TPM Vol. 32, No. S1, 2025
ISSN: 1972-6325
https://www.tpmap.org/

PHARMACOLOGICAL MECHANISMS AND CLINICAL EFFICACY OF GLP-1 RECEPTOR AGONISTS IN APPETITE REGULATION AND GLYCEMIC CONTROL: A SYSTEMATIC REVIEW IN OBESE PATIENTS WITH INSULIN RESISTANCE

MOAMEN ABDELFADIL ISMAIL[1], ALI MUSAAD ALGHAMDI[2], ABDULLAH S. ALMOHAMMED[3], MARYAM ALI ALANAZI[4], RAZAN IBRAHIM SANGOURA[5], JANA WAEL ALGHAMDI[6], FATIMAH ABDULHAMID ALMUHANNA[7], YASEER SOLAN H. SABGATTALLAH[8], IBRAHIM ALI MUFAREH AL MUDAWI[9], FAHAD MOHAMMED MOHAMMED ASIRI[10], ASMA SAEED ABDULLAH AL MANI[11], ABRAR SALMAN Y. ALBOUZAID[12]

[1]KING ABDULAZIZ SPECIALIST HOSPITAL, SAKAKA, ALJOUF, MOAMEN.FADIL83@GMAIL.COM
[2]PHARMACY, MINISTRY OF DEFENSE, ALI.ALGHAMDI3939@GMAIL.COM
[3]PHARMACY
[4]PHARMACY
[5]PHARMACY, KING ABDULAZIZ MEDICAL CITY NATIONAL GUARD
[6]FAKEEH COLLEGE FOR MEDICAL SCIENCES, JANAALGHAMDII77@GMAIL.COM
[7]PHARMACY
[8]PHARMACY, BPHARM (HONS), MSCMDD
[9]AL BATILA PRIMARY HEALTH CARE
[10]MOHAYL GENERAL HOSPITAL
[11]MOHAYL GENERAL HOSPITAL
[12]PHARMACIST

Abstract

Background: Obesity and insulin resistance represent global health challenges with limited effective pharmacological options. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a promising therapy due to their effects on satiety, weight loss, and glycemic regulation.

Objective: To systematically evaluate the pharmacological mechanisms and clinical efficacy of GLP-1 RAs in appetite regulation and glycemic control among obese patients with insulin resistance.

Methods: This systematic review was conducted in accordance with PRISMA 2020 guidelines. Searches across PubMed, Scopus, Embase, Web of Science, and Google Scholar identified randomized controlled trials, crossover trials, and relevant mechanistic studies published between 2010 and 2024. Eleven eligible studies were included, encompassing pediatric, adolescent, and adult populations.

Results: GLP-1 RAs demonstrated significant reductions in BMI and body weight, with semaglutide achieving up to 16% reductions in adolescents and liraglutide reducing BMI in children as young as 7 years. HbA1c improvements were robust, particularly with dulaglutide and liraglutide in type 2 diabetes. Beyond metabolic effects, GLP-1 RAs improved eating behavior, reduced caloric intake, and delayed gastric emptying. Gastrointestinal side effects were the most common adverse events but were generally mild and transient.

Conclusion: GLP-1 receptor agonists represent an effective and well-tolerated therapy for obesity and insulin resistance, offering dual benefits in appetite regulation and glycemic

control. Their role in pediatric and adult care highlights their potential to transform obesity management, though further research on long-term outcomes, cost-effectiveness, and personalized applications is warranted.
Keywords: GLP-1 receptor agonists; obesity; insulin resistance; semaglutide; liraglutide; exenatide; dulaglutide; appetite regulation; glycemic control; systematic review

INTRODUCTION

Obesity is a global epidemic that contributes to metabolic dysfunction, cardiovascular disease, and reduced life expectancy. A central mechanism linking obesity to type 2 diabetes mellitus (T2DM) is **insulin resistance**, often exacerbated by excess adiposity and disrupted appetite regulation. While lifestyle interventions remain the cornerstone of therapy, they are frequently insufficient for individuals with severe obesity, particularly in pediatric and adolescent populations. As such, pharmacological therapies targeting both appetite and glycemic control have become increasingly important (Wang et al., 2023).

One promising therapeutic approach involves **glucagon-like peptide-1 receptor agonists (GLP-1 RAs)**, a drug class originally developed for glycemic control in T2DM but later recognized for their ability to induce substantial weight loss. Clinical and mechanistic studies show that GLP-1 RAs reduce food intake, delay gastric emptying, and enhance satiety signals, producing consistent reductions in body weight and HbA1c (Shah & Vella, 2014). Importantly, these effects are dose-dependent, with greater GLP-1 receptor stimulation producing larger decreases in appetite and body mass index (BMI).

