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Comparative Efficacy of Dual and Triple GLP-1, GIP, and Glucagon Receptor Agonists: A Systematic Review and Network Meta-analysis

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Abstract: Dual and triple agonists targeting GLP-1, GIP, and glucagon receptors have emerged as promising therapies for obesity and type 2 diabetes mellitus (T2DM). Although individual trials have demonstrated substantial metabolic benefits, the comparative efficacy across available multi-receptor agonists remains uncertain. A systematic search of PubMed, Embase, and Scopus was conducted through January 27, 2024, to identify randomized controlled trials evaluating dual or triple incretin- and glucagon-pathway receptor agonists versus placebo in adults with overweight, obesity, or T2DM. Primary outcomes were changes in body weight and HbA1c. Secondary outcomes included fasting plasma glucose, fasting insulin, waist circumference, blood pressure, and lipid parameters. A frequentist random-effects network meta-analysis was performed, and treatment rankings were estimated using surface under the cumulative ranking curve (SUCRA). Heterogeneity was explored with subgroup and meta-regression analyses. Twenty-one trials involving 5568 participants were included. All seven agonists significantly improved weight and glycemic outcomes compared with placebo. Tirzepatide, particularly at 10–15 mg, achieved the greatest reductions in HbA1c, fasting glucose, and waist circumference. Retatrutide 12 mg produced the strongest lipid improvements, including total cholesterol, triglycerides, LDL-C, and VLDL-C. Mazdutide 6 mg achieved the largest decreases in systolic and diastolic blood pressure. Dual and triple receptor agonists confer broad metabolic benefits but differ in their efficacy profiles. Tirzepatide exhibits superior glycemic and weight-lowering effects, Retatrutide offers greater lipid improvements, and Mazdutide provides enhanced blood pressure reduction. These distinctions support individualized therapeutic selection in obesity and T2DM management.

Keywords: Type 2 Diabetes Mellitus; GLP-1 Receptor Agonists; Glucose-dependent Insulinotropic Polypeptide; Glucagon Receptors.

1. Introduction

Obesity and type 2 diabetes mellitus (T2DM) have risen to become leading causes of cardiometabolic morbidity and premature mortality worldwide[1]. Longitudinal global analyses attribute this increase to interacting drivers such as shifts in dietary composition, declining physical activity, and population aging[2]. The pathophysiology linking obesity to T2DM involves insulin resistance, dysregulated lipid metabolism, hypertension, and chronic low-grade inflammation, which together accelerate end-organ complications[3]. Incretin-based therapies have transformed clinical management of metabolic disease by leveraging gut-hormone signaling to improve glucose regulation and body weight[4].

GLP-1 receptor agonists (GLP-1RAs) reduce hyperglycemia primarily via glucose-dependent insulin secretion and also promote weight loss through appetite suppression and delayed gastric emptying[5]. Nevertheless, GLP-1 monotherapy has limitations in addressing the full spectrum of obesity-related metabolic abnormalities, prompting interest in complementary hormonal targets[6]. Glucose-dependent insulinotropic polypeptide (GIP) has been reappraised for therapeutic use because, when pharmacologically modulated, it can enhance insulinotropic responses and improve peripheral insulin sensitivity[7]. Conversely, glucagon receptor activation increases energy expenditure and stimulates hepatic lipid oxidation, mechanisms that can potentiate weight loss and improve dyslipidemia[8]. Preclinical models show that co-activation of GLP-1, GIP, and glucagon pathways yields synergistic effects on appetite, energy expenditure, and substrate metabolism[9]. Rational peptide engineering has therefore produced dual and triple receptor agonists designed to combine complementary mechanisms into single molecules[10].

Early clinical development of peptide multi-agonists has demonstrated favorable pharmacokinetics and promising metabolic effects in phase 1 and 2 studies[11]. Tirzepatide, a GLP-1/GIP dual agonist, has set a new benchmark by producing marked HbA1c reductions and substantial weight loss in randomized trials[12]. Several newer agents—Retatrutide, Mazdutide, Survodutide, SAR425899, JNJ-64565111, and RG7697—are being evaluated for their potential to extend benefits to lipid profiles, blood pressure, and other cardiometabolic endpoints[13]. Phase 2 studies of triple-agonists have reported pronounced weight loss and favorable changes in metabolic biomarkers, prompting larger confirmatory trials[14]. Mechanistic and translational studies suggest that differences in receptor affinity, tissue distribution, and dose-response profiles may explain the heterogeneous clinical effects observed across distinct multi-agonist molecules[15].

Despite these advances, head-to-head randomized trials comparing the full range of dual and triple agonists are scarce, leaving clinicians uncertain about relative efficacy for specific metabolic targets[16][17]. Network meta-analysis offers a robust framework to synthesize direct and indirect evidence and to rank multiple interventions when comparative trials are incomplete. Accordingly, a systematic evaluation that integrates evidence across available randomized trials is needed to clarify how individual multi-receptor agonists compare for weight, glycemia, and broader cardiometabolic outcomes[18]. The present study therefore applies frequentist network meta-analytic methods to quantify comparative efficacy and to explore heterogeneity related to dose and baseline diabetes status.

