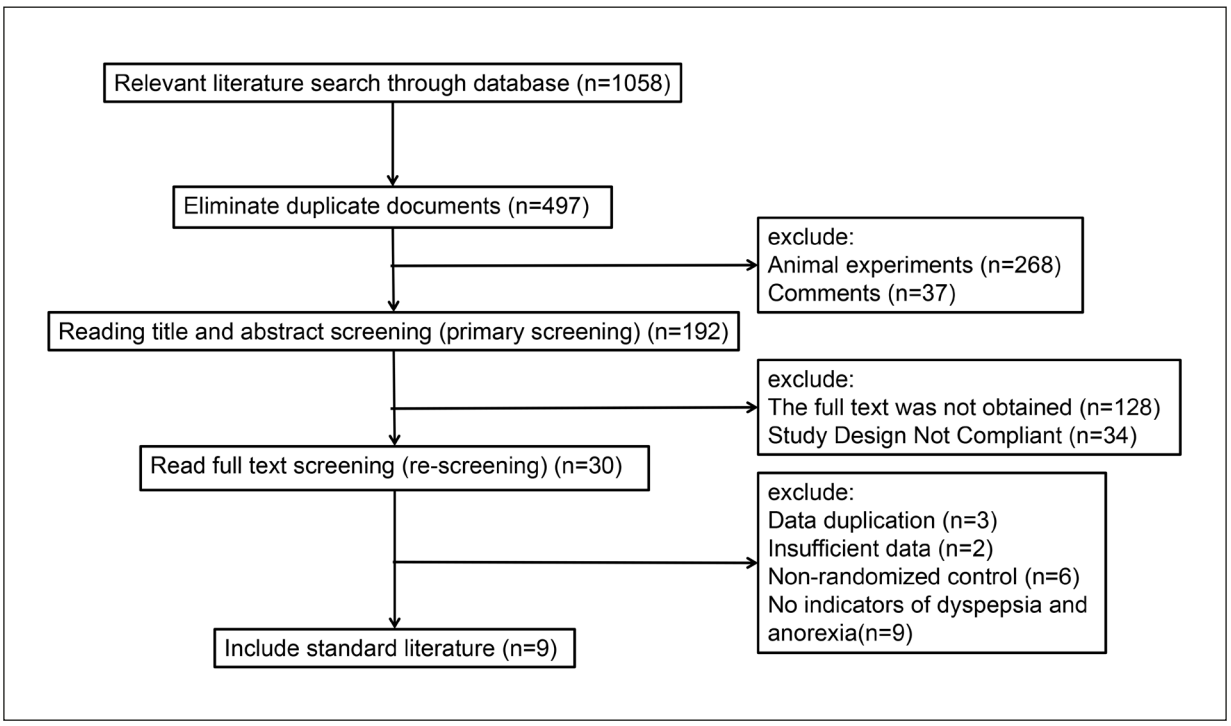

Figure 1. Flow chart of the literature search of network meta-analysis.

Table I. Basic characteristics and quality evaluation.

Researcher	Number of cases	Average age (years)	Disease course (years)	Course of treatment (weeks)	Intervention	Medication background	Efficacy index	HbA1c (%)	Jadad score
Pratley et al[29] (2014)	812	55.6	8.4	32	Albiglutide, liraglutide	-	①②	8.2	4
Wysham et al[31] (2014)	835	55.6	9	26	Dulaglutide, placebo, exenatide	Metformin + pioglitazone	①②	8.1	4
Nauck et al[27] (2014)	921	54	7	52	Dulaglutide, placebo, Sitagliptin	Diet + exercise / monotherapy / metformin + monotherapy	①②	8.1	4
Heine et al[24] (2005)	549	58.9	9.6	26	Exenatide, insulin	Metformin + sulphonylureas	①②	8.2	4
Nauck et al[28] (2007)	501	58.5	9.6	52	Exenatide, insulin	Metformin/ sulphonylureas	①②	8.6	4
Nauck et al[26] (2009)	1,087	57	7.9	104	Liraglutide, sulfonylurea	Metformin placebo	①②	8.4	5
Charbonnel et al[23] (2013)	650	57.3	6	26	Liraglutide, sitagliptin	Metformin	①②	8.2	5
Seino et al[30] (2012)	311	58.4	13.9	24	Tasiglutide, placebo	Metformin	①②	8.5	5
Hollander et al[25] (2013)	292	53.5	5.1	24	Tasiglutide, placebo	Metformin	①②	7.6	4

