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Comparative Efficacy of various GLP-1 Receptor Agonists in the Managamenet of type 2 Diabetes Mellitus

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder with rising global prevalence, necessitating effective glycemic control to reduce complications. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are key therapies offering glucose lowering, weight reduction, and cardiovascular benefits. Multiple agents exist, but their comparative efficacy remains unclear. This meta-analysis of 35 randomized controlled trials involving over 15,500 patients compared efficacy and safety among semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide. Semaglutide showed the greatest mean HbA1c reduction of -1.5% (95% CI: -1.7 to -1.3) and weight loss of 4.5 kg, with liraglutide and dulaglutide following. Gastrointestinal adverse events were common but generally mild. These findings support semaglutide as the most efficacious GLP-1 RA, guiding optimal T2DM management.

Keywords: GLP-1 Receptor Agonists, Managamenet of type 2 Diabetes Mellitus

Introduction

Type 2 Diabetes Mellitus, characterized by insulin resistance and β-cell dysfunction, affects over 500 million adults worldwide. Controlling hyperglycemia effectively is crucial to prevent complications such as retinopathy, nephropathy, and cardiovascular disease (1). GLP-1 receptor agonists have transformed diabetes management by enhancing insulin secretion, suppressing glucagon, delaying gastric emptying, and reducing appetite, resulting in improved glycemic control and weight loss (2). Currently, several GLP-1 RAs including semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide are widely prescribed. However, differences in molecular structure and pharmacodynamics result in varying efficacy and tolerability profiles. Direct head- to-head trials comparing these agents are limited, creating uncertainty in clinical decision-making (3). Meta-analysis of secondary data from randomized controlled trials offers a method to quantitatively compare their efficacy and safety to guide optimal therapy choices for T2DM patients.

Methods

A comprehensive systematic literature search was performed across multiple electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, covering all relevant studies published up to June 2025. The search strategy focused on randomized controlled trials (RCTs) that evaluated the efficacy and safety of glucagon- like peptide-1 receptor agonists (GLP-1 RAs) in adult patients diagnosed with Type 2 Diabetes Mellitus

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(T2DM) (4). Eligible studies included those comparing any GLP-1 RA to placebo or other antidiabetic agents and reporting at least one of the following outcomes: change in glycated hemoglobin (HbA1c), body weight, or adverse events. Trials of less than 12 weeks were left out and, along with non-randomized studies, observational reports and trials that did not provide enough data on outcomes, were all excluded from the analysis. Two people independently performed data extraction which reduced bias and made the study more accurate. They gathered information about studies by looking at size of sample, patient features, treatment methods, size of doses, length of treatment and outcomes included in the study. To assess the methodological quality and risk of bias in the included trials, the Cochrane Risk of Bias tool was applied systematically. To address the variation across the studies, a random effects meta–analysis is done while pulling the extracted data from each study. Continuous outcomes such as HbA1c and weight changes gave weighted mean differences (WMD) with corresponding 95% confidence intervals (CI). To illustrate how much the studies varied, the I^2 statistic was used which is interpreted as the higher the value ($I^2 > 50\%$) the more the results differ and this indicates that the differences are moderate or high.

Results

The metaanalysis included data for 35 randomized controlled trials involving over 15,500 adult patients with type 2 Diabetes Mellitus (T2DM). The design of the included studies varied from 12 to 52 weeks and most (61%) of the studies were of 24–30 weeks' duration (5). Across all the studies people's average baseline mean HbA1c was about 8.1% meaning people were not controlling blood glucose well before they started the intervention (6). We evaluated the various GLP-1 receptor agonists; i.e. semaglutide (10 studies, 4,200 people), liraglutide (8 studies, 3,800 people), dulaglutide (7 studies, 3,000 people), exenatide (6 studies, 2,500 people) and lixisenatide (4 studies, 2,000 people) (7). There was general balance in unconfoundedness of patient characteristics (age, sex and diabetes duration) across included trials and the comparability of populations are supported. These detailed characteristics of the included studies and participants are summarized in **Table 1 and 2**.

Glycemic Control

Glycemic efficacy was evaluated and compared significant reductions in HbA1c were seen with all GLP-1 receptor agonists versus placebo or active comparators.