2. Methods

2.1. Search Strategy and Study Selection

A systematic search of PubMed, Embase, and Scopus was conducted from database inception to January 27, 2024. The search strategy combined controlled vocabulary and free-text terms related to "dual agonist," "triple agonist," "GLP-1," "GIP," "glucagon," "multi-receptor agonist," "obesity," and "type 2 diabetes." No language or geographical restrictions were applied. All search strategies were adapted for each database and reviewed by an independent investigator to ensure completeness.

All retrieved records were screened in two stages. Titles and abstracts were first screened to remove non-relevant studies, followed by full-text evaluation against predefined eligibility criteria. Randomized controlled trials were included if they (1) evaluated dual or triple agonists targeting at least two of the GLP-1, GIP, and glucagon receptors; (2) enrolled adults with overweight, obesity, or type 2 diabetes mellitus; (3) compared the intervention against placebo; and (4) reported at least one prespecified metabolic outcome. Observational studies, single-arm trials, non-randomized designs, conference abstracts, pediatric studies, and trials lacking extractable quantitative data were excluded.

2.2. Outcomes

Primary outcomes were the changes in body weight and HbA1c from baseline to the end of the treatment period. Secondary outcomes included changes in fasting plasma glucose, fasting insulin, waist circumference, systolic and diastolic blood pressure, and lipid parameters, including total cholesterol, triglycerides, LDL-C, VLDL-C, and HDL-C. When available, achievement of clinically relevant thresholds (e.g., ≥5% or ≥10% weight reduction, or HbA1c <7.0%, <6.5%, or <5.7%) was extracted for binary analyses.

2.3. Data Extraction and Quality Assessment

Two investigators independently extracted data using a standardized template capturing study characteristics, participant demographics, intervention details, comparator information, outcome definitions, mean or least squares mean changes, effect estimates, and measures of variance. When trials reported multiple dose arms, all eligible doses were included to retain within-study comparisons. Discrepancies were resolved through discussion or consultation with a third reviewer.

Risk of bias for each included trial was assessed using the Cochrane Risk of Bias 2.0 tool[19], evaluating randomization processes, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Each domain was graded as "low risk," "some concerns," or "high risk."

2.4. Statistical Analysis

A frequentist random-effects network meta-analysis was performed to synthesize direct and indirect evidence across all interventions. Pairwise mean differences were calculated for continuous outcomes using the difference in least squares mean or general linear model estimates, prioritizing adjusted effect sizes when available. For binary outcomes, risk ratios were calculated. The network structure was examined for consistency and transitivity, and global inconsistency was assessed using the design-by-treatment interaction model.

Ranking probabilities for each intervention were estimated using the surface under the cumulative ranking curve (SUCRA), with higher values indicating a greater likelihood of being the most effective treatment. Heterogeneity was quantified using τ^2 and I^2 statistics. Prespecified subgroup analyses examined the effects of intervention class (dual vs triple agonists), diabetes status, study region, dose range, and treatment duration. Sensitivity analyses were conducted by sequentially omitting individual studies and by restricting models to consistency assumptions. All analyses were performed using STATA18.0.

3. Results

3.1. Study Selection

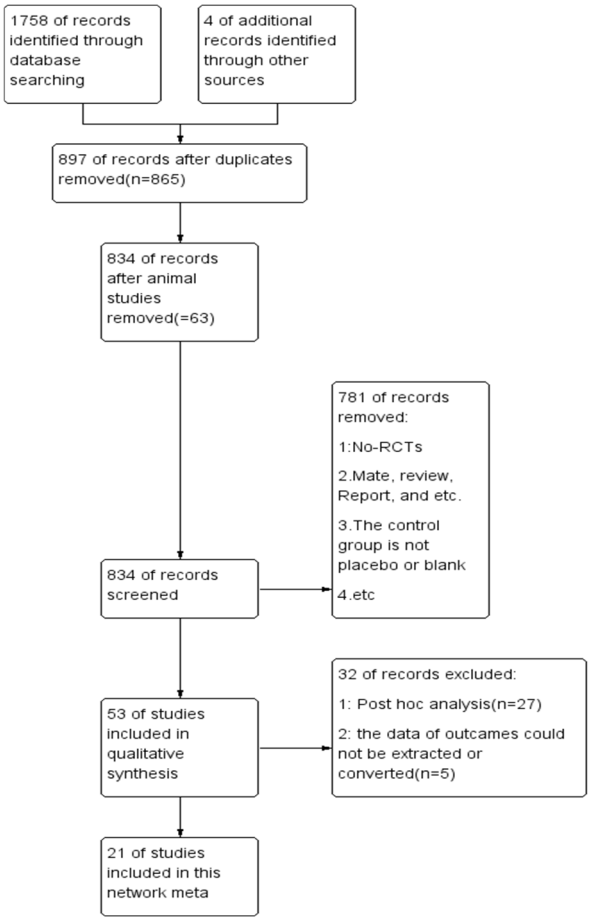

Figure 1. PRISMA Flow Diagram.

