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Efficacy and safety of GLP-1 agonists in the treatment of T2DM: A systematic review and network meta-analysis

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To compare efficacy and safety of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in subjects with type 2 diabetes (T2DM). Electronic databases were searched from inception to 2nd October 2024 for randomised controlled trials comparing GLP-1RAs treating T2DM. Bayesian network meta-analyses were conducted to analyze metabolic and safety outcomes. 64 trials comprising of 25,572 participants were identified. Compared to placebo, tirzepatide showed the greatest reduction in HbA1-c (MD: -2.3%) and FPG (MD: -3.1mmol/L); semaglutide was second (HbA1-c: MD: -1.5%; FPG: MD: -2mmol/L); liraglutide was third (HbA1-c: MD: -1.2% FPG: MD: -1.6mmol/L) (*P*<0.05). All treatments showed no statistically significant differences in BMI, SBP, DBP, TC, HDL-C and LDL-C compared to placebo. Tirzepatide (MD: -9.1 kg), semaglutide (MD: -2.8 kg) and liraglutide (MD: -1.2 kg) (*P*<0.05) had significant reduction in body weight compared to placebo. GLP-1 RAs had higher risk of gastrointestinal symptoms. Semaglutide increased the risk of hypoglycemia compared to placebo while liraglutide reduced the risk of hypoglycemia compared to traditional antidiabetic drugs. GLP-1RAs improve glycaemic control, with tirzepatide, semaglutide and liraglutide exhibiting the most significant improvements. Tirzepatide is more suitable for treating T2DM with obesity. For individuals with normal weight, both semaglutide and liraglutide are generally more effective for treating T2DM. However, considering the potential for semaglutide to cause hypoglycemia, liraglutide may be the optimal choice for T2DM treatment to minimize the risk of hypoglycemia.

Keywords Network meta-analysis, Glucagon-like peptide-1 receptor agonists, Type 2 diabetes mellitus

Abbreviations

ADA	American Diabetes Association
BMI	Body Mass Index
Cis	Confidence Intervals
CNKI	Chinese database China National Knowledge Internet
DBP	Diastolic Blood Pressure
DDP-4	Dipeptidylpeptidase-4
DIC	Deviance Information Criterion
EASD	European Association for the Study of Diabetes
EBID	Twice-daily Exenatide
EQW	Once-weekly Exenatide
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GIP	Glucose-dependent Insulinotropic Polypeptide
GLP-1	Glucagon-like Peptide
GLP-1 RAs	Glucagon-like Peptide Receptor Agonists
HbA1-c	Glycosylated Hemoglobin, Type A1C
HDL-C	High-Density Lipoprotein Cholesterol

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LDL-C	Low-Density Lipoprotein Cholesterol
MD	Mean Difference
NMA	Network Meta-analysis
OR	Odds ratio
RCT	Randomized Controlled Trail
RR	Relative Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGLT-2	Sodium-dependent Glucose Transporter 2
SUCRA	Surface Under the Cumulative Ranking Curve
T2DM	Type II Diabetes Mellitus
TC	Total Cholesterol

Type II Diabetes Mellitus (T2DM) is a metabolic disease characterized by insulin resistance and damage to islet β cells, which has attracted extensive attention because of its high incidence and multiple complications[1]. The tenth edition of the Global Diabetes Overview released by the International Diabetes Federation predicts that the number of people with diabetes worldwide will reach 643 million by 2030, accounting for 11.3% of the global population, and will rise to 783 million, accounting for 12.2% of the global population by 2045[2]. T2DM has become a serious threat to public health worldwide in recent years and the variety of T2DM drugs is also increasing.

Glucagon-like peptide (GLP-1) is an insulin-stimulating hormone secreted by L cells during the digestion of food in the small intestine, which shows trophic effects on β cells and can promote the secretion of insulin to maintain the glucose homeostasis[3,4]. By fine-tuning the molecular structure of GLP-1, its pharmacological characteristics can be modified to generate therapeutic biological effects suitable for clinical applications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce glucose levels by mimicking the action of the gut hormone GLP-1 to bind to GLP-1 receptors, stimulating the release of insulin and inhibiting glucagon secretion[5]. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) endorse the use of GLP-1RAs as an alternative when metformin alone fails to achieve the desired glycemic control, and also as a supplementary therapy to lifestyle modification[6,7].

As of now, the US Food and Drug Administration (FDA) has approved EBID, once-weekly exenatide, semaglutide, dulaglutide, liraglutide, albiglutide, lixisenatide, and tirzepatide for the management of T2DM. However, clinical trials and development of taspoglutide were ceased in 2010, rendering it inaccessible for clinical utilization[8].

While numerous randomized controlled trials (RCTs) have been conducted to evaluate the efficacy of GLP-1 RAs in the treatment of diabetes, no such studies have directly compared GLP-1 drugs with traditional antidiabetic drugs, in addition to comparing different GLP-1 drugs. Therefore, our study aimed to comprehensively compare the clinical profiles of GLP-1RAs. We conducted the most extensive network meta-analysis to date, evaluating not only the efficacy and safety of different GLP-1RAs but also comparing them directly with traditional antidiabetic drugs.

Materials and methods

The network meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA)[9,10], and it was performed prospectively registered in the PROSPERO (CRD42024595773).

Literature search

We performed a systematic literature search using PubMed, Cochrane, Embase, Web of Science, Chinese database China National Knowledge Internet (CNKI) WangFang database and China Science and Technology Journal Database (VIP) up to October 2024. The primary screening direction was an RCT of GLP-1 RAs in the treatment of T2DM. The included GLP-1 RAs were once-weekly exenatide, twice-daily exenatide, semaglutide, dulaglutide, liraglutide, albiglutide, tirzepatide and lixisenatide. We searched the databases using the following terms: "Glucagon-Like Peptide-1 Receptor Agonists", "Exenatide", "Semaglutide", "Dulaglutide", "Liraglutide", "Albiglutide", "Tirzepatide", "Lixisenatide", "Diabetes mellitus, type 2" and "Randomized Controlled Trials". The detail search strategy is presented in **Additional file 1**. In addition, the reference lists of all eligible studies were manually reviewed. Two investigators searched and evaluated the included studies independently. Any disagreement in literature search was resolved by consensus.

Criteria for inclusion

Studies were included if they met the following criteria: (1) The study design was randomized controlled trail (RCT); (2) Studies were conducted in adults with T2DM (≥ 18 years old); (3) Studies comparing GLP-1 RAs with traditional antidiabetic drugs or placebo; (4) At least one outcomes indicator required by this study was reported; (5) The intervention time being at least 2 months. (6) English or Chinese studies; (7) Sufficient data to calculate relative ratio (RR) or odds ratio (OR) or mean difference (MD). Two investigators searched and evaluated the included studies independently. Any disagreement in literature search was resolved by consensus.

Exclusion criteria

Studies were excluded if they were: (1) letters, replies, comments, opinions, conference abstracts, awarded grants, trail registry records and erratum. (2) reviews, meta-analysis, case reports, adolescent articles, pediatric articles,

animal articles, economic articles and non-randomized controlled trail articles. (3) unpublished articles, non-English articles and non-Chinese articles. (4) the required data cannot be obtained, or the existing data cannot be converted into the desired format required for network meta-analysis.

Data extraction

Data extraction was performed by two investigators independently. Any disagreement was resolved by another investigator to make the final decision. We extracted the following data from included studies: first author, publication year, country of study, duration of study, study design, intervention strategies, diabetes duration, sample size, age, gender, HbA1-c, FPG and BMI in baseline. We collected data on arm-specific number of participants, mean difference and standard error (SE) or standard deviation (SD) for continuous data (HbA1-c, FPG, body weight, BMI, systolic and diastolic blood pressure, total cholesterol, low- and high-density lipoprotein cholesterol). We also collected dichotomous data on the total number of participants and participants with safety outcomes (nausea, diarrhoea, vomiting, dyspepsia, constipation, decreased appetite, nasopharyngitis, headache, lipase increased and hypoglycemia). When continuous variables in the study were reported as median with interquartile range, we calculated the mean ± standard deviation (M ± SD) through the validated mathematical method[11,12]. When data were missing or not reported in the study, we contacted the corresponding authors to obtain the completed data if available.