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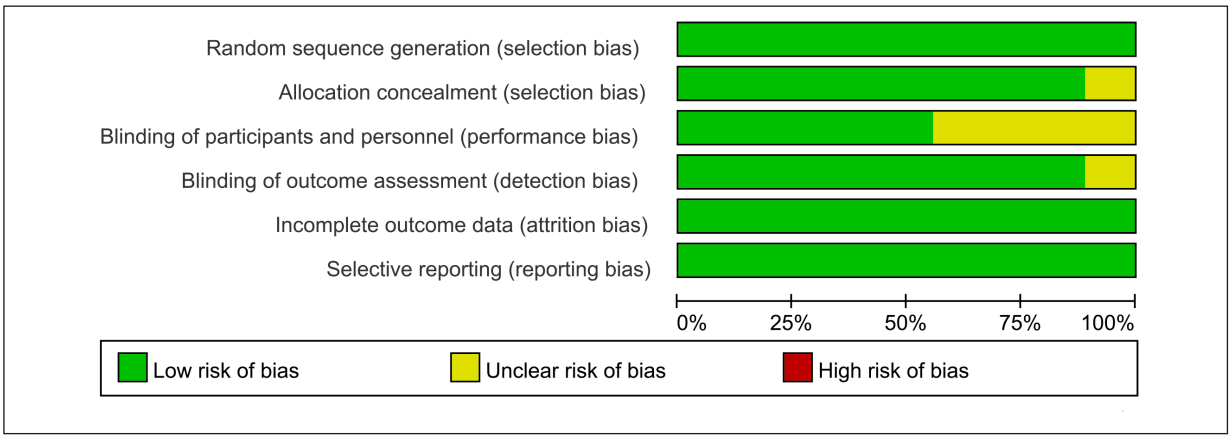

Figure 2. Risk of bias bar plot.