This figure outlines the identification, screening, eligibility assessment, and inclusion of studies in the analysis.

The initial search retrieved 1762 records. After removal of

duplicates and screening of titles and abstracts, 834 articles underwent full-text review. Of these, 21 randomized controlled trials met the eligibility criteria and were included in the final analysis [20–40]. The PRISMA flow diagram summarizing the selection process is presented in fig 1.

3.2. Characteristics of Included Studies

The 21 included RCTs evaluated seven multi-receptor agonists—Tirzepatide, Retatrutide, Mazdutide, Survodutide, SAR425899, JNJ-64565111, and RG7697—across doses ranging from low-dose monotherapy to maximally titrated regimens. These trials enrolled a total of 5568 adults with overweight, obesity, or T2DM [20–40]. The baseline characteristics of participants in each experiment are shown in Table 1.

Table 1. Baseline Characteristics of Included Randomized Controlled Trials.

	first author	year	type	intervation	time	number (woman)	age	weight (kg)	HbA1c
[20]	Maria Alba	2020	RCT	JNJ- 64565111 (5mg,7.4mg,10mg)	26W	355(267)	46.5±11.76	112.75±16.29	5.5±0.4
[21]	Louis J. Aronne	2023	RCT	Tirzepatide(10mg,15mg)	52W	670(473)	49±13	84.6±19.8	5.07±0.3
[22]	Juan Pablo Frias	2018	RCT	LY3298176 (1 mg,5 mg,10 mg,15 mg)	26W	262(118)	56.89±8.68	91.86±21.7	8.1±0.97
[23]	W Timothy Garvey	2023	RCT	Tirzepatide(10mg,15mg)	72W	938(476)	54.2±10.6	100.7±21.1	8.02±0.89
[24]	Tim Heise	2022	RCT	Tirzepatide(15mg)	28W	73(21)	60.83±7.25	95.91±14.31	7.86±0.64
[25]	Ania M. Jastreboff	2023	RCT	Retatrutide (1mg,4mg,8mg,12mg)	48W	338(163)	48.2±12.7	107.7±21.4	5.5±0.4
[26]	Linong Ji	2021	RCT	Mazdutide (3mg,4.5mg,6mg)	12W	36(18)		84.28±12.85	5.3
[27]	Linong Ji	2022	RCT	Mazdutide(9mg,10mg)	16W	24(17)	37.93±9.91	81±13.82	-
[28]	Linong Ji	2023	RCT	Mazdutide (3mg,4.5mg,6mg)	24W	248(129)	35.52±9.39	89.46±15.28	5.4±0.33
[29]	Hongwei Jiang	2022	RCT	IBI362(3mg,4.5mg,6mg)	12W	36(16)	52.37±9.04	68.52±11.19	8.74±0.87
[30]	Nicholas A. Di Prospero	2020	RCT	JNJ- 64565111 (5mg,7.4mg,10mg)	26W	195(118)	56.6±9.0	113.0±18.4	7.6±0.9
[31]	Julio Rosenstock	2021	RCT	Tirzepatide (5mg,10mg,15mg)	40W	478(231)	54.1±11.9	85.8±19.8	7.94±0.87
[32]	Julio Rosenstock	2023	RCT	Retatrutide (0.5mg,4mg,8mg,12mg)	36W	235(123)	56.2±9.7	98.2±21.1	8.3±1.1
[33]	Shweta Urva	2022	RCT	LY3437943 (0.5mg,1.5mg,3mg,6mg, 12mg)	12W	67(36)	58.89±7.23	86.67±18.29	8.62±0.53
[34]	Thomas A. Wadden	2023	RCT	Tirzepatide(10mg,15mg)	72W	579(364)	45.6 ±12.2	101.9 ±21.4	5.4 ±0.4
[35]	Matthias Blüher	2023	RCT	survodutide(0.3mg(qw), 0.9mg(qw),1.8mg(qw), 2.7mg(qw),1.2mg(biw), 1.8mg(biw))	16W	361(162)	57.26±9.68	96.54±21.76	8.08±0.84
[36]	Dominik Dahl	2022	RCT	Tirzepatide (5mg,10mg,15mg)	40W	475(211)	60.74±10	95.17±21.64	8.31±0.85
[37]	Michele Schiavon	2021	RCT	SAR425899 (0.12mg,0.16mg,0.2mg)	26W	70(-)	56.1 ± 9.6	96.8 ± 17.5	8.2 ± 0.9
[38]	Christophe Schmitt	2017	RCT	RG7697(0.25mg,0.75mg, 1.1mg,1.5mg,2.0mg, 2.5mg)	2W	56(24)	53.5±8.0	96.8±17.3	7.75±1.08
[39]	Joachim Tillner	2019	RCT	SAR425899 (0.09mg,0.18mg)	4W	36(8)	58.9±8.7	98.6 ±13.9	-
[40]	Rie Yazawa	2023	RCT	BI 456906(1.8mg(qw), 4.8mg(qw),2.4mg(biw))	16W	36(0)	34.2±7.6	75.1±6.9	-

This table summarizes sample sizes, demographic variables, baseline anthropometric and metabolic parameters, intervention doses, and treatment durations for all included trials.