This study includes other traditional antidiabetic drugs in addition to GLP-1 RAs. In addition to the network and forest plots for HbA1-c and FPG, we have combined these drugs into a single category termed "traditional drugs" for further analysis. The reasons are as follows: (1) To more comprehensively reflect the overall effects and characteristics of traditional antidiabetic drugs. (2) To increase the sample size and enhance the reliability of statistical analysis. (3) To simplify the analysis process and avoid the complexity caused by too many types of drugs. (4) To better compare with GLP-1 RAs.

Quality assessment

The Cochrane collaborative risk assessment tool was used to assess the risk of bias for included studies[13]. The following aspects were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. Two investigators evaluated the quality of eligible studies independently, and discrepancies were resolved through discussion.

Statistical analysis

Statistical analyses of this NMA were performed with Review Manager 5.4 (Cochrane Collaboration, Oxford, UK), Stata 14.0 (StataCorp LP, College Station, Texas) package "net meta" and R. Mean difference (MD) was used to compare continuous variables and Risk ratio (RR) was used to compare dichotomous variables. The heterogeneity in studies was assessed through the Chi-squared (χ^2) test (Cochran's Q) and inconsistency index (I^2)[14]. χ^2 p value<0.05 or I^2 >50% was considered as significant heterogeneity. χ^2 p value<0.05 or I^2 >50% was considered as significant heterogeneity and a random-effect model was used to estimate the combined MD or RR. Otherwise, the fixed-effect model was applied (p value>0.05 or I^2 <50%). 95% confidence intervals (CIs) were used to determine the clinical effect of the included studies.

We performed a frequency NMA by using Stata software and R software to analyze indirect comparison between the difference interventions. For each outcome, we graphically summarised the evidence by using a network diagram[15]. We assessed consistency between direct and indirect evidence by using the "design by treatment" interaction model[16]. Deviance information criterion (DIC) statistics calculated from the random effects model was compared to the "design by treatment" model, with smaller DIC values indicating better fit. If the "design by treatment" model could not be fitted, the pairwise meta-analysis was used to compare the results from the NMA. Results were defined as consistent if NMA effect estimates fell within the 95% confidence intervals estimated from the pairwise meta-analysis.

The probability of one intervention being the most effective and safest was estimated by using the surface under the cumulative ranking curve (SUCRA). The node-splitting method and Bayes P value was used to confirm the inconsistencies of the results, and the league tables were used to express the effect values and 95CIs of pair-to-pair comparisons between the interventions. Meanwhile, as NMA included multiple closed loops, the inconsistency tests of direct and indirect evidence were carried out using the loop-specific approach. "Comparison-adjusted" funnel plots and Egger's regression tests (only for outcomes with ten or more studies) were used to assess publication bias or other small study effects for all available comparisons[15]. p value<0.05 was considered as statistically significant publication bias.

Results

Literature search and study characteristics

The flowchart of the systematic search and selection process was presented in Fig. 1. A total of 12,074 relevant articles in PubMed (n = 1,596), Embase (n = 3,496), Cochrane (n = 4,639), Web of Science (n = 2,265) and Chinese database (78) were yielded through systematic literature search. After removing duplicate articles, 8,523 titles and abstracts were reviewed. Finally, 64 full-text articles involving 25,572 patients were included for the NMA. Figure 2 showed the risk assessment using the Cochrane Collaboration risk assessment tool. The overall risk was moderate to low, which was mainly caused by performance bias and other bias.

Table 1 showed the characteristics of each included study. A total of 64 eligible articles involving 25,572 patients were included for the evidence synthesis[17–80].

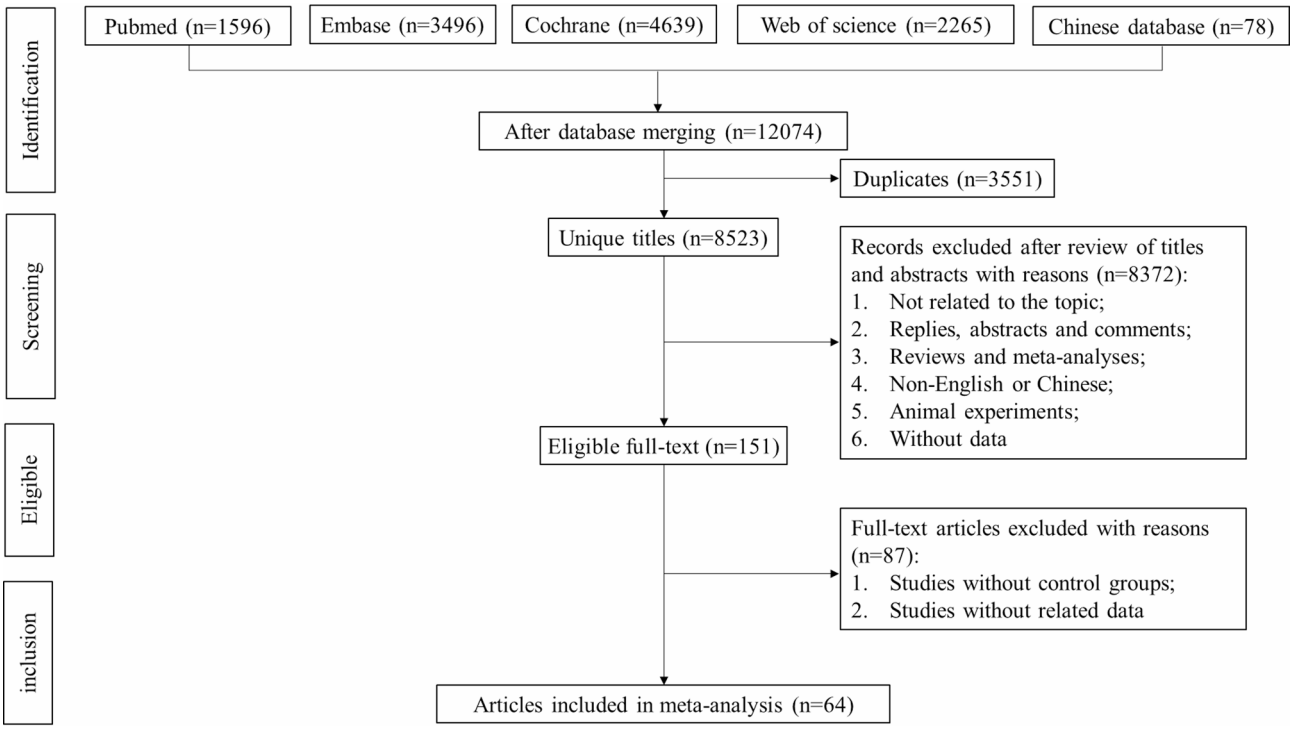


Fig. 1. Flowchart of the systematic search and selection process.