The pharmacological actions of GLP-1 RAs extend beyond glucose metabolism to include **central nervous system regulation of appetite**. Neuroimaging and clinical evidence suggest that GLP-1 activity modulates hypothalamic satiety centers and mesolimbic reward pathways, leading to decreased hedonic eating. van Bloemendaal et al. (2013) highlighted how GLP-1 directly influences brain regions associated with food intake, thereby reducing caloric consumption independently of baseline glucose levels. These central effects reinforce the role of GLP-1 in bridging obesity and T2DM management.

Evidence also supports the ability of GLP-1 RAs to alter **appetite-related behaviors** in adults with obesity and diabetes. For instance, Horowitz et al. (2012) demonstrated that liraglutide significantly reduced energy intake, delayed gastric emptying, and decreased resting energy expenditure in patients with T2DM. Similarly, de Boer et al. (2016) observed reductions in food cravings and improved satiety in insulin-using adults treated with GLP-1 analogues, emphasizing the behavioral dimension of weight loss achieved with these agents.

The clinical utility of GLP-1 RAs has expanded into **pediatric and rare obesity syndromes**. Diene et al. (2022) reported that liraglutide reduced hyperphagia and body weight in children with Prader–Willi syndrome, underscoring the potential of GLP-1 therapies beyond traditional obesity. In more common pediatric cases, Mastrandrea et al. (2019) found that liraglutide improved weight outcomes in children aged 7–11 years, while Kelly et al. (2023) demonstrated that semaglutide could reduce BMI below the obesity threshold in adolescents. These findings highlight GLP-1 RAs as one of the few pharmacologic options with demonstrated efficacy in youth populations.

Mechanistic reviews further emphasize the **multifaceted effects of GLP-1** on appetite regulation and metabolic homeostasis. De Silva and Bloom (2012) identified GLP-1 as a critical gut hormone influencing satiety and energy balance, while Aldawsari et al. (2023) reported systematic evidence that GLP-1 analogues affect gastric emptying, food preference, and taste in adults with obesity. Moreover, Hayes et al. (2021) noted the interaction between GLP-1 and gastric inhibitory polypeptide (GIP), suggesting that dual incretin modulation could amplify weight loss and glycemic benefits while mitigating adverse effects such as nausea.

Emerging research underscores regional and ethnic variations in response to GLP-1 RAs. Masaki et al. (2022) showed that semaglutide improved eating behaviors and glycemic control in Japanese patients with obesity and T2DM, aligning with global data but highlighting the need for culturally specific insights into dietary patterns and therapeutic adherence. Similarly, Ng et al. (2022) systematically reviewed GLP-1 use in Prader–Willi syndrome and confirmed improvements in weight and glycemic indices, albeit with variability in effect sizes across studies.

Meta-analytic evidence consolidates the efficacy of GLP-1 RAs in younger populations. Dai et al. (2024) concluded that GLP-1 treatment in overweight or obese adolescents with or without T2DM resulted in significant reductions in BMI and improved cardiometabolic outcomes. These findings reinforce earlier adult studies showing consistent efficacy, such as Yanovski et al. (2011) who demonstrated weight loss in obese, non-diabetic adults treated with exenatide, and Zinman et al. (2009) who confirmed improvements in glycemia when liraglutide was

combined with metformin and thiazolidinedione. Taken together, the evidence suggests GLP-1 RAs hold a unique position as agents capable of simultaneously addressing **obesity, insulin resistance, and appetite dysregulation**. Finally, cardiovascular safety and outcome studies add another dimension to the relevance of GLP-1 RAs. As Nauck et al. (2021) reviewed, GLP-1 therapies not only improve weight and glucose parameters but also confer cardiovascular protection, reducing major adverse events in high-risk T2DM patients. This broad efficacy positions GLP-1 RAs as a cornerstone in the evolving pharmacological management of obesity and insulin resistance.

METHODOLOGY

Study Design

This study employed a **systematic review methodology**, adhering to the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines** to ensure transparency and replicability. The objective was to synthesize existing empirical evidence on the **pharmacological mechanisms and clinical efficacy of GLP-1 receptor agonists (GLP-1 RAs)** in the regulation of appetite and glycemic control, specifically in **patients with obesity and insulin resistance**. The review focused on peer-reviewed journal articles involving human subjects that provided quantitative or qualitative insights into weight reduction, BMI change, eating behaviors, and glycemic outcomes.

