GLP-1 Receptor Agonists for Hypertriglyceridemia- A Meta Analysis

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ABSTRACT

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| **Aims:** Hypertriglyceridemia, a prevalent lipid disorder linked to cardiovascular disease and metabolic complications, arises from genetic, lifestyle, or secondary factors like diabetes and obesity. While lifestyle changes and conventional treatments help, many patients need alternative therapies. Glucagon-like peptide-1 receptor agonists, initially for type 2 diabetes, have shown lipid-lowering effects through delayed gastric emptying and enhanced insulin sensitivity. Emerging evidence suggests liraglutide and semaglutide may significantly reduce triglycerides. This meta-analysis evaluates their efficacy in lowering triglycerides across randomized controlled trials, highlighting their potential as adjunct therapy.  **Study design:** Meta Analysis as per PRISMA guidelines  **Place and Duration of Study:** Department of Medicine, Bangladesh Institute of Laser and Cell Surgery Hospital, Dhaka, Bangladesh between 2018- 2024  **Methodology:** RCTs from 2018–2024 in patients with obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS). Fifteen RCTs (n = 3,450) met inclusion criteria. Informed written consent was obtained. Studies included adults (≥18 years) with TG >150 mg/dL, comparing GLP-1 RAs to placebo or lipid-lowering agents with ≥12-week follow-up. Observational studies, non-randomized trials, and studies without TG data were excluded. The primary outcome was the mean percentage change in TG levels; secondary outcomes included total cholesterol, LDL, HDL, and body weight. A random-effects model was used for statistical analysis, assessing heterogeneity with Cochran’s Q test and I² statistics. Subgroup and sensitivity analyses confirmed findings, supporting GLP-1 RAs as a potential therapy for hypertriglyceridemia.  **Results:** Fifteen RCTs (n = 3,450) evaluated GLP-1 RAs for TG reduction. Semaglutide (5 studies), Liraglutide (4), Dulaglutide (3), and Exenatide (3) were assessed over 12–104 weeks. GLP-1 RAs significantly reduced TG by -19.2% (95% CI: -22.8 to -15.6, p < 0.001) vs. placebo. Greater reductions occurred in obese (-22.1%), T2DM (-20.3%), NAFLD (-21.5%), and PCOS (-18.4%) patients. Higher baseline TG (>250 mg/dL) showed a greater mean reduction (-24.1%). Semaglutide had the greatest reduction (-22.5%), followed by Liraglutide (-20.1%), Dulaglutide (-18.7%), and Exenatide (-16.9%). Moderate heterogeneity (I² = 48%) was noted, and sensitivity analysis confirmed result consistency. Findings support GLP-1 RAs as effective TG-lowering therapy, especially in metabolic conditions.  **Conclusion:** GLP-1 RAs significantly lower triglycerides, making them a valuable option for hypertriglyceridemia, particularly in patients with obesity, T2DM, and NAFLD. Semaglutide provides the greatest TG reduction but has higher gastrointestinal side effects, while Liraglutide offers better tolerability. Individualized therapy is key, balancing efficacy and adherence. The dual benefit of GLP-1 RAs in lipid and glycemic control highlights their role in cardiometabolic risk reduction. Further research should explore long-term cardiovascular benefits and combination therapies to optimize treatment**.** |

*Keywords***: Hypertriglyceridemia, GLP-1 receptor agonists, triglyceride reduction, semaglutide, liraglutide, type 2 diabetes mellitus, obesity, non-alcoholic fatty liver disease, polycystic ovary syndrome, lipid metabolism, cardiovascular risk, insulin sensitivity, gastrointestinal side effects**

1. INTRODUCTION

Hypertriglyceridemia is a prevalent lipid disorder characterized by elevated triglyceride levels, which is associated with an increased risk of cardiovascular disease (CVD), acute pancreatitis, and metabolic complications. It can result from genetic predisposition, lifestyle factors, or secondary conditions such as diabetes, obesity, and hypothyroidism. The primary mechanisms underlying hypertriglyceridemia involve impaired triglyceride clearance due to dysfunctional lipoprotein lipase activity or excessive hepatic production of very-low-density lipoproteins (VLDL). Typically, lifestyle modifications, including dietary changes, physical activity, and weight loss helps in lowering triglyceride level. However, in individuals with persistently high triglyceride levels despite lifestyle interventions, pharmacological treatments such as fibrates, statins, and omega-3 fatty acids are commonly prescribed. Despite these therapies, many patients continue to experience elevated triglycerides, necessitating the exploration of alternative pharmacological options.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for type 2 diabetes mellitus (T2DM), have demonstrated beneficial effects on lipid metabolism, beside glycemic control. These agents reduce triglyceride levels through multiple mechanisms, including delayed gastric emptying, decreased intestinal lipoprotein production, and enhanced insulin sensitivity. Additionally, GLP-1 RAs contribute to weight loss, lower blood pressure, and improve endothelial function, all of which play a role in reducing cardiovascular risk. However, the extent of triglyceride reduction observed with GLP-1 RAs varies across clinical studies, necessitating a comprehensive evaluation of their efficacy. Recent studies suggest that medications such as liraglutide and semaglutide may provide clinically meaningful reductions in triglyceride levels, making them a promising therapeutic option for hypertriglyceridemia.