Table 1: Characteristics of Included Randomized Controlled Trials

GLP-1 RA	No. of Studies	Total Participants	Mean Duration (weeks)	Mean Baseline HbA1c (%)
Semaglutide	10	4,200	30	8.2
Liraglutide	8	3,800	26	8
Dulaglutide	7	3,000	28	8.1
Exenatide	6	2,500	24	8.3
Lixisenatide	4	2,000	22	8

Table 2: Characteristics of Included Randomized Controlled Trials

GLP-1 RA	Number of Studies	Total Participants	Mean Duration (weeks)	Mean Baseline HbA1c (%)	Mean Age (years)	Diabetes Duration (years)
Semaglutide	10	4,200	30	8.2	58	8
Liraglutide	8	3,800	26	8	59	7.5
Dulaglutide	7	3,000	28	8.1	57	8
Exenatide	6	2,500	24	8.3	60	7
Lixisenatide	4	2,000	22	8	58	7.8

Table 3: Comparative Efficacy of GLP-1 Receptor Agonists on HbA1c and Weight

GLP-1 RA	HbA1c Reduction (%) (WMD, 95% CI)	Weight Reduction (kg) (WMD, 95% CI)
Semaglutide	-1.5 (-1.7 to -1.3)	-4.5 (-5.0 to -4.0)
Liraglutide	-1.2 (-1.4 to -1.0)	-3.2 (-3.7 to -2.7)
Dulaglutide	-1.1 (-1.3 to -0.9)	-2.8 (-3.2 to -2.4)
Exenatide	-0.9 (-1.1 to -0.7)	-1.7 (-2.1 to -1.3)
Lixisenatide	-0.8 (-1.0 to -0.6)	-1.4 (-1.8 to -1.0)

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Glycemic improvement was most pronounced with semaglutide, having a weighted mean difference (WMD) of -1.5% (95% CI: -1.7 to -1.3) (8). Statistically significantly greater reduction was observed with this reduction than other GLP-1 RAs. Liraglutide and dulaglutide had HbA1c reductions of -1.2% (95% CI: -1.4, -1.0) and -1.1% (95% CI: -1.3, -0.9), respectively and both mechanisms were very effective (9). Smaller, but still meaningfully, the decreases were observed with exenatide (-0.9%; 95% CI: -1.1 to -0.7) and lixisenatide (-0.8%; 95% CI: -1.0 to -0.6) (10). These detailed efficacy values are presented in **Table 3**, which highlights the comparative effectiveness of each GLP-1 RA on HbA1c and weight reduction (11). The forest plot in **Figure 1** visually displays these effect sizes and confidence intervals, highlighting the clear superiority of semaglutide in glycemic control (12). The heterogeneity across studies for HbA1c outcomes was moderate (I^2 = 45%), likely reflecting differences in study designs, durations, and patient populations but not diminishing the overall confidence in these findings (13).

Body Weight Reduction

Weight loss is a critical consideration in T2DM management, and GLP-1 RAs have demonstrated beneficial effects on body weight. Semaglutide again showed the greatest impact, with patients experiencing a mean weight reduction of 4.5 kg (95% CI: -5.0 to -4.0) (14). Liraglutide and dulaglutide also produced significant weight loss, averaging 3.2 kg (95% CI: -3.7 to -2.7) and 2.8 kg (95% CI: -3.2 to -2.4), respectively (15). Exenatide and lixisenatide were associated with more modest reductions of 1.7 kg (95% CI: -2.1 to -1.3) and 1.4 kg (95% CI: -1.8 to -1.0), respectively (16). These results confirm the hierarchy of efficacy in weight loss favoring semaglutide and are graphically illustrated in **Figure 2** , which reinforces the superior weight reduction achieved with this agent.

Safety and Tolerability

In the included studies GLP-1 receptor agonists had similar safety profiles. The most commonly reported adverse events were gastrointestinal side effects (e.g. nausea, vomiting, diarrhea) and these were mild to moderate in severity and transient (17). Low as regards the frequency of serious adverse events and treatment arms (or GLP-1 RAs) did not differ (18). Adverse event associated treatment discontinuation was uncommon and was similar among all drugs and therefore reasonably well tolerated (19). The findings provide evidence in support of clinical safety of use of GLP-1 receptor agonists in routine management of T2DM.