3.3. Risk of Bias Assessment

Most trials provided adequate details regarding randomization and allocation concealment. Blinding of participants and investigators was unclear in several studies owing to differences in injection devices or dose-escalation schedules. Outcome reporting was generally complete. The risk-of-bias summary is shown below fig 2.

This figure 2 summarizes the methodological quality of included trials across the Cochrane Risk of Bias 2.0 domains.

3.4. Sensitivity Analysis

We conducted sensitivity analysis on the data of each group, and found that Aronne2023, Wadden2023, Garvey2023-1 and Dahl2023-3 articles affected the robustness of the model in the body weight group, so we deleted them and conducted sensitivity analysis again, and no articles affecting the robustness of the model were found. Then, regression analysis was performed for each of the 7 potential influencing factors to verify whether they were the source of heterogeneity. Different drugs and dosages affected the outcome data of the punishment part, according to the subgroup analysis, the heterogeneity was significantly reduced. The cycle of diabetes also affects glycolipid metabolism.

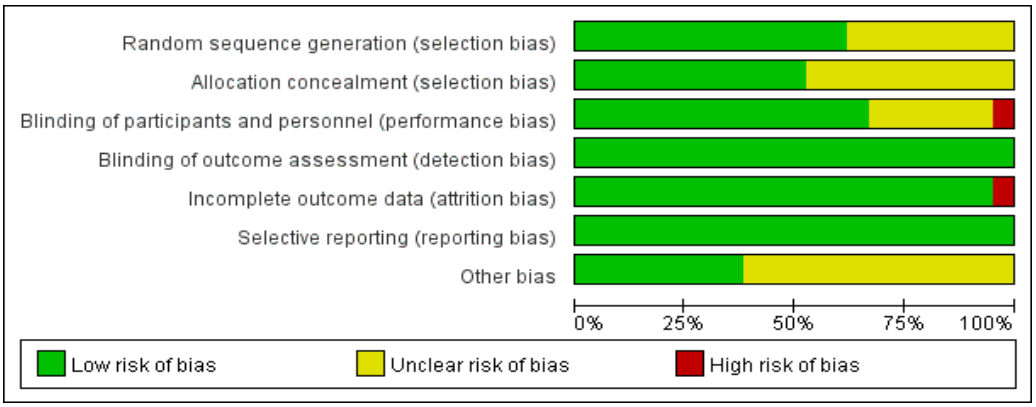

Figure 2. Risk of Bias Assessment.

3.5. Network Geometry

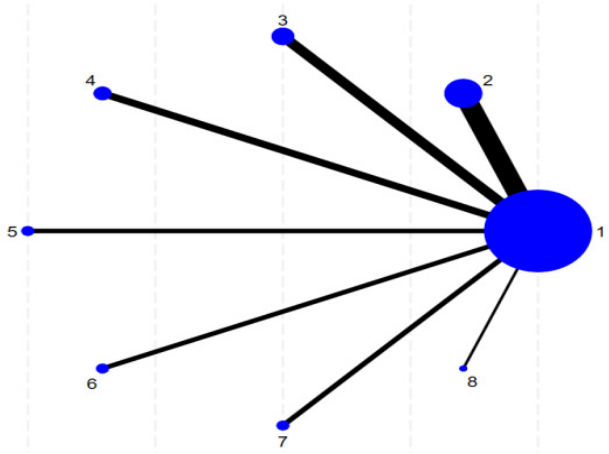

Figure 3. Network Plots for All drugs

Nodes represent interventions, and edge thickness reflects the number of direct comparisons.1: Placebo, 2: Tirzepatide, 3: Mazdutide, 4: Retatrutide, 5: JNJ-64565111, 6: Survodutide, 7: SAR425899, 8: RG7697

After egger and begg tests, no publication bias was found in the data of this paper. After sensitivity analysis, statistical analysis was performed after removing articles that significantly affected the robustness of the data.

A total of 7 drugs is involved, and the network diagram drawn is shown in Figure 3. Among them, 17 literatures related to the impact on body weight, 19 literatures related to the impact on glycosylated hemoglobin, 14 literatures related to the impact on fasting blood glucose, 8 literatures related to the impact on fasting insulin, 10 literatures related to the impact on waist circumference, and 7 literatures related to the impact on blood lipid.

3.6. Primary Outcomes

3.6.1. Body Weight

All 21 included trials contributed data on change in body weight from baseline. Compared with placebo, each of the seven agonists produced significant weight reductions. In the overall network, the pooled mean difference favored active treatment, with reductions ranging from modest effects at lower doses to substantial reductions with higher-dose regimens.

Tirzepatide (10–15 mg) consistently produced large and clinically meaningful weight loss across diabetic and non-diabetic cohorts [21][23][24][31][34][36]. Retatrutide (8–12 mg) demonstrated the greatest magnitude of weight reduction among all agents evaluated, particularly in non-diabetic individuals with severe obesity[25][32]. Mazdutide (4–6 mg) also induced meaningful decrements in body weight, though with slightly smaller absolute reductions than dual or triple agonists [27][28].