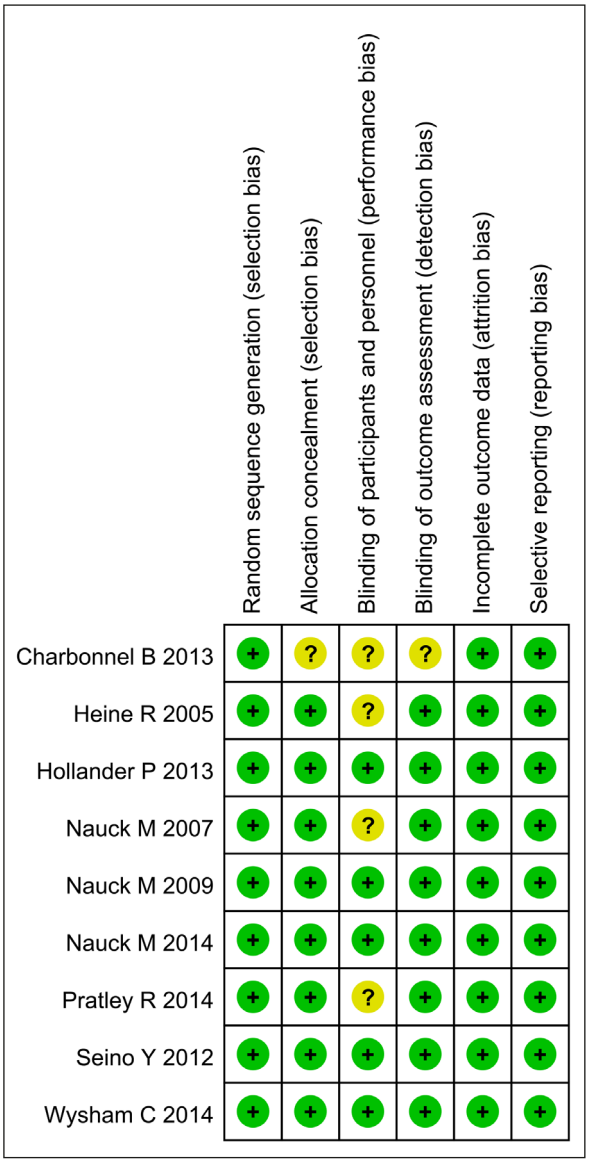

Figure 3. Risk of bias summary.

Dyspepsia and Anorexia

The 9 included studies[23-31] specifically described dyspepsia (RR=1.85, 95% CI 1.57-2.17) and anorexia (RR=1.57, 95% CI 1.35-1.81) in the experimental and control groups (Figures 5-6).

Network Meta-Graph Analysis

The network meta-diagram of different interventions is shown in Figure 7. For both dyspepsia and anorexia, the number of studies directly comparing exenatide with placebo was the largest. The study with liraglutide as the intervention had the largest total sample size (p<0.01).

Risk Ranking of Dyspepsia and Anorexia in Patients with T2DM

We ranked all interventions by DSAE risk (Table II). The results showed that the interventions leading to the highest risk of dyspepsia and anorexia in patients with T2DM were liraglutide and dulaglutide, respectively.

Discussion

GLP-1 is one of the gut-derived hormone incretins produced by intestinal L cells. It can increase insulin secretion, protect β cells, and act on α cells to reduce glucagon secretion. After a research institute[32] observed the effect of incretin in 1986, more and more studies[33,34] have shown that GLP-1 RA can not only act on the pancreas, liver, and peripheral tissues to participate in blood glucose regulation, but it may also act on the central nervous system and digestive system, playing a role in regulating appetite, blood pressure, blood lipids, and improving cardiac function and en-

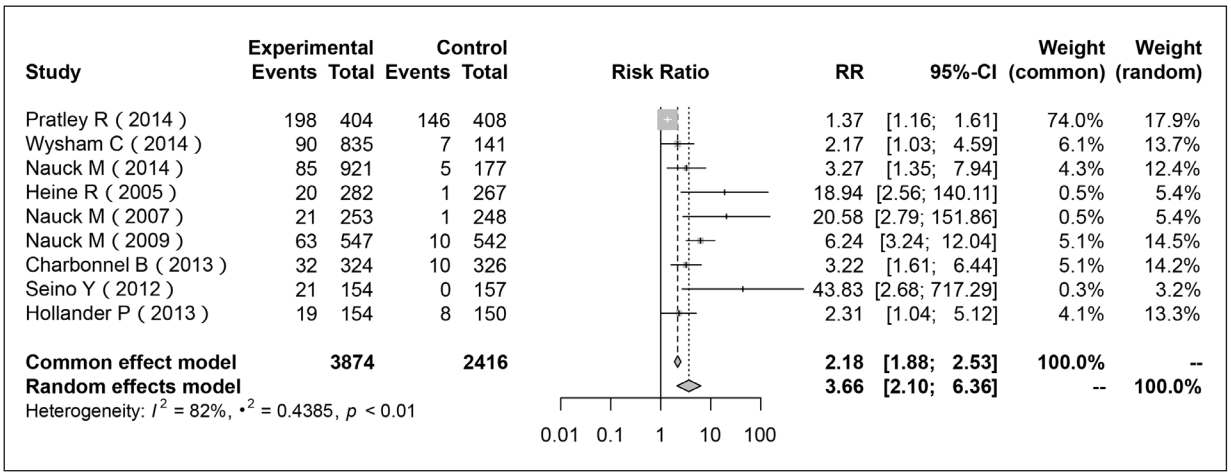

Figure 4. Meta-analysis forest plot of total gastrointestinal adverse reactions in 2 groups.