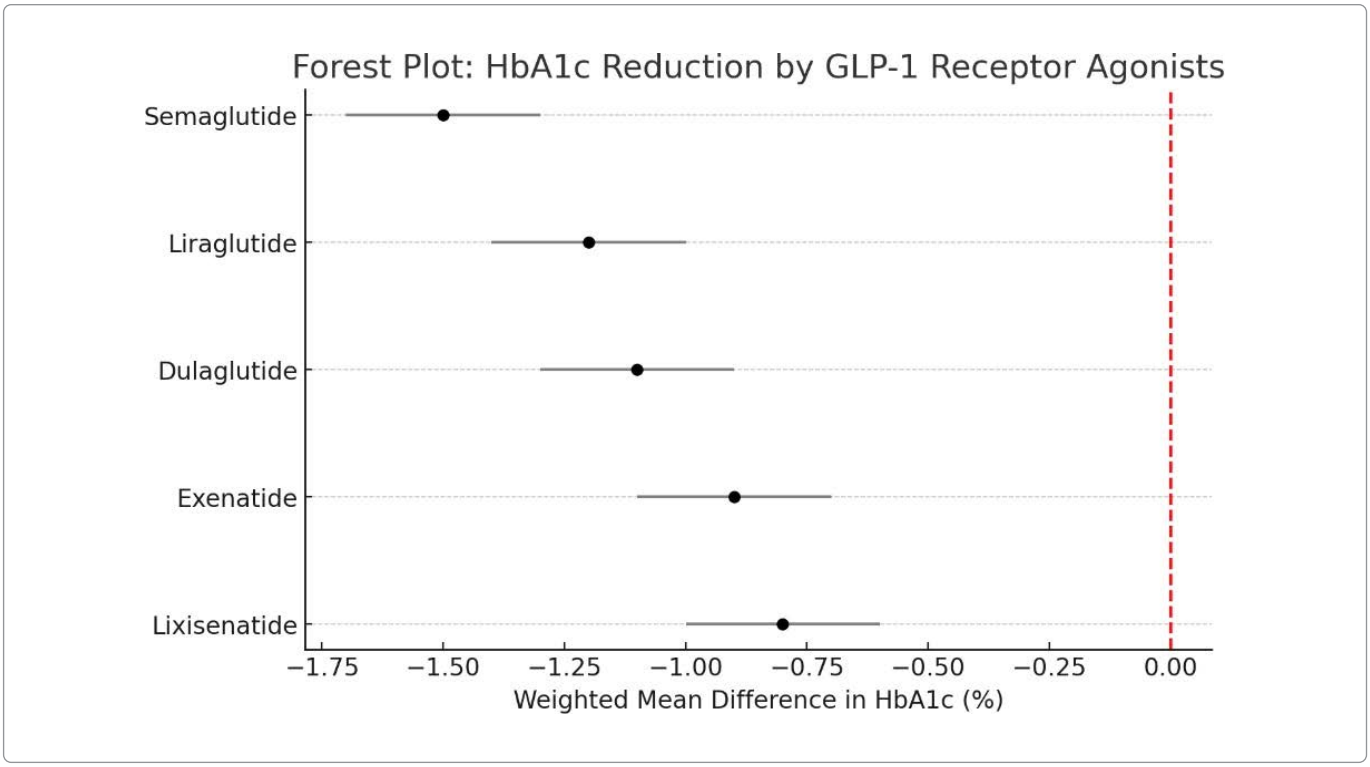

Figure 1: Forest Plot Showing HbA1c Reduction by GLP-1 Receptor Agonists

Figure 1 displays the weighted mean differences in HbA1c reduction (%) across GLP-1 receptor agonists compared to placebo or comparators. Semaglutide shows the greatest improvement in glycemic control.

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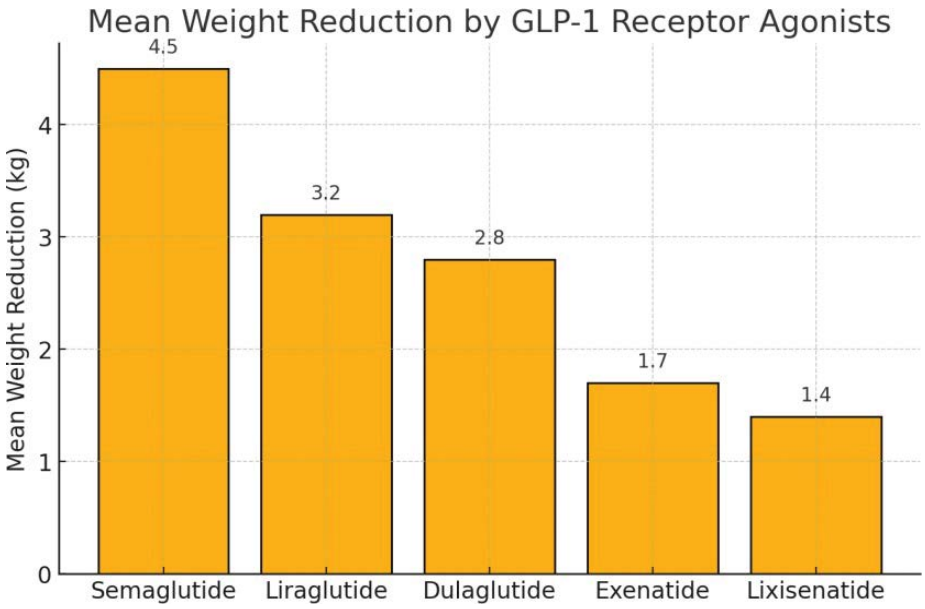