The complete pairwise comparisons for weight outcomes are shown below.

This figure presents mean differences and 95% confidence intervals for each intervention versus placebo. Alba2020-1: JNJ-64565111(5mg), Alba2020-2: JNJ-64565111(7.4mg), Alba2020-3: JNJ- 4565111(10mg), Frias2018-1: Tirzepatide (1mg), Frias2018-2: Tirzepatide(5mg), Frias2018-3: Tirzepatide (10mg), Frias2018-4: Tirzepatide(15mg), Garvey 2023-2: Tirzepatide(15mg), Heise2022: Tirzepatide(15mg), Jastreboff2023-1: Retatrutide(1mg), Jastreboff2023-2: Retatrutide (4mg), Jastreboff2023-3: Retatrutide(8mg), Jastre boff2023-4: Retatrutide(12mg), Ji2021-1: Mazdutide(3mg), Ji2021-2: Mazdutide(4.5mg), Ji2021-3: Mazdutide(6mg), Ji2022-1: Mazdutide(9mg), Ji2022-2: Mazdutide(10mg), Ji2023-1: Mazdutide(3mg), Ji2023-2: Mazdutide(4.5mg), Ji2023-3: Mazdutide(6mg), Jiang2022-1: Mazdutide(3mg), Jiang2022-2: Mazdutide(4.5mg), Jiang2022-3: Mazdutide (6mg), Prospero2020-1: JNJ- 64565111(5mg), Prospero 2020 -2: JNJ- 64565111(7.4mg), Prospero2020-3: JNJ- 64565111 (10mg), Rosenstock2021-1: Tirzepatide(5mg), Rosenstock 2021-2: Tirzepatide(10mg), Rosenstock2021-3: Tirzepatide (15mg), Rosenstock2023-1: Retatrutide(0.5mg) , Rosenstock 2023-2: Retatrutide (4mg), Rosenstock 2023-3: Retatrutide (8mg), Rosenstock2023-4: Retatrutide(12mg), Urva2022-1: Retatrutide (1.5mg), Urva2022-2: Tirzepatide(3mg), Urva 2022 -3: Tirzepatide(4mg), Urva2022-4: Tirzepatide(12mg), Dahl2022-1: Tirzepatide(5mg), Dahl2022-2: Tirzepatide (10mg), Tillner2019-1: SAR425899(0.09mg), Tillner2019-2: SAR425899 (0.18mg), Schmitt2017-1: RG7697(0.25mg),

Schmitt 2017-2: RG7697(0.75mg), Schmitt2017-3: RG7697 (1.1mg), Schmitt2017-4: RG7697(1.5mg), Schmitt2017-5: RG7697 (2.0mg), Schmitt2017-6: RG7697(2.5mg), Schiavon 2021-1: SAR425899(0.12mg), Schiavon2021-2: SAR4258 99(0.16mg), Schiavon2021-3: SAR425899(0.2mg), Blüher 2023-1: Survodutide(0.3mgqw), Blüher2023-2: Survodutide (0.9mgqw), Blüher2023-3: Survodutide(1.8mgqw), Blüher 2023-4: Survodutide (2.7mgqw), Blüher2023-5: Survodutide (1.2mgbiw), Blüher2023-6:Survodutide(1.8mgqw), Yazawa 2023-1: Survodutide(1.8mgqw), Yazawa2023-2: Survodutide (4.8mgqw), Yazawa2023-3: Survodutide (2.4mgbiw).