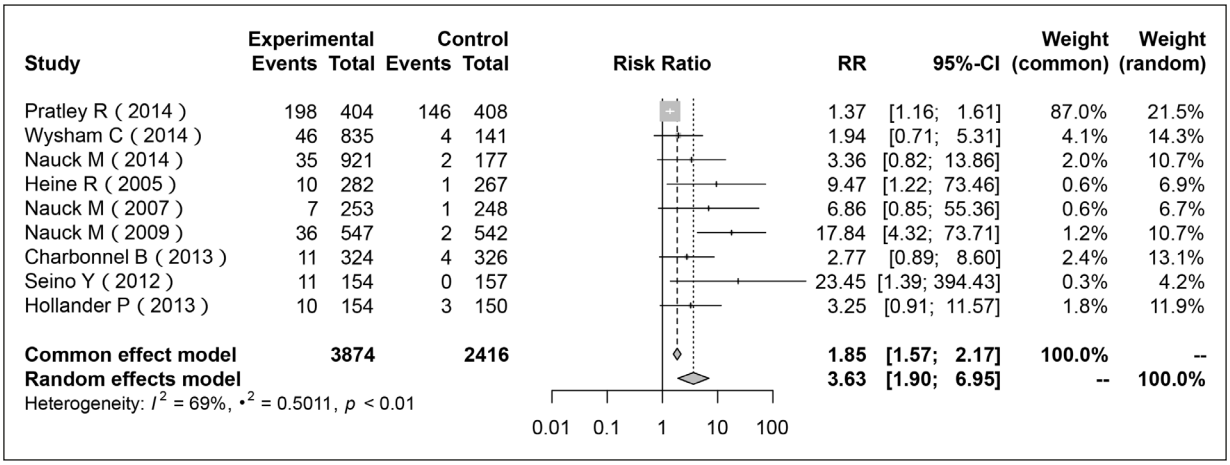

Figure 5. Meta-analysis forest plot of dyspepsia in 2 groups.

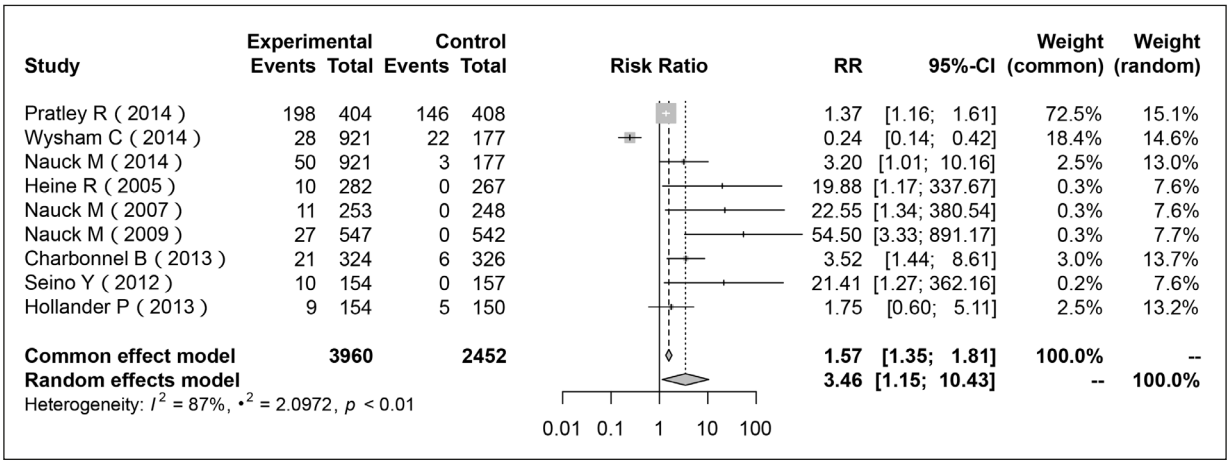

Figure 6. Meta-analysis forest plot of anorexia in 2 groups.

Table II. Ranking of the risks of dyspepsia and anorexia due to different intervention measures in patients with T2DM.