This meta-analysis aims to systematically assess the impact of GLP-1 RAs on triglyceride levels across multiple randomized controlled trials (RCTs). By consolidating current evidence, this study seeks to determine the potential role of GLP-1 RAs as an adjunct therapy for hypertriglyceridemia, particularly in individuals with metabolic disorders such as obesity and type 2 diabetes.

2. METHODOLOGY

A systematic review and meta-analysis have been done to evaluate the impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on triglyceride (TG) levels in patients with hypertriglyceridemia. The study analyzed data from randomized controlled trials (RCTs) and systematic reviews published between 2018 to 2024, focusing on the efficacy of GLP-1 RAs in reducing triglyceride levels in various patient subgroups, including individuals with obesity, type 2 diabetes mellitus (T2DM), non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS). This study adhered to the PRISMA guidelines to ensure methodological transparency, accuracy, and replicability in study selection, data extraction, and synthesis. A comprehensive search was conducted in PubMed to identify relevant studies. Two independent reviewers screened the identified studies based on predefined eligibility criteria. Any disagreements were resolved through discussion, and if necessary, a third reviewer was consulted. Informed written consents were taken from the participants before this trial.

A total of 15 RCTs met the inclusion criteria and were included in the meta-analysis. The total study population consisted of 3,450 participants, ensuring sufficient statistical power for meaningful conclusions. The study included only RCTs, systematic reviews, and meta-analyses published between 2018 and 2024, focusing on adults (≥18 years) diagnosed with hypertriglyceridemia (TG > 150 mg/dL) and comparing GLP-1 RAs with a placebo or other lipid-lowering agents. A minimum follow-up of 12 weeks and reporting of baseline and post-treatment TG levels were required. Observational studies, case reports, and non-randomized trials were excluded, along with studies focusing only on glycemic control without triglyceride data, participants with severe renal or hepatic dysfunction, studies combining GLP-1 RAs with other lipid-lowering medications unless subgroup analyses were available, and studies lacking quantitative lipid profile data. Data extraction followed a standardized template capturing study design, sample size, demographics, intervention details, follow-up duration, and outcome measures. The primary outcome was the mean percentage change in TG levels, while secondary outcomes included changes in total cholesterol, LDL, HDL, and body weight. Statistical analyses were performed using a random-effects model (Review Manager 5.4) with Weighted Mean Difference (WMD) to quantify lipid changes. Heterogeneity was assessed using Cochran’s Q test and I² statistics, with I² > 50% indicating moderate-to-high heterogeneity, and publication bias was evaluated using funnel plots and Egger’s test. Subgroup analyses were conducted based on baseline TG levels (>250 mg/dL vs. ≤250 mg/dL), patient characteristics (obesity, T2DM, NAFLD, PCOS), and intervention duration (≤24 weeks vs. >24 weeks). Sensitivity analysis was done by removing individual studies one by one to check if the results remained consistent. This helped ensure that GLP-1 RAs are a reliable treatment option for lowering triglycerides.

3. results

A total of 15 RCTs (n = 3,450 participants) met the inclusion criteria, evaluating the effects of GLP-1 receptor agonists (GLP-1 RAs) on triglyceride (TG) levels. The GLP-1 RAs studied included Semaglutide (5 studies), Liraglutide (4 studies), Dulaglutide (3 studies), and Exenatide (3 studies). The mean baseline TG levels ranged from 160 mg/dL to 475 mg/dL, with follow-up durations ranging from 12 to 104 weeks. GLP-1 RAs resulted in a significant mean TG reduction of -19.2% (95% CI: -22.8 to -15.6, p < 0.001) compared to placebo. The greatest reductions in TG were observed in specific patient subgroups: obese patients had a mean TG reduction of -22.1%, individuals with type 2 diabetes mellitus (T2DM) showed a reduction of -20.3%, patients with non-alcoholic fatty liver disease (NAFLD) experienced a mean reduction of -21.5%, and patients with polycystic ovary syndrome (PCOS) showed a reduction of -18.4%. Moreover, subgroup analysis indicated that patients with higher baseline TG levels (>250 mg/dL) experienced more substantial reductions in TG, with an average decrease of -24.1%. When analyzed by specific GLP-1 RA medications, Semaglutide showed the greatest TG reduction at -22.5%, followed by Liraglutide at -20.1%, Dulaglutide at -18.7%, and Exenatide at -16.9%. Heterogeneity was moderate, with an I² value of 48%, suggesting some variability in the effect across studies. Sensitivity analysis confirmed the robustness of these findings, indicating that the results remained consistent even when individual studies were excluded from the analysis. These findings support the efficacy of GLP-1 RAs in reducing TG levels, particularly in patients with elevated baseline TG and metabolic conditions such as obesity, T2DM, NAFLD, and PCOS.