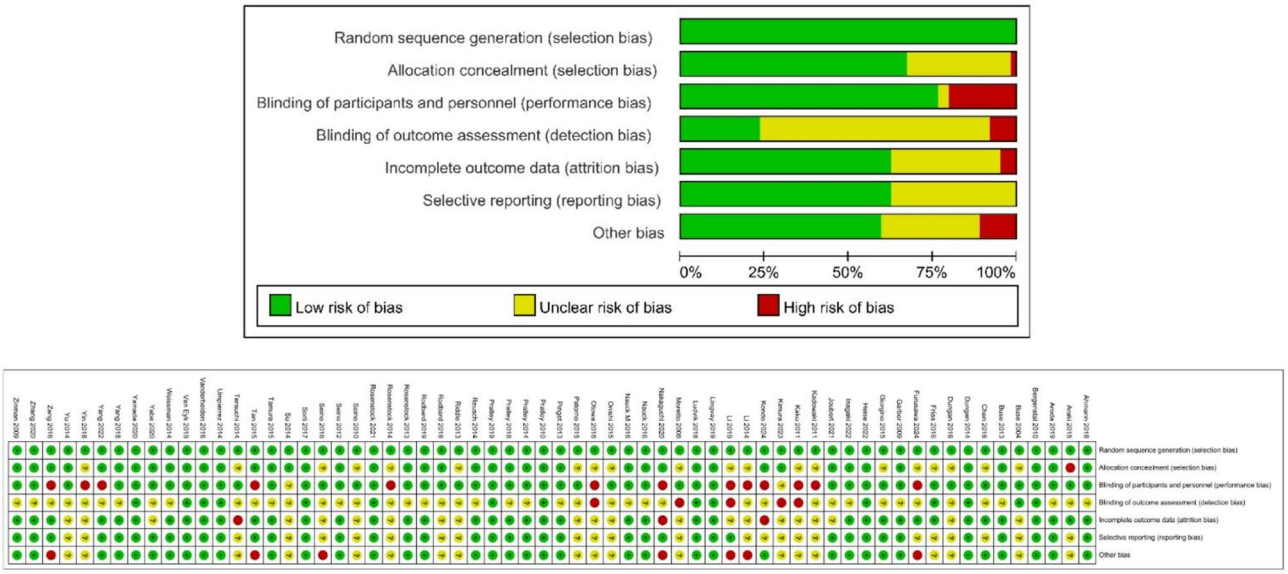


Fig. 2. The distribution for each risk of bias item and risk of bias items for each study.

Primary outcomes

Outcome 1: HbA1-c

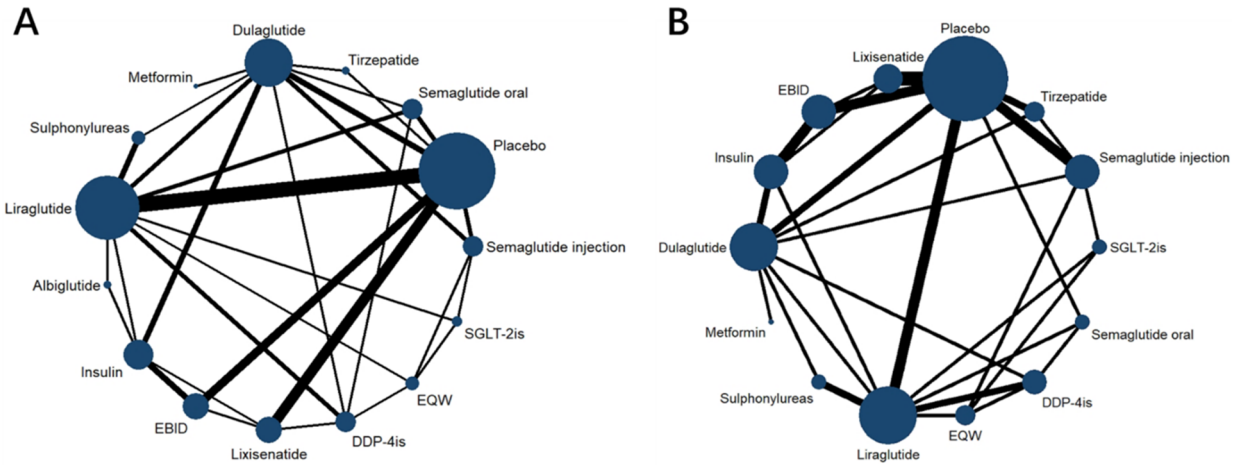
Analysis of primary outcome HbA1-c was conducted in 53 trails with 21,486 patients and the network plot was shown in Fig. 3A. NMA results of GLP-1 RAs compared to placebo were shown in Fig. 4A and all treatments reduced the level of HbA1-c from baseline compared to placebo. Tirzepatide showed the greatest reduction in HbA1-c (MD: −2.3%, 95% CI: −2.7, −1.9) in comparison to placebo. The reduction in HbA1-c of semaglutide was second (MD: −1.5%, 95%CI: −1.7, −1.3) and liraglutide (MD: −1.2%, 95% CI: −1.3, −1.0) was third while lixisenatide (MD: −0.56%, 95%CI: −0.75, −0.37) was last.

Compared to insulin, sulfonylureas, DDP-4 inhibitors and SGLT-2 inhibitors, tirzepatide, semaglutide oral, semaglutide injection, liraglutide, and dulaglutide showed statistically significant reduction in HbA1-c from

Study	Year	Country	Background therapy	Study duration	Intervention and GLP-1 RAs doses (Arm1/2/3)	T2DM duration (years)	*N*	Male	Age (years)	FPG (mmol/L)	HbA1-c (%)	BMI
Ahmann	2018	UK	OADs	56w	Sem 1 mg/EQW 2 mg	9.2	809	447	56.6	——	8.3	33.8
Araki	2015	Japan	Sul/BG	26w	Dul 0.75 mg/Ins	8.9	361	258	56.8	8.7	8.1	26.0
Aroda	2019	USA	Diet	26w	Sem 14 mg/Pla	3.4	353	175	54.0	8.9	7.9	31.9
Bergenstal	2010	USA	Met	26w	EQW 2 mg/Sit	5.7	491	254	52.3	9.1	8.5	32.0
Buse	2004	USA	Sul	30w	EBID 5ug/EBID 10ug/Pla	6.2	377	225	55.3	10.2	8.6	33.3
Buse	2013	USA	OADs ± Diet	26w	EQW 2 mg/Lir 1.8 mg	8.5	911	499	57.0	9.7	8.5	32.3
Chen	2018	China	OADs	26w	Dul 1.5 mg/Dul 0.75 mg/Glim	3.8	720	391	52.9	——	8.0	25.9
Dungan	2014	USA	Met	30w	Dul 1.5 mg/Lir 1.8 mg	7.2	599	287	56.7	9.3	8.1	33.6
Dungan	2016	USA	Glim	24w	Dul 1.5 mg/Pla	7.6	299	132	57.8	9.9	8.4	31.2
Frías	2016	USA	Met	28w	EQW 2 mg/Dap	7.2	457	226	54.5	10.9	9.3	32.5
Furusawa	2024	Japan	DPP-4 is	24w	Sem 14 mg/DDP-4i	——	157	98	62.9	——	7.6	26.2
Garber	2009	USA	OADs ± Diet	52w	Lir 1.2 mg/Lir 1.8 mg/Glim	5.3	746	371	53.1	9.4	8.3	33.1
Giorgino	2015	Italy	Met + Gli	52w	Dul 1.5 mg/Dul 0.75 mg/Ins	9.0	807	414	56.7	9.1	8.2	31.7
Heise	2022	Germany	Met + lifestyle	28w	Tir 15 mg/Sem 1 mg/Pla	10.4	117	86	61.9	7.3	7.8	31.4
Inagaki	2022	Japan	OADs	52w	Tir 15 mg/Dul 0.75 mg	5.1	319	249	56.7	8.9	8.2	28.0
Joubert	2021	Ftance	Ins	26w	EBID 10ug/Pla	18.9	46	20	59.8	——	8.8	35.3
Kadowaki	2011	Japan	Sul/BG	24w	EBID 5ug/EBID 10ug/Pla	12.0	179	122	58.5	9.1	8.3	25.5
Kaku	2011	Japan	OADs	52w	Lir 0.9 mg/Glib	8.2	400	269	58.3	——	9.3	24.8
Kimura	2023	Japan	GLP-1RAs	24w	Dul 0.75 mg/Sem 1 mg	13.9	107	59	62.7	——	8.0	29.3
Kondo	2024	Japan	Met	24w	Dul 0.75 mg/Tre	10.2	48	25	65.6	7.0	6.9	25.4
Li	2014	China	OADs	24w	Lir 1.2 mg/Sax/Vil	5.5	178	109	47.1	8.9	8.5	26.3
Li	2019	China	Sul ± Met	52w	Dul 1.5 mg/Dul 0.75 mg/Ins	7.9	591	360	54.5	9.7	8.4	26.0
Lingvay	2019	USA	Met	52w	Sem 1 mg/Can	7.4	788	424	56.6	9.4	8.3	32.4
Ludvik	2018	Austria	Met ± Diet	26w	Dul 1.5 mg/Dul 0.75 mg/Pla	9.4	423	212	57.3	8.8	8.0	32.7
Moretto	2008	USA	Diet	24w	EBID 5ug/EBID 10ug/Pla	1.7	232	169	54.0	8.9	7.8	31.3
Nakaguchi	2020	Japan	Ins	24w	Lir 0.9 mg/Emp	18.9	61	42	66.7	9.1	8.1	26.1
Nauck	2016	Germany	Met	26w	Lir 1.8 mg/Lix 20ug	6.4	404	120	56.2	10.4	8.4	34.7
Nauck	2016	Germany	Diet	52w	Alb 50 mg/Alb 30 mg/Pla	4.0	301	166	53.0	——	8.1	33.5
Onishi	2015	Japan	Sul ± Met	24w	Lix 20ug/Pla	12.2	127	83	59.3	9.2	8.5	25.4
Otowa	2018	Japan	Sit	12w	Lix 20ug/Vil	16.4	38	22	63.1	7.2	7.8	25.5
Patorno	2015	Japan	Ins ± Sul	24w	Lix 20ug/Pla	12.4	159	105	58.0	8.0	8.5	25.0
Pinget	2013	France	Pio ± Met	24w	Lix 20ug/Pla	8.1	484	104	55.8	9.1	8.1	33.9
Pratley	2019	USA	Met ± SGLT2 is	52w	Sem 14 mg/Lir 1.8 mg/Pla	7.6	711	370	56.2	9.3	8.0	32.9
Pratley	2018	USA	Met	40w	Sem 1 mg/Dul 1.5 mg	7.4	599	333	55.5	9.7	8.2	33.4
Pratley	2010	USA	Met	26w	Lir 1.8 mg/Sit	6.4	440	236	55.0	9.9	8.4	32.9
Pratley	2014	USA	OADs	32w	Alb 50 mg/Lir 1.8 mg	8.3	812	409	55.6	——	8.2	32.8
Reusch	2014	USA	Pio ± Met	52w	Alb 30 mg/Pla	7.9	301	180	55.0	9.3	8.1	34.2
Riddle	2013	USA	Ins ± Met	24w	Lix 20ug/Pla	12.5	495	228	57.0	——	8.4	32.1
Rodbard	2018	USA	Ins ± Met	30w	Sem 0.5 mg/Sem 1 mg/Pla	13.3	396	222	58.8	8.7	8.4	32.2
Rodbard	2019	USA	Met	52w	Sem 14 mg/Emp	7.4	821	415	57.5	9.6	8.1	32.9
Rosenstock	2014	USA	Sul ± Met	24w	Lix 20ug/Pla	9.3	859	434	57.3	9.6	8.3	30.2
Continued												