Intervention	Dyspepsia		Anorexia	
	SUCRA	Rank	SUCRA	Rank
Liraglutide	0.9231	1	0.7398	5
Tasiglutide	0.8545	2	0.8255	3
Lixisenatide	0.8112	3	0.4122	7
Albiglutide	0.6853	4	0.4327	6
Exenatide	0.6271	5	0.7415	4
Dulaglutide	0.4688	6	0.9262	1
Sulphonylureas	0.3573	7	0.1598	10
Metformin	0.3414	8	0.8261	2
Sitagliptin	0.2487	9	0.4119	8
Placebo	0.1241	10	0.3759	9
Insulin	0.0225	11	0.0412	11

*SUCRA=area under the cumulative ranking curve (p<0.05).

dothelial function. However, the risks associated with the digestive system also need to be considered during treatment[35,36]. At present, many studies have shown that GLP-1RA-based treatment may increase the risk of DSAE in patients with T2DM[37,38]. There are also research results[39] showing that patients with GLP-1RA are prone to gastrointestinal discomfort. Some meta-analysis results[40] showed that patients receiving GLP-1RA are prone to DSAEs such as nausea, vomiting, and diarrhea. The mechanism leading to this increased risk may be related to the delay of gastric emptying by modulating the appetite center of these drugs[41,42]. However, the above studies[35-42] on

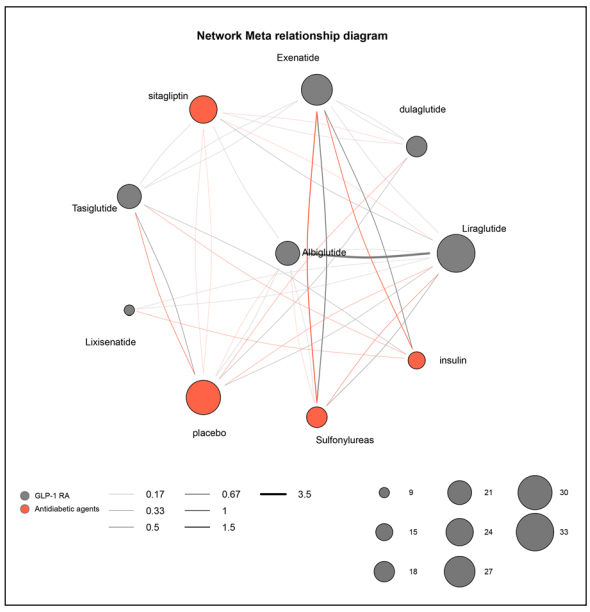

Figure 7. Network Meta relationship diagram.

adverse reactions of the GLP-1RA digestive system are mostly exploratory analyses, not the main research conclusions. Moreover, most of the research objects are small samples, lack large-scale clinical research confirmation after listing, and it is difficult to provide a quantitative reference for clinical practice. Therefore, it is necessary to use evidence-based medicine to summarize the evidence of GLP-1RA-related DSAE.

This study collected all current RCTs on dyspepsia and anorexia in GLP-1RA-induced T2DM patients. The result obtained is that the traditional meta-analysis results showed that the dyspepsia risk of total GLP-1RA is 3.01 times that of placebo, and the risk of anorexia is 2.56 times that of placebo. This is consistent with the conclusion of the experimental study by Krieger[38], which states that GLP-1 RA can significantly reduce food intake in rats. All types of GLP-1 RAs were compared with placebo, and the results also showed a tendency to increase the risk of DSAE. In addition, compared with placebo, with the extension of the course of treatment, the risk of dyspepsia increased with exenatide and liraglutide, and the risk of anorexia decreased with exenatide. Compared with placebo, total GLP-1RA tended to reduce the risk of dyspepsia with the prolongation of the course of treatment. This is consistent with the research conclusion of Kao et al[43], that is, in the early stage of GLP-1, depressive disorder patients will have DSAE such as dyspepsia and anorexia, but with the continuation of treatment, the above symptoms can be weakened on their own and will not affect subsequent treatment. Other studies[44] have also shown that with the prolongation of treatment time, the adverse reac-