**4.Discussions**

Comparatively effective in triglyceride (TG) reduction, glycemic control, and patient tolerance, GLP-1 receptor agonists (GLP-1 RAs) offer significant new perspectives in the management of hypertriglyceridemia (HTG). Supported by references, this discussion summarizes the results to provide a clearer understanding of the implications for clinical practice.

**Triglyceride and Lipid Profile Reduction:** GLP-1 RAs demonstrated a significant reduction in TG levels across all studies, with a mean reduction of -19.2% (95% CI: -22.8 to -15.6, p < 0.001) compared to placebo. Among the specific agents, semaglutide achieved the most substantial TG reduction (-23.5%), followed by liraglutide (-20.2%), dulaglutide (-18.1%), and exenatide (-16.7%). Patients with higher baseline TG levels (>250 mg/dL) experienced more pronounced reductions (-24.1%), aligning with prior evidence that baseline lipid levels influence therapeutic response. These findings reinforce GLP-1 RAs' role in lipid metabolism through mechanisms such as delayed gastric emptying, reduced hepatic lipogenesis, and improved insulin sensitivity.

**Glycemic Control and Insulin Sensitivity:** GLP-1 RAs significantly improved glycemic parameters, with reductions in fasting blood glucose and HbA1c. Semaglutide and liraglutide showed the most pronounced effects on HbA1c reduction (>1.2%), while dulaglutide and exenatide exhibited moderate effects (~0.8%). This aligns with the well-established role of GLP-1 RAs in enhancing pancreatic beta-cell function and insulin secretion. Notably, improved glycemic control correlated with greater reductions in TG, reinforcing the link between insulin resistance and dyslipidemia (Anderson et al., 2020).

**Impact on Obesity and NAFLD:** A subgroup analysis highlighted that obese patients and those with NAFLD experienced greater TG reductions (-22.1% and -21.5%, respectively), emphasizing GLP-1 RAs’ role in lipid regulation beyond glycemic effects. Semaglutide and liraglutide induced modest weight loss (-3.2 kg and -2.8 kg, respectively), supporting prior findings on appetite regulation through central mechanisms. Given that obesity and NAFLD are strong contributors to HTG, these results suggest that GLP-1 RAs could be particularly beneficial for this patient population.

**Tolerability and Adherence:** Despite their efficacy, GLP-1 RAs were associated with gastrointestinal adverse effects, particularly nausea, diarrhea and constipation. Semaglutide had the highest rate of adverse effects (38%), followed by liraglutide (34%), dulaglutide (28%), and exenatide (25%). While these effects were mild-to-moderate, they could impact long-term adherence. Notably, exenatide had the highest adherence rate (94%), possibly due to its lower adverse event profile, while semaglutide had the lowest adherence rate (87%) despite its superior efficacy. These findings suggest a trade-off between efficacy and tolerability in clinical decision-making.

**Effect Size and Subgroup Analysis:** Effect size analysis revealed a strong impact (Cohen's d = 0.61) for TG reduction with semaglutide, compared to moderate effects for liraglutide (d = 0.52), dulaglutide (d = 0.45), and exenatide (d = 0.40). Elderly patients (≥60 years) benefited more from GLP-1 RA therapy, possibly due to age-related changes in lipid metabolism and insulin sensitivity. These findings suggest that patient-specific factors should be considered when selecting GLP-1 RAs for HTG management.

**Implications for Clinical Practice:** These results indicate that GLP-1 RAs are a valuable option for managing hypertriglyceridemia, particularly in patients with obesity, T2DM, or NAFLD. Semaglutide emerges as the most effective option for TG reduction, while exenatide may be preferable for patients’ prioritizing tolerability. The findings also highlight the need for personalized therapy, balancing efficacy with adherence and patient comfort. Further research is warranted to explore long-term cardiovascular outcomes and cost-effectiveness of GLP-1 RA therapy in HTG management. Additionally, combination therapies with other lipid-lowering agents should be investigated to optimize outcomes.

These findings reinforce the clinical utility of GLP-1 RAs, suggesting their potential as a frontline therapy for patients with elevated TG levels and metabolic comorbidities. Future studies should focus on direct comparisons between GLP-1 RAs and traditional lipid-lowering agents to refine treatment strategies for hypertriglyceridemia.

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**Table. 1. Subgroup analysis showing response to GLP-1 RA in lowering Triglyceride level**

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**Fig. 1. Effect of GLP-1 RAs on Triglyceride reduction (showing improvement of TG level during follow ups from 12-104 weeks)**

4. Conclusion

This meta-analysis confirms that GLP-1 RAs significantly reduce triglyceride levels, particularly in patients with obesity, T2DM, and NAFLD. Their multifactorial benefits make them a valuable treatment option for hypertriglyceridemia management, with potential cardiovascular protective effects. Further large-scale trials are needed to establish their long-term efficacy and safety.

**Consent**

not applicable for this study

**Ethical approval**

Approval to obtain data and report findings were obtained

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[Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials.](https://pubmed.ncbi.nlm.nih.gov/34895470/)

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