Study	Year	Country	Background therapy	Study duration	Intervention and GLP-1 RAs doses (Arm1/2/3)	T2DM duration (years)	*N*	Male	Age (years)	FPG (mmol/L)	HbA1-c (%)	BMI
Rosenstock	2013	USA	Met	24w	Lix 20ug/EBID 10ug	6.8	634	338	57.4	9.7	8.0	33.6
Rosenstock	2021	USA	Diet	40w	Tir 10 mg/Tir 15 mg/Pla	4.8	357	191	54.1	8.5	8.0	31.0
Seino	2016	Japan	Ins	36w	Lir 0.9 mg/Pla	14.5	257	144	60.5	8.7	8.8	25.7
Seino	2012	Japan	Ins ± Sul	24w	Lix 20ug/Pla	13.9	311	149	58.3	7.6	8.5	25.3
Seino	2010	Japan	OADs ± Diet	24w	Lir 0.9 mg/Glib	8.2	400	133	58.3	11.3	8.9	24.5
Sorli	2017	USA	Diet	30w	Sem 0.5 mg/Sem 1 mg/Pla	4.2	387	210	53.7	——	8.1	33.0
Su	2014	China	Met	52w	EBID 10ug/Ins	0.6	60	——	46.0	9.0	8.2	38.4
Tamura	2015	Japan	Diet	26w	Dul 0.75/Lir 0.9 mg/Pla	6.6	487	396	57.4	9.3	8.2	25.5
Tan	2015	USA	Sul ± Met	24w	Lir 1.8 mg/Ins	8.5	944	513	57.2	9.8	9.0	31.9
Terauchi	2014	Japan	OADs ± Diet	12w	Dul 0.75 mg/Pla	4.7	72	57	51.9	8.9	8.0	27.3
Umpierrez	2014	USA	Diet	26w	Dul 1.5 mg/Dul 0.75 mg/Met	3.0	807	353	55.7	9.0	7.6	33.3
Van Eyk	2019	Netherlands	Standard care	26w	Lir 1.8 mg/Pla	17.0	47	19	55.0	——	8.4	29.4
Vanderheiden	2016	USA	Ins	26w	Lir 1.8 mg/Pla	17.0	71	38	54.1±	11.9	8.9	41.2
Weissman	2014	USA	Sul ± Met	52w	Alb 30 mg/Ins	8.7	745	418	55.4	9.5	8.3	33.1
Yabe	2020	Japan	OADs	52w	Sem 14 mg/Dul 0.75 mg	9.4	195	118	58.3	9.4	8.4	26.2
Yamada	2020	Japan	Diet ± OADs	52w	Sem 14 mg/Lir 0.9 mg/Pla	7.7	145	119	59.7	9.2	8.2	25.6
Yang	2022	China	Met ± OADs	24w	Lix 20ug/Ins	8.9	527	282	56.4	9.9	8.3	26.0
Yang	2018	China	Ins ± Met	24w	Lix 20ug/Pla	10.3	448	203	55.1	7.0	7.9	27.7
Yin	2018	China	Met	16w	EBID 10ug/Ins	5.4	39	22	48.1	8.8	8.2	27.5
Yu	2014	China	Sul ± Met	24w	Lix 20ug/Pla	6.6	390	192	54.8	8.8	8.0	26.9
Zang	2016	China	Met	26w	Lir 1.8 mg/Sit	5.2	367	219	51.5	9.4	8.1	27.2
Zhang	2020	China	OADs	52w	EBID 10ug/Ins	7.3	59	33	58.4	10.4	8.5	24.0
Zinman	2009	Canada	OADs	26w	Lir 1.2 mg/Lir 1.8 mg/Pla	9.0	300	170	55.0	10.1	8.5	33.6

Table 1. Baseline characteristics of include studies. Baseline characteristics of trials are reported as mean.



A: Network for HbA1-c (%); B: Network for FPG (mmol/L).
Lines represent direct comparisons between treatments; line thickness is weighted so that a thicker line represents a higher number of direct comparisons.
Dots represent relevant studies; dots size is weighted so that a larger dot represents a larger number of studies.
DDP-4 is: DPP-4 inhibitors; EBID: Twice-daily exenatide; EQW: Once-weekly exenatide; SGLT2 is: SGLT2 inhibitors

Fig. 3. Network plot for primary outcomes.

baseline, while lixisenatide, EBID, EQW and albiglutide showed no statistically significant difference. Compared with metformin, only tirzepatide showed statistically significant reduction in HbA1-c from baseline (Fig. 4B-F). Since the analysis showed that semaglutide oral and semaglutide injection were almost identical, they would be combined into semaglutide to increase the sample size and enhance the reliability of the statistical analysis for further analysis.