tions of the digestive system caused by GLP-1RA can be weakened or disappear on their own. This may be due to the development of gastrointestinal tolerance in patients with the advancement of treatment, which reduces the incidence of DSAE[32]. Therefore, early symptomatic treatment is particularly important. Some studies[45] suggest that the clinical use of GLP-1RA should start with a low dose and then gradually increase; if DSAE occurs during the medication, the dose can be temporarily reduced until the patient's tolerance improves. If the symptoms are severe, the drug can be suspended or kept at a low dose within the first month.

The main advantage of network meta-analysis is that it makes up for the shortcomings of traditional meta-analysis and studies the effect of the relationship between any two groups in the body of evidence. The results of the comparison with placebo by network meta-analysis in this study were similar to those of the traditional meta-analysis, both suggesting that GLP-1RA had a higher risk of dyspepsia and anorexia than the placebo group. DSAEs related to GLP-1RA and traditional hypoglycemic drugs were compared through network meta-analysis, and the results were consistent with Huthmacher et al[36]'s meta-analysis, which is, compared with insulin, the risk of DSAE of GLP-1RA was clearly increased. Network meta-analysis also showed that, compared with insulin, metformin, sulfonylurea, and sitagliptin, the risk of dyspepsia in T2DM patients induced by GLP-1RA was increased. Among them, liraglutide is the riskiest. Compared with insulin and sulfonylureas, GLP-1RA can increase the risk of anorexia. Compared with metformin, except dulaglutide, which may increase the risk of anorexia in patients with T2DM, the rest of the GLP-1RAs have been shown to reduce the risk of anorexia. This is consistent with the current conclusion[46] that metformin can cause a high incidence of gastrointestinal reactions.

In addition, network meta-analysis based on Bayesian theory can also rank the risk of adverse events related to interference measures. This study showed that among all interventions included, liraglutide was the one with the highest risk of dyspepsia in T2DM patients, and dulaglutide was the one with the highest risk of anorexia. However, because GLP-1RA is a new type of hypoglycemic drug, except for exenatide, the number of studies on GLP-1RAs is very limited, and there are fewer studies on pairwise comparisons, so the results of this study are only exploratory results. To draw a definite conclusion, more GLP-1RA direct comparison and pairwise comparison studies are still needed.

The advantages of this study are as follows: (1) The search is more comprehensive, including all RCTs comparing 7 GLP-1RAs with placebo and 5 traditional hypoglycemic drugs. (2) During the analysis process, subgroups were studied according to the course of treatment to make the analysis more detailed. (3) We performed a network meta-analysis when there were multiple interventions and a lack of direct comparative evidence in the included studies. Simultaneous evaluation and risk ranking of multiple interventions with the help of indirect comparison technology is of great significance in guiding clinicians in individualized drug administration.

However, this analysis is still based on the research level, and it is not possible to analyze each study based on the individual level. Furthermore, the included RCTs were not short-term, small-sample studies reporting DSAE as the primary outcome measure. Different RCTs may have inconsistent criteria for judging outcome events, so there are inevitable biases, and the research results still need to be further explored and supplemented.

Conclusions

In summary, the results of this study suggest that GLP-1RA can increase the risk of dyspepsia and anorexia in T2DM patients, but it still needs to be verified by large prospective studies designed specifically for DSAE. Network meta-analysis, a new evidence-based evaluation method, can provide new ideas for the clinical evaluation of other drugs.

Acknowledgements

We thank Jinzhou Central Hospital and Henan Provincial People's Hospital for helpful discussions. We apologize to the scientists whose work could not be cited due to space limitations.

Authors' Contributions

Bolun Jiao conceived the structure of the manuscript. Jin Zhao and Bing Wang did the data analysis and made the figures. Boyan Liu and Tian Wu reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding
Not received.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent
Not applicable due to the design of the study.

Conflict of Interest
The authors declare that they have no competing interests.

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