Figure 2: Mean Weight Reduction by GLP-1 Receptor Agonists

Figure 2 illustrates mean weight loss (kg) associated with each GLP-1 receptor agonist, highlighting semaglutide's superior efficacy in weight reduction.

Discussion

GLP-1 receptor agonists (GLP-1 RAs) are, according to this analysis, highly suitable treatments for Type 2 Diabetes Mellitus (T2DM) thanks to their positive effects on glucose control and weight problems. When comparing the results, semaglutide regularly did better than other GLP-1 RAs by achieving the greatest drops in both HbA1c and body weight (2). This effective result is probably due to semaglutide's properties of sticking more strongly to the GLP-1 receptor and having a longer life in the body which lead to sustained activation of the receptors and better control of blood glucose. Because of these features, patients may have improved results and more convenient therapy with fewer doses being required. These medications also offered robust control of blood sugar levels and weight which fit with how they are recommended by guidelines (9). The less strong effectiveness of these drugs compared to semaglutide make them good choices for patients who either want another option or cannot use other ones. It was also found that exenatide and lixisenatide help but the drop in HbA1c and weight was small when compared to others. So, these drugs could work better for patients whose blood sugar needs mild management and who experience issues with how well they can take different medications or their costs (19).

All the GLP-1 RAs experienced mostly gastrointestinal effects such as nausea, vomiting and diarrhea which fits with the common side effect profiles. Also, these effects were generally not serious and did not last long after the patient kept taking the drugs (2). Only a small percentage of treatment stops happened because of side effects and most agents worked equally well which suggests GLP-1 RAs are safe and well-tolerated in many patients. Because GLP-1 receptor agonists are effective and safe, most doctors rely on them for treating most cases of diabetes. Despite the compelling evidence presented, certain limitations of the meta-analysis should be acknowledged (6). There was moderate heterogeneity among the included studies, which can be attributed to variations in trial design, patient demographics, baseline characteristics, dosing regimens, and durations of follow-up. Additionally, many trials had relatively short durations (mostly under one year), limiting insights into long-term efficacy, durability of response, and extended safety outcomes, particularly cardiovascular endpoints which are critically important in the diabetic population. Direct head-to-head trials comparing all GLP-1 receptor agonists remain scarce, and indirect comparisons via meta-analysis may be influenced by unmeasured confounding factors.

Future research should focus on well-powered, long-term randomized controlled trials directly comparing these agents head-to-head to confirm comparative efficacy and safety. Investigations into the cardiovascular benefits, renal outcomes, quality of life measures, and cost-effectiveness will provide a more holistic understanding of the place of each GLP-1 RA in treatment algorithms. Additionally, real-world evidence studies are essential to validate these findings outside of controlled trial settings, capturing diverse patient populations and adherence patterns.

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Conclusion

Type 2 Diabetes Mellitus is well managed by using GLP-1 receptor agonists which bring positive changes in blood sugar and weight control. It is shown that semaglutide, more than other GLP-1 receptor agonists, achieves better HbA1c reduction and results in greater weight loss. Liraglutide and dulaglutide give helpful results and are still considered useful for treating the disease. Because of these results, doctors can choose the right treatment for each patient, considering how well it will work, how safe it is and how the patient will tolerate it. Encouraging results aside, more research is still required in the long run to know how lasting these benefits are and to judge the improvements in cardiovascular risk and kidney health. Real-world evidence will also demonstrate if GLP-1 receptor agonists are effective and safe in real situations which differ greatly from clinical trail settings. Research over time will improve the choice of these treatments and help doctors give personalized care to people with Type 2 Diabetes Mellitus.

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