Subsequently, insulin, metformin, sulfonylureas, DDP-4 inhibitors and SGLT-2 inhibitors were merged into a single category termed "traditional antidiabetic drugs" and semaglutide oral and semaglutide injection were combined into "semaglutide" for further analysis. NMA results of GLP-1 RAs compared to placebo were shown in Fig. 6A and all treatments reduced the level of HbA1-c from baseline compared to placebo. Compared to traditional antidiabetic drugs, tirzepatide (MD: −1.5%, 95%CI: −1.9, −1.1), semaglutide (MD: −0.73%, 95%CI: −0.91, −0.55), liraglutide (MD: −0.4%, 95%CI: −0.54, −0.26), EQW (MD: −0.36%, 95%CI: −0.6, −0.12) and dulaglutide (MD: −0.34%, 95%CI: −0.49, −0.2) showed statistically significant reduction in HbA1-c from baseline, while EBID and albiglutide showed no statistically significant difference. Lixisenatide (MD: 0.23%, 95%CI: 0.002, 0.45) had statistically significant increase in HbA1-c in comparison to other hypoglycemic agents (Fig. 6B).

Tirzepatide (100%) also showed the greatest probability of being the most effective treatment in the reduction of HbA1-c, followed by semaglutide in second (88.9%) and liraglutide (70.6%) in third while lixisenatide (11.9%) was last, as shown in S1 Figure A.

The results of pair-to-pair comparisons between the treatments in reduction of HbA1-c were shown in Table 2. Compared to all the other treatments, tirzepatide had statistically significant reduction in HbA1-c. Semaglutide also had statistically significant reduction in HbA1-c compared to other treatments while liraglutide had statistically significant reduction compared to EBID, lixisenatide and traditional antidiabetic drugs. Heterogeneity test was shown in S1 Table; funnel plot of publication bias was shown in S2 Fig A and the egger's test values for comparisons of each drug with the placebo and with the traditional antidiabetic drugs were both 0.22, indicating no publication bias.

Outcome 2: FPG

Analysis of primary outcome FPG was conducted in 41 trails with 17,621 patients and the network plot was shown in Fig. 3B. NMA results of treatment compared to placebo were shown in Fig. 5A and except for lixisenatide, all treatments reduced the level of FPG from baseline compared to placebo. Tirzepatide showed the greatest reduction in FPG (MD: −3.1mmol/L, 95% CI: −3.8, −2.4) in comparison to placebo and other treatments in the network. The reduction in FPG of semaglutide was second (MD: −2mmol/L, 95%CI: −2.5, −1.5) and liraglutide (MD: −1.6mmol/L, 95% CI: −2.1, −1.0) was third.

Compared to insulin, metformin sulfonylureas, DDP-4 inhibitors and SGLT-2 inhibitors, only tirzepatide showed statistically significant reduction in FPG from baseline. Semaglutide injection showed statistically significant reduction in FPG from baseline compared to sulfonylureas and DDP-4 inhibitors. Liraglutide and dulaglutide showed statistically significant reduction in FPG from baseline compared with DDP-4 inhibitors,

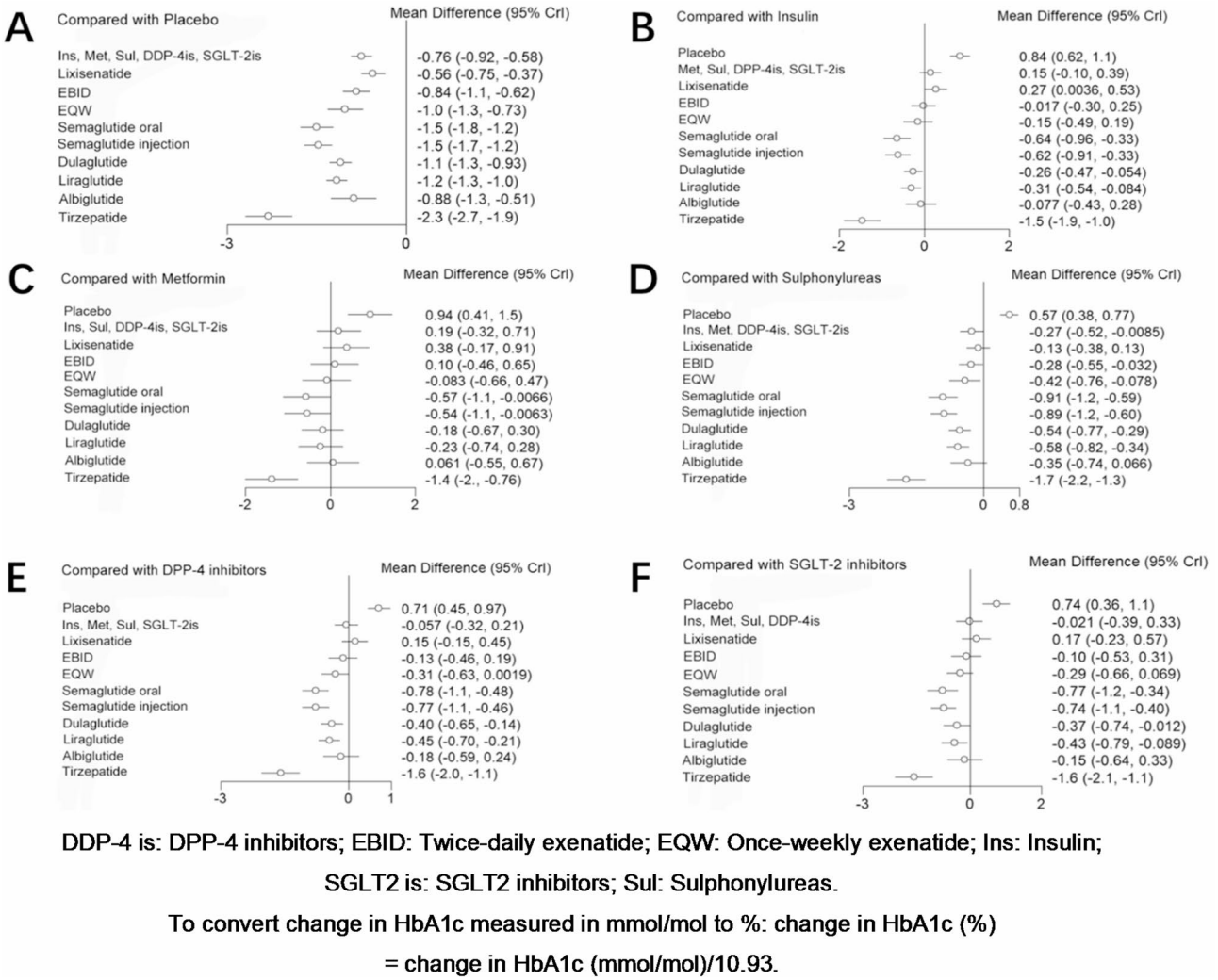


Fig. 4. NMA results for the mean difference in HbA1c (%) in comparison to placebo and traditional antidiabetic drugs.

while EBID, EQW and lixisenatide showed no statistically significant difference compared to traditional antidiabetic drugs (Fig. 5B-F).

Subsequently, insulin, metformin, sulfonylureas, DDP-4 inhibitors and SGLT-2 inhibitors were merged into a single category termed "traditional antidiabetic drugs" and semaglutide oral and semaglutide injection were combined into "semaglutide" for further analysis. NMA results of treatment compared to placebo were shown in Fig. 6C and except for lixisenatide, all treatments reduced the level of FPG from baseline compared to placebo. Compared to traditional antidiabetic drugs, tirzepatide (MD: −1.8mmol/L, 95%CI: −2.6, −1.0), semaglutide (MD: −0.69mmol/L, 95%CI: −1.2, −0.19) showed statistically significant reduction in FPG from baseline, while lixisenatide (MD: 0.96mmol/L, 95%CI: 0.31, 1.6) had statistically significant increase in FPG from baseline. EQW, EBID, dulaglutide and liraglutide had no statistically significant difference in FPG in comparison to other hypoglycemic agents (Fig. 6D).

Tirzepatide (100%) showed the greatest probability of being the most effective treatment in the reduction of FPG, followed by semaglutide in second (85.4%) and liraglutide (66%) in third while lixisenatide (11.7%) was last (S1 FigB).