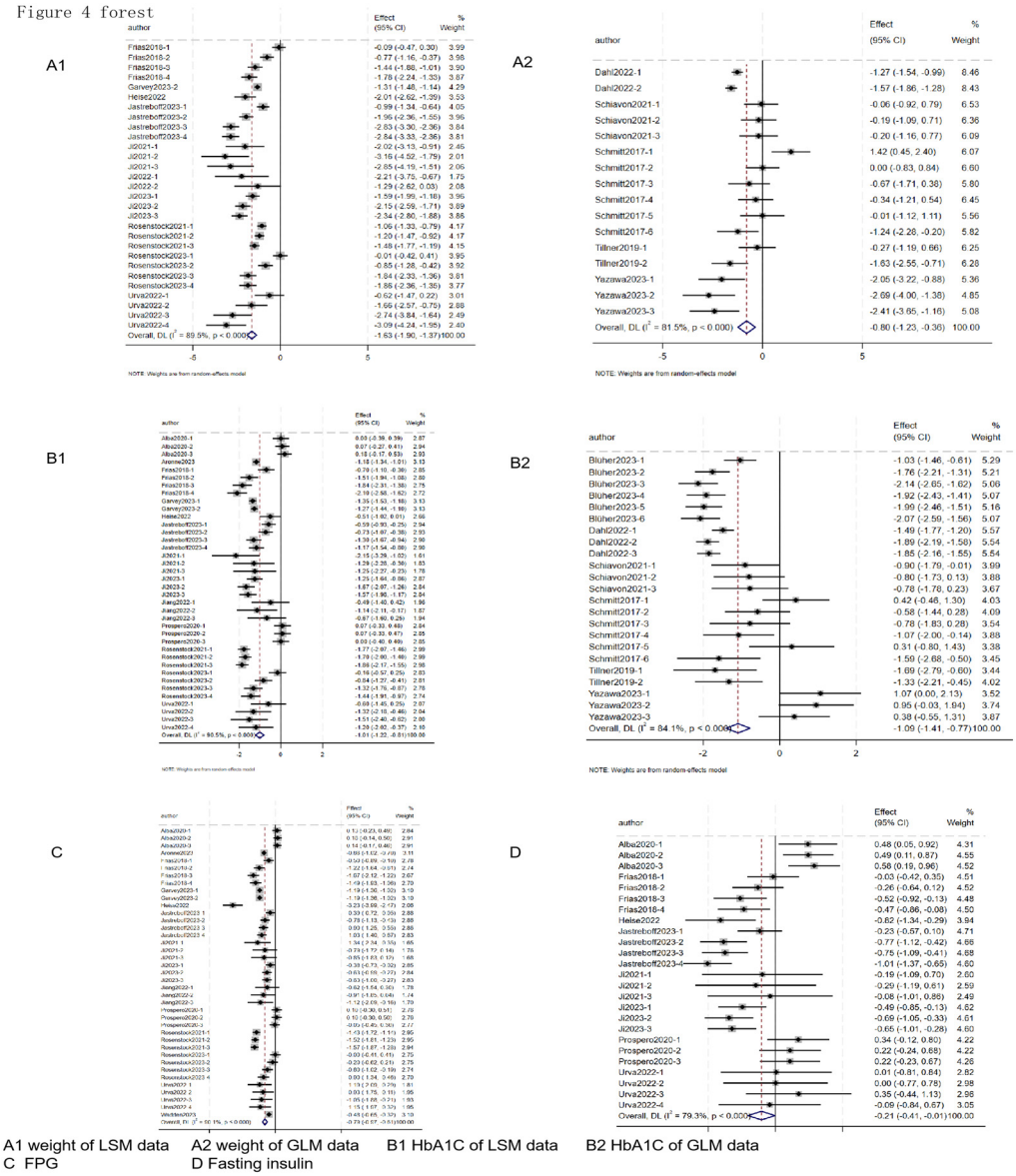

Figure 4A. Forest Plot for Body Weight.

Sucra curve showed that compared with Survodutide, SAR425899, JNJ-64565111 and RG7697, Tizepatide 10mg had a significant weight loss effect, and sucra value was 93.6%. (Figure 5) In addition, we also discussed the weight loss of subjects in 11 studies by 5%, 10% and 15%. The results showed that ritarutide 12mg had the best effect on weight loss by 5% and 10%, and sucra values were 86.6% and 86.8%, respectively. Mazdupeptide 6mg had a greater advantage in weight loss of 15%, with sucra value of 73.1%.

This figure shows ranking probabilities for each intervention across weight, HbA1C, fasting glucose and insulin. T1mg: Tirzepatide 1mg, T5mg: Tirzepatide 5mg, T10mg: Tirzepatide 10mg, T15mg: Tirzepatide 15mg, T(10/15mg): Tirzepatide 10/15mg, R0.5mg: Retatrutide 0.5mg, R1mg: Retatrutide 1mg, R1.5mg: Retatrutide 1.5mg, R3mg: Retatrutide 3mg, R4mg: Retatrutide 4mg, R6mg: Retatrutide 6mg, R8mg: Retatrutide 8mg, R12mg: Retatrutide 12mg, M3mg: Mazdutide 3mg, M4.5mg: Mazdutide 4.5mg, M6mg: Mazdutide 6mg, M9mg: Mazdutide 9mg, M10mg: Mazdutide 10mg, Sur0.3mg(qw): Survodutide 0.3mg(qw), Sur0.9mg(qw): Survodutide 0.9mg (qw), Sur1.8mg(qw): Survodutide 1.8mg(qw), Sur2.7mg (qw): Survodutide 2.7mg(qw), Sur1.2mg(biw): Survodutide 1.2mg (biw), Sur1.8mg(biw): Survodutide 1.8mg (biw), Sur4.8mg (qw): Survodutide 4.8mg(qw), Sur2.4mg (biw): Survodutide 2.4mg(biw), SAR0.09mg: SAR425899 0.09mg, SAR0.12mg : SAR425899 0.12mg, SAR0.16mg: SAR 425 899 0.16mg, SAR0.18mg: SAR425899 0.18mg, SAR0.20mg : SAR425899 0.20mg, JNJ5mg: JNJ-64565111 5mg, JNJ7.4mg: JNJ-64565111 7.4mg, JNJ10mg: JNJ-64565111 10mg, RG0.25mg: RG7697 0.25mg, RG0.75mg: RG7697 0.75mg, RG1.1mg: RG7697 1.1mg, RG1.5mg: RG7697

1.5mg, RG2.0mg: RG7697 2.0mg, RG2.5mg: RG7697 2.5mg.