The results of pair-to-pair comparisons between the treatments in reduction of FPG were shown in Table 2. Compared to all the other treatments, tirzepatide had statistically significant reduction in FPG. Semaglutide and liraglutide had statistically significant reduction in FPG compared to EBID and lixisenatide and semaglutide also had statistically significant reduction in FPG compared to traditional antidiabetic drugs. Heterogeneity test was shown in S2 Table and funnel plot of publication bias was shown in S2 FigB. The egger's test values for comparisons of each drug with the placebo was 0.83 and with the traditional antidiabetic drugs was 0.28, indicating no publication bias.

According to the primary outcomes HbA1-c and FPG, tirzepatide was the most effective treatment for T2DM, followed by semaglutide in second, liraglutide in third.

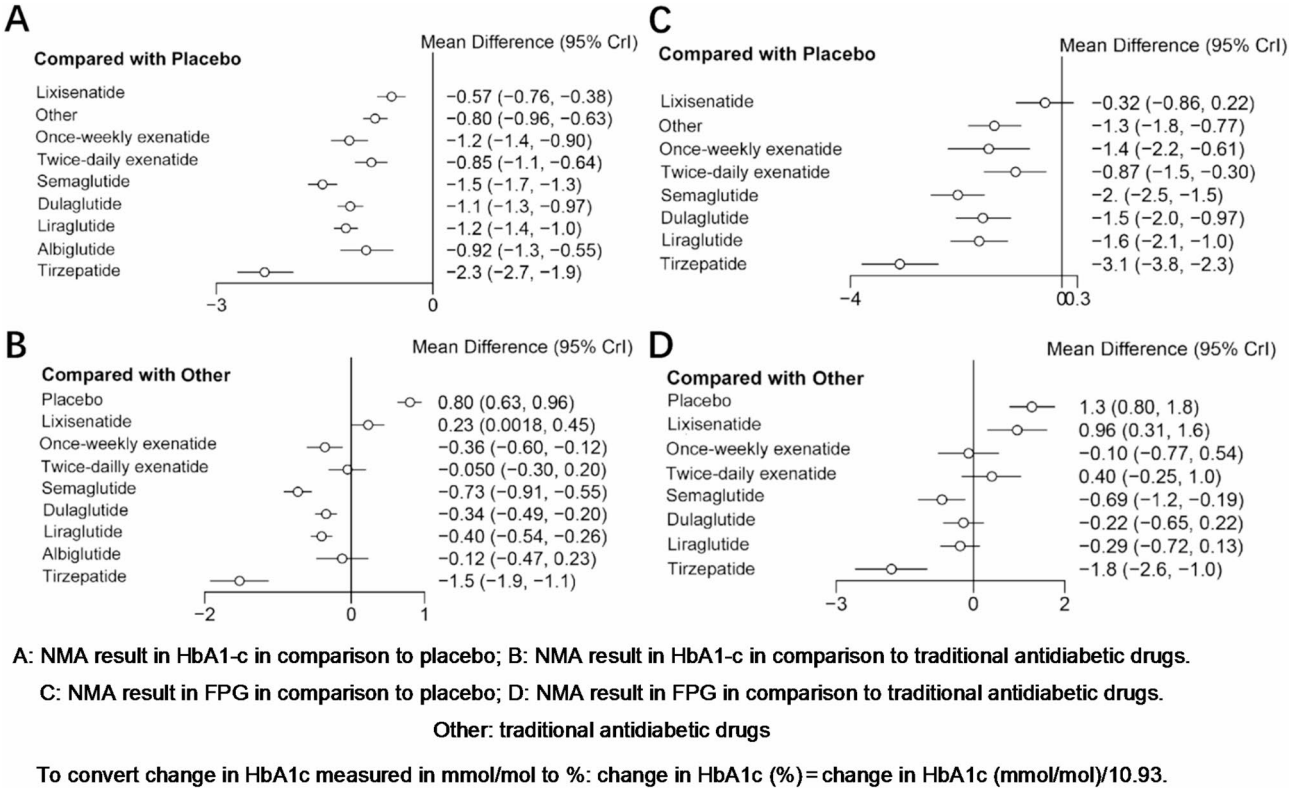


Fig. 6. NMA results for the mean difference in primary outcomes in comparison to placebo and traditional antidiabetic drugs.

FPG (mmol/L)									
Tir	−1.10 (−1.83, −0.37)	−1.50 (−2.28, −0.73)	−1.58 (−2.29, −0.86)	−1.69 (−2.61, −0.77)		−2.19 (−3.04, −1.34)	−1.79 (−2.53, −1.06)	−2.75 (−3.58, −1.92)	−3.07 (−3.75, −2.39)
−0.80 (−1.19, −0.40)	**Sem**	−0.41 (−0.95, 0.14)	−0.48 (−1.01, 0.05)	−0.59 (−1.28, 0.10)		−1.09 (−1.77, −0.41)	−0.70 (−1.19, −0.21)	−1.65 (−2.32, −0.99)	−1.97 (−2.45, −1.49)
−1.12 (−1.50, −0.74)	−0.32 (−0.51, −0.13)	**Lir**	−0.07 (−0.58, 0.44)	−0.18 (−0.85, 0.48)		−0.68 (−1.37, −0.00)	−0.29 (−0.69, 0.12)	−1.25 (−1.92, −0.58)	−1.57 (−2.08, −1.05)
−1.18 (−1.55, −0.81)	−0.38 (−0.57, −0.20)	−0.06 (−0.22, 0.10)	**Dul**	−0.11 (−0.83, 0.61)		−0.61 (−1.29, 0.06)	−0.22 (−0.63, 0.20)	−1.17 (−1.83, −0.51)	−1.49 (−1.99, −1.00)
−1.17 (−1.59, −0.74)	−0.37 (−0.62, −0.12)	−0.05 (−0.28, 0.19)	0.01 (−0.24, 0.26)	**EQW**		−0.50 (−1.35, 0.34)	−0.11 (−0.73, 0.52)	−1.06 (−1.90, −0.23)	−1.38 (−2.11, −0.66)
−1.40 (−1.90, −0.91)	−0.60 (−0.97, −0.24)	−0.28 (−0.61, 0.05)	−0.22 (−0.57, 0.13)	−0.23 (−0.62, 0.16)	**Alb**				
−1.47 (−1.89, −1.05)	−0.68 (−0.95, −0.40)	−0.35 (−0.60, −0.10)	−0.29 (−0.55, −0.04)	−0.31 (−0.62, 0.00)	−0.07 (−0.47, 0.33)	**EBID**	−0.40 (−1.01, 0.22)	−0.56 (−1.22, 0.10)	−0.88 (−1.44, −0.33)
−1.52 (−1.90, −1.15)	−0.73 (−0.91, −0.55)	−0.40 (−0.54, −0.27)	−0.34 (−0.48, −0.20)	−0.36 (−0.59, −0.13)	−0.12 (−0.45, 0.21)	−0.05 (−0.29, 0.19)	**Oth**	−0.96 (−1.57, −0.35)	−1.28 (−1.75, −0.81)
−1.76 (−2.16, −1.35)	−0.96 (−1.21, −0.71)	−0.63 (−0.86, −0.41)	−0.57 (−0.81, −0.34)	−0.59 (−0.88, −0.30)	−0.35 (−0.74, 0.03)	−0.28 (−0.53, −0.03)	−0.23 (−0.45, −0.01)	**Lix**	−0.32 (−0.83, 0.19)
−2.33 (−2.69, −1.96)	−1.53 (−1.72, −1.34)	−1.20 (−1.36, −1.05)	−1.14 (−1.31, −0.97)	−1.16 (−1.40, −0.92)	−0.92 (−1.28, −0.57)	−0.85 (−1.06, −0.64)	−0.80 (−0.96, −0.64)	−0.57 (−0.75, −0.39)	**Pla**
HbA1-c (%)									

Table 2. League table comparing the effects of treatments for primary outcomes. The top half of the table represents pair-to-pair comparisons for FPG (mmol/L); the bottom half represents pair-to-pair comparisons for HbA1-c (%). Alb: Albiglutide; Dul: Dulaglutide; EBID: Twice-daily exenatide; EQW: Once-weekly exenatide; Lir: Liraglutide; Lix: Lixisenatide; Sem: Semaglutide; Tir: Tirzepatide; Pla: Placebo; Oth: Traditional antidiabetic drugs (insulin, metformin, sulfonylureas, DDP-4 is and SGLT-2 is).

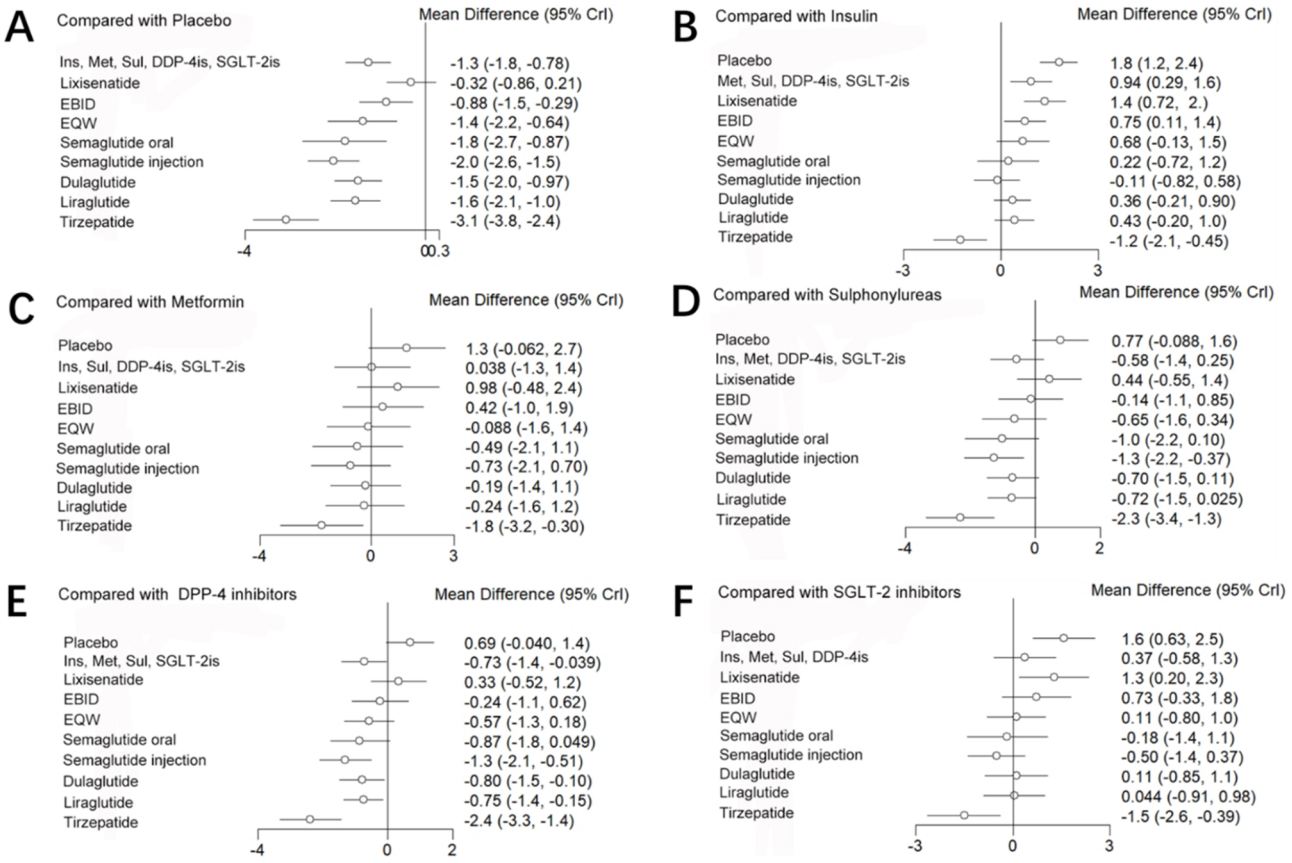


Fig. 5. NMA results for the mean difference in FPG (mmol/L) in comparison to placebo and traditional antidiabetic drugs.

Secondary outcomes

Changes from baseline in body weight, BMI, SBP, DBP, TC, HDL-C and LDL-C were analyzed and network plots for these secondary outcomes were presented in S3 and S4 Figs. Treatment ranking had been reported in S5 and S6 Figs and the top three treatments ranking was as follows: Body weight: tirzepatide > semaglutide > EBID; BMI: EBID > semaglutide > liraglutide; SBP: EBID > lixisenatide > liraglutide; TC: semaglutide > EBID > liraglutide; HDL-C: dulaglutide > semaglutide > lixisenatide; LDL-C: semaglutide > liraglutide > EBID.

NMA results of treatments compared to placebo were reported in S7 Fig. Compared to placebo, all treatments showed no statistically significant differences in BMI, SBP, DBP, TC, HDL-C and LDL-C. Tirzepatide (MD: −9.1 kg, 95% CI: −11, −7.4) > semaglutide (MD: −2.8 kg, 95% CI: −3.9, −1.8) > EBID (MD: −1.8 kg, 95% CI: −3, −0.64) > liraglutide (MD: −1.2 kg, 95% CI: −2.2, −0.12) had significant reduction in body weight in comparison to placebo.

Compared to traditional antidiabetic drugs, GLP-1 RAs showed no statistically significant differences in BMI, SBP, DBP, TC, HDL-C and LDL-C. Tirzepatide (MD: −10 kg, 95%CI: −12, −8.2), semaglutide (MD: −3.8 kg, 95%CI: −4.9, −2.7), EBID (MD: −2.8 kg, 95%CI: −4.2, −1.4), liraglutide (MD: −2.1 kg, 95%CI: −3.2, −1.1), lixisenatide (MD: −2.0 kg, 95%CI: −3.3, −0.75) and dulaglutide (MD: −1.2 kg, 95%CI: −2.1, −0.25) showed statistically significant reduction in weight from baseline in comparison to traditional antidiabetic drugs (S8 Fig).

The results of pair-to-pair comparisons between the treatments were shown in S3-S6 Tables. Compared to all treatments, tirzepatide had statistically significant reduction in body weight. Semaglutide also had statistically significant reduction in body weight compared to other GLP-1RAs and traditional antidiabetic drugs. No differences were found comparing treatments with each other in BMI, SBP, DBP, TC, HDL-C and LDL-C. Heterogeneity test was shown in S7-S9 Tables and funnel plots of publication bias were shown in S2 Fig C-F.

Adverse events

Nausea, diarrhoea, vomiting, constipation, dyspepsia, decreased appetite, nasopharyngitis, headache, lipase increased and hypoglycemia were analyzed and network plots of adverse events outcomes were presented in S9 and S10 Figs. Treatment ranking had been reported in S11 and S12 Figs.

Compared to placebo, all treatments showed no statistically significant differences in nasopharyngitis, headache and lipase increased. Semaglutide, dulaglutide, liraglutide, lixisenatide and tirzepatide had higher risk of nausea, diarrhoea, vomiting, constipation, dyspepsia and decreased appetite in the comparison to placebo. EBID (RR: 3.3, 95%CI: 1.6, 6.9) and semaglutide (RR: 4.6, 95%CI: 1.6, 10.0) significantly increased the risk of hypoglycemia while the other GLP-1 RAs showed no statistically significant difference in hypoglycemia compared to placebo (S13 and S14 Figs).

Compared to traditional antidiabetic drugs, GLP-1 RAs showed no statistically significant differences in nasopharyngitis, headache, lipase increased and dyspepsia while showed higher risk of nausea and vomiting. Semaglutide, dulaglutide, liraglutide and tirzepatide had risk of diarrhoea, constipation, and decreased appetite in the comparison to traditional antidiabetic drugs. For hypoglycemia, liraglutide and lixisenatide significantly reduced the risk of hypoglycemia compared to traditional antidiabetic drugs (S15 and S16 Figs).