Figure 5. The Scura of weight, HbA1C, FPG and Fasting insulin.

3.6.2. HbA1c

Nineteen of the included trials reported changes in HbA1c. All active agents significantly lowered HbA1c relative to placebo. Tirzepatide (10–15 mg) demonstrated the largest reductions across both general linear model and least-squares mean datasets. Retatrutide produced substantial glycemic improvements in diabetic cohorts but achieved smaller decrements than Tirzepatide in comparable populations. Mazdutide yielded modest yet clinically meaningful HbA1c reductions in both phase 1 and 2 studies.

Sucra curve showed that the maximum dose of tizepatide (10mg, 15mg) had the best hypoglycemic effect, and the sucra value was 95.1%. (Figure 6) Five studies involved the outcome of glycation compliance with Tirzepatide and Retatrutide interventions. Tirzepatide10mg had the best effect on achieving the target of 7% saccharification, with sucra value of 91.1%. Retatrutide8mg was the most effective in achieving the target of 6.5% saccharification, with a sucra value of 81.5%. Tirzepatide10mg had the best effect on achieving the target of 5.7%, with a sucra value of 96.0%. (Appendix)

3.7. Secondary Outcomes

3.7.1. FPG

We investigated the changes of fasting blood glucose in 14 studies. The MD and 95% confidence intervals for overall drug HBA1c reduction versus placebo were -0.79 (-0.97, -0.61). (FIG. 5) Compared with Mazdutide, Ritalutide and JNJ-64565111, Tizepatide (10mg) had the best hypoglycemic effect, with a sucra value of 93.8%. (Figure 6)

3.7.2. Fasting Insulin

We investigated the effects of four drugs (Mazdutide, Ritarutide, Tezepatide, JNJ-64565111) on fasting insulin in eight studies. Compared with placebo, the MD and 95% confidence intervals for fasting insulin changes for each drug were -0.21 (-0.41, -0.01). (Figure 5) Sucra curve indicated that Retatrutide 12mg had the greatest effect on fasting insulin, with sucra value of 67.3%. (Figure 6)

3.7.3. Waist Circumference

We analyzed the effects of three drugs (mazdutide, ritarutide, tezepatide) on waist circumference in seven studies. Compared with placebo, the MD and 95% confidence intervals for the effects of each drug on waist circumference were -0.98 (-1.16, -0.80). The Sucra curve showed that the maximum tolerated dose of Tirzepatide (10mg/15mg) had the greatest effect on waist circumference, with sucra value of 95.2%.

3.7.4. BP

The effects of three drugs (Tezepatide, ritarutide and mazdutide) on blood pressure were reported in 7 literatures. From the forest map, the MD and 95% confidence intervals for the overall effect of each intervention on systolic blood pressure were -0.53 (-0.63, -0.43) and -0.33 (-0.43, -0.22) for the overall effect on diastolic blood pressure compared with placebo. We calculated the surface area under the cumulative ranking curve (SUCRA) and found that mazdupeptide 6mg had the greatest effect on the reduction of systolic and diastolic blood pressure, with sucra values of 86.4% and 89.1%, respectively.

3.7.5. Blood Lipid

We analyzed data on total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides from seven studies involving three drugs, Tezepatide, Rittalutide, and mazdutide. The overall effect of the three drugs on triglycerides compared with placebo MD and 95% confidence intervals were -0.74 (-0.87, -0.61); The overall effect on LDL versus placebo MD and 95% confidence intervals were -0.41 (-0.55, -0.27). The overall effect on total cholesterol compared with placebo MD and 95% confidence intervals were -0.65 (-0.81, -0.48); And the overall effect on HDL versus placebo MD and 95% confidence intervals were -0.03 (-0.21, 0.15); The overall effect on very low-density lipoprotein compared to placebo MD and 95% confidence interval was -0.67 (-0.81, -0.53). We also calculated the surface area (SUCRA) under the cumulative ranking curve. Among mazdutide, Ritarutide and Tizepatide, Retatrutide12mg has obvious effects on lowering cholesterol, triglycerides, LDL, LDL and VLDL. The sucra values were 94.3%, 83.3%, 90.5% and 85.5%, respectively. Tizepatide 15mg has better effect on improving high-density lipoprotein.

4. Discussion

The findings of this network meta-analysis demonstrate that dual and triple incretin- and glucagon-pathway receptor agonists achieve broad metabolic benefits, but their relative efficacy varies in a receptor- and dose-dependent manner. These observations are consistent with contemporary translational research indicating that multi-receptor activation produces synergistic hormonal effects not attainable with single-pathway therapies [41]. The distinct clinical profiles we identified closely reflect the mechanistic diversity by which GLP-1, GIP, and glucagon receptors regulate appetite, energy expenditure, lipid flux, and insulin dynamics [42].