The results of pair-to-pair comparisons between the treatments were shown in S10-S13 Tables and almost no differences were found comparing GLP-1 RAs with each other for adverse events. Heterogeneity test was shown in S14-S22 Tables and funnel plots of publication bias were shown in S17 Fig.

Inconsistency test

Assessment of inconsistency between direct and indirect comparisons using a node-splitting model showed that there were no inconsistencies among most studies ($P > 0.05$) (S23-S34 Tables). The results of loop inconsistency test were shown in S35-S40 Tables. The results showed no significant inconsistencies between GLP-1 RAs.

Discussion

GLP-1RAs represent a category of medications used for treating hyperglycaemia in individuals with T2DM. GLP-1 RAs are now classified by duration of action into long-acting (EQW, albiglutide, semaglutide, dulaglutide, liraglutide and tirzepatide) and short-acting (EBID and lixisenatide)[8]. In RCTs, it has been demonstrated that GLP-1RAs enhance glycaemic management and promote weight reduction more effectively than conventional hypoglycemic agents. However, no studies have comprehensively evaluated both the efficacy and safety of different GLP-1RAs and compared them with traditional antidiabetic drugs. Therefore, by integrating both direct and indirect evidence, we conducted a systematic review and NMA to compare the efficacy and tolerability of different GLP-1RAs and to contrast them with traditional antidiabetic drugs, thereby offering valuable guidance for clinical treatment.

Semaglutide is available in two formulations: injection and oral tablet. Semaglutide injection involves the addition of a fatty acid side chain at the 26th position of the natural GLP-1 peptide chain, which can inhibit the degradation by DPP-4, thereby extending the half-life of semaglutide injection to one week[81]. Semaglutide oral tablet is based on the original peptide chain, with the addition of an absorption enhancer that can increase the local pH in the stomach, thereby inhibiting the degradation of semaglutide by pepsin and improving the oral bioavailability of semaglutide tablets[82]. However, there is no significant difference in efficacy between the two formulations. The oral semaglutide, due to its simplicity and convenience, is more likely to improve patient adherence. Therefore, in this study, the two formulations are collectively referred to as semaglutide for analysis.

In this systematic review and NMA involving 64 studies with a total of 25,572 participants, long-acting GLP-1RAs demonstrated more significant reductions in HbA1-c and FPG compared to short-acting GLP-1 RAs. In particular, tirzepatide, semaglutide and liraglutide treatments showed greater reductions in HbA1-c and FPG levels in comparison to other GLP-1 RAs, traditional antidiabetic drugs as well as placebo. The results are consistent with previous researches which have also indicated long-acting GLP-1RAs had a better hypoglycemic effect than short-acting GLP-1 RAs[8,83].

Previous studies have shown that GLP-1RAs are effective in reducing body weight and blood pressure in comparison to placebo[84,85]. However, our results showed that GLP-1 RAs had no statistically significant differences in BMI, SBP, DBP, TC, HDL-C and LDL-C compared to placebo and traditional antidiabetic drugs. The study by Yao et al. demonstrated that all GLP-1 RAs can significantly improve weight conditions[86], but their research was limited to comparisons only with placebo. Our study indicates that tirzepatide, semaglutide, EBID and liraglutide showed a significant reduction in body weight in comparison to placebo and traditional antidiabetic drugs. However, only tirzepatide and semaglutide had statistically significant reduction in body weight compared to other GLP-1RAs while no difference was found when compared liraglutide to other treatments. Our study not only compared GLP-1 receptor agonists with placebo groups but also with traditional antidiabetic drugs. Therefore, our conclusions differ from those of Yao et al. Tirzepatide is a new molecule capable of controlling blood glucose levels by combining the dual agonism of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors[87] and it was approved by FDA in May 2022. Recent studies have shown that compared with selective GLP-1 RAs, GIP and GLP-1 receptor combined agonists have more significant effects in controlling blood glucose and body weight[88]. This NMA results indicate when there is no particular need to lose weight, liraglutide can be chosen for treatment. And we speculated that liraglutide's weight-neutral profile might be particularly advantageous for older adults with low body weight or sarcopenia. If the treatment is for T2DM accompanied by obesity, tirzepatide and semaglutide might be the best chosen.

T2DM patients with poor blood glucose control or long duration of T2DM often have impaired gastric motility and delayed gastric emptying will lead to gastrointestinal symptoms[89–94]. Our NMA results showed that semaglutide, dulaglutide, liraglutide, and tirzepatide had higher risk of gastrointestinal symptoms in comparison to placebo and traditional antidiabetic drugs. As regards hypoglycemia, EBID and semaglutide significantly increased the risk of hypoglycemia while the other GLP-1 RAs showed no statistically significant difference in hypoglycemia compared to placebo. Compared to traditional antidiabetic drugs, liraglutide and lixisenatide significantly reduced the risk of hypoglycemia. However, almost no differences were found comparing GLP-1 RAs with each other for adverse events. These findings indicate that when selecting the best personalized

strategy for reducing blood glucose, individuals with good gastrointestinal health may be prioritized for the use of liraglutide in T2DM treatment. Additionally, those who have experienced hypoglycemic reactions while using traditional antidiabetic drugs may be encouraged to consider switching to liraglutide in their subsequent treatment.

Therefore, hypoglycemic effect (HbA1-c and FPG), body weight, hypoglycemia and gastrointestinal symptoms are important factors when choosing GLP-1 RAs. The NMA suggests tirzepatide, semglutide and liraglutide are the three most effective GLP-1 RAs for T2DM. Given that semaglutide may increase the risk of hypoglycemia, tirzepatide appears to be a more suitable option for the treatment of T2DM in patients with obesity. For individuals with normal weight, both semaglutide and liraglutide are generally more effective for treating T2DM compared to other GLP-1 RAs. However, considering the potential for semaglutide to cause hypoglycemia, liraglutide may be the optimal choice for T2DM treatment to minimize the risk of hypoglycemia.

By performing systematic review and NMA of RCTs, it was possible to obtain comparisons among GLP-1 RAs by combining results from a large number of RCTs to synthesise direct and indirect evidence. However, there are still some limitations. First, because of the sparsity of several networks, the inconsistency could not be all assessed using the design-by-treatment models for all efficacy and safety outcomes. Inconsistency is one of the most important assumptions which need to be considered when conducting a NMA[95]. However, most effect estimates from the NMA were within the confidence intervals of pairwise meta-analysis, indicating that the results were mostly consistent. Second, some baseline characteristics, such as included population, duration of study, background therapies and quality of studies are different across included RCTs which are particularly relevant as cardiometabolic effects of GLP-1RAs may differ when these agents are added to insulin, metformin, sulfonylureas, DDP-4 inhibitors and SGLT-2 inhibitors. Third, this review only included published RCTs. Although the risk of publication bias of RCTs should be lower than other study types, it is possible that some conducted RCTs have not been registered or reported. Fourth, this NMA shares the same drawbacks common to other NMAs[96].

Conclusions

In conclusions, GLP-1RAs improve glycaemic control and long-acting GLP-1RAs demonstrated more significant reductions in HbA1-c and FPG compared to short-acting GLP-1 RAs, with tirzepatide, semaglutide and liraglutide exhibiting the most significant improvements. Tirzepatide is more suitable for the treatment of T2DM with obesity. For individuals with normal weight, both semaglutide and liraglutide are generally more effective for treating T2DM compared to other GLP-1 RAs. However, considering the potential for semaglutide to cause hypoglycemia, liraglutide may be the optimal choice for T2DM treatment to minimize the risk of hypoglycemia. The evidence suggested the choice of GLP-1 RAs should be tailored taking into account their differences in efficacy and safety along with the targets and needs of patients.

Data availability

The data supporting the conclusions of this article will be made available by the authors, without undue reservation. And the original contributions presented in the study are included in the articles and supplementary material. If someone wants to request the data from this study, please contact the first author or corresponding author.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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