Tirzepatide exhibited the strongest glycemic and weight-lowering efficacy across included studies, reinforcing findings from earlier investigations showing that dual GLP-1/GIP signaling amplifies glucose-dependent insulinotropic responses and enhances postprandial metabolic flexibility [43]. The marked reductions in waist circumference and fasting glucose observed with Tirzepatide further support its positioning as a leading multi-agonist for individuals with obesity complicated by impaired glycemic regulation [44]. However, the high potency observed at doses of 10–15 mg highlights the need for individualized titration strategies, especially in patients at risk for gastrointestinal intolerance or rapid weight loss [21].Tirzepatide is a dual receptor agonist for GLP-1 and GIP[45]. Julio Rosenstock's study collected blood glucose and body weight data after 4-week Tirzepatide discontinuation. Analysis revealed that 86% (5 mg), 74% (10 mg), and 67% (15 mg) of participants-maintained weight changes below 3%, with only mild blood glucose elevation compared to baseline [46]. Valentina Pirro's research demonstrated Tirzepatide's efficacy in weight reduction and glycemic control, with superior triglyceride-lowering effects than dulaglutide and metabolic regulation aligning with health benefits[47]. Based on this web-based meta-analysis, Tirzepatide exhibits excellent weight and blood glucose control, delivering health benefits beyond discontinuation and improving blood pressure and lipid profiles.

Mazdutide, a synthetic peptide analog of mammalian oxytocin modulator, is a once-weekly dual agonist of GLP-1 and glucagon receptors [26]. A 20-week study demonstrated that mazdutide (4.5mg and 6mg doses) showed superior weight loss efficacy compared to dulaglutide, with glucose-lowering effects comparable to dulaglutide [48]. Mazdutide exhibited the most significant effects in reducing both systolic and diastolic blood pressure, indicating that glucagon receptor activation moderately enhances thermogenesis and regulates vascular tone. Although mazdutide's absolute weight loss effect is less pronounced than that of tirazapipide or retaraptide, its hemodynamic effects may hold clinical significance, particularly for patients with obesity-related hypertension. Future head-to-head trials are required to clarify whether these blood pressure reductions translate into differences in long-term cardiovascular outcomes.

Retatrutide, the only evaluated triple agonist[49], demonstrated the greatest probability of improving lipid metabolism, consistent with mechanistic evidence that glucagon receptor activation stimulates hepatic fatty acid oxidation and VLDL clearance. The pronounced reductions in triglycerides and atherogenic lipoproteins observed in this analysis raise the possibility that Retatrutide may offer advantages for patients with mixed dyslipidemia or metabolic-associated steatotic liver disease, although longer-term outcomes remain to be established. These findings reinforce the concept that the relative balance of receptor affinities, rather than absolute potency alone, shapes the lipid-modulating effects of multi-agonists.

Several sources of heterogeneity were identified in this analysis. Variability in baseline metabolic status, intervention class, dose escalation schedules, and regional differences likely contributed to the moderate-to-high heterogeneity observed across weight and glycemic outcomes. Such heterogeneity has been reported previously in multi-agonist trials and is likely to reflect the interplay between underlying metabolic phenotypes and receptor-specific pharmacodynamics. Although subgroup and sensitivity analyses reduced unexplained variability, residual heterogeneity underscores the importance of cautious interpretation when comparing agents with differing trial designs, dosing regimens, or target populations.

This study has several strengths, including a comprehensive evidence base, rigorous assessment of network consistency, and incorporation of both continuous and threshold-based outcomes. Nonetheless, important limitations should be acknowledged. First, several triple-agonist and dual-agonist trials had relatively short durations, which may not fully capture long-term glycemic durability or weight trajectories. Second, safety outcomes were not uniformly reported across trials, precluding robust comparative evaluation of adverse events. Lastly, indirect comparisons—although methodologically sound—cannot fully replace head-to-head randomized studies, which remain essential for determining true comparative effectiveness among multi-receptor agonists.

In summary, this analysis highlights clear differentiations among dual and triple receptor agonists across metabolic domains. These findings support a precision-therapy framework in which treatment selection is guided by predominant patient phenotypes, such as hyperglycemia, dyslipidemia, or hypertension. As multi-receptor agonists progress through late-phase development, comparative clinical trials and long-term safety studies will be essential to refine their roles in obesity and T2DM management.

5. Conclusion

This network meta-analysis demonstrates that dual and

triple incretin- and glucagon-pathway receptor agonists provide substantial and clinically meaningful metabolic improvements across weight, glycemic control, and broader cardiometabolic outcomes. Despite shared mechanisms, individual agents display distinct efficacy profiles: Tirzepatide achieves the most pronounced glycemic and weight reductions, Retatrutide offers superior lipid-lowering effects, and Mazdutide provides greater decreases in blood pressure. These differentiated profiles highlight the therapeutic diversity within the multi-receptor agonist class and underscore the need for individualized treatment selection based on predominant metabolic phenotypes.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

QN J: Propose research methods, Data collection, collation and analysis, and writing of initial drafts. YQ W: Propose research methods, Data collection, collation and analysis, and writing of initial drafts. JH L: Data collection, Data Management and Editing. Z G: Monitor project progress and participate in finalizing the draft.

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