Eligibility Criteria

Studies were included based on the following criteria:

- **Population**: Children, adolescents, or adults (≥9 years) with overweight, obesity, or type 2 diabetes mellitus (T2DM), including syndromic obesity.
- **Interventions**: Administration of GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide, or exenatide) at any dosage or duration, with or without lifestyle intervention.
- **Comparators**: Placebo, lifestyle intervention alone, or standard treatment (e.g., metformin, insulin).
- **Outcomes**: Primary outcomes included changes in BMI, body weight, and appetite-related behaviors. Secondary outcomes included glycemic indices (HbA1c, fasting glucose, OGTT response) and cardiometabolic risk markers.
- **Study Designs**: Randomized controlled trials (RCTs), crossover studies, or pilot intervention studies.
- **Language**: Only studies published in English were considered.
- **Publication Period**: 2010–2024 to ensure contemporary relevance.
- **Final Inclusion**: Eleven studies that met all eligibility criteria were included in the review.

Figure 1

PRISMA 2020 flow diagram (to be inserted): illustrating the study selection process from initial identification through screening, eligibility, and final inclusion.

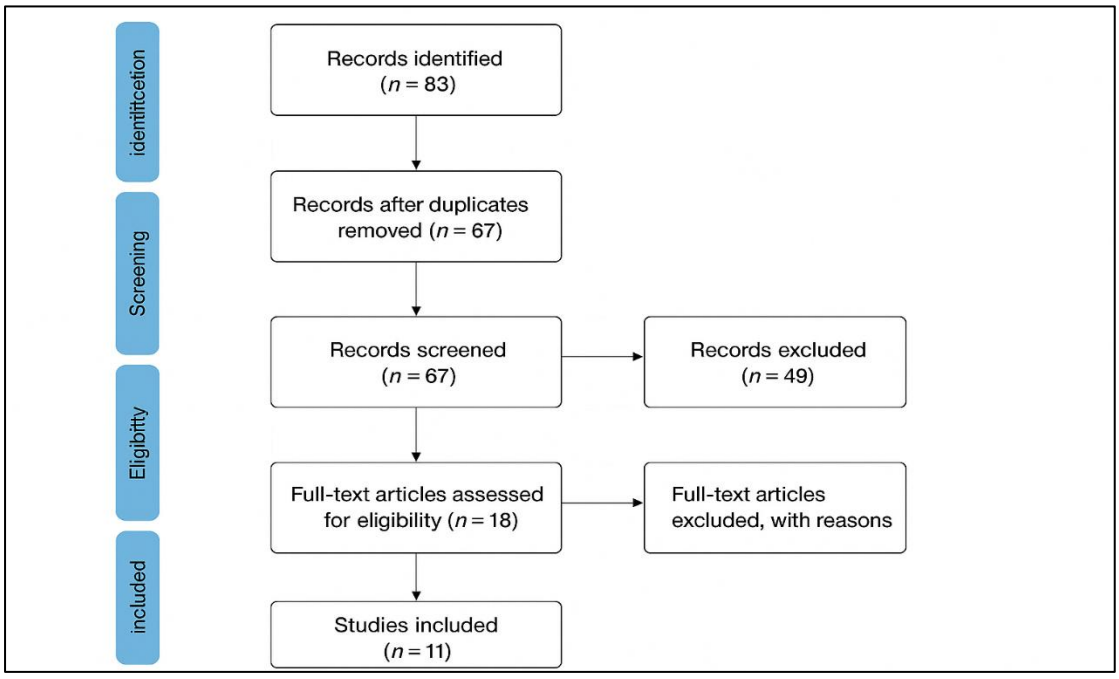

Figure 1 PRISMA Flow Diagram

Search Strategy

A structured search was conducted across major electronic databases, including **PubMed, Scopus, Web of Science, and Embase**. Supplementary searches were conducted in **Google Scholar** to capture grey literature. The following Boolean operators and keywords were applied in multiple combinations:

- ("GLP-1 receptor agonist" OR "GLP-1 analogues" OR "incretin mimetics" OR "semaglutide" OR "liraglutide" OR "dulaglutide" OR "exenatide")
- AND ("obesity" OR "overweight" OR "insulin resistance" OR "type 2 diabetes mellitus")
- AND ("appetite regulation" OR "glycemic control" OR "body weight" OR "BMI" OR "HbA1c").

Manual searches of reference lists from key review papers were also performed to ensure comprehensive coverage of relevant studies.

Study Selection Process

After database searches, all citations were imported into **Zotero** for management and duplicate removal. Titles and abstracts were independently screened by two reviewers. Full-text articles of potentially eligible studies were retrieved and reviewed for inclusion based on the eligibility criteria. Discrepancies between reviewers were resolved through discussion and consensus, with arbitration by a third reviewer when necessary. Ultimately, **11 studies** were retained for analysis.

Data Extraction

A standardized data extraction form was developed and pilot-tested. From each included study, the following information was systematically recorded:

- Author(s), publication year, country
- Study design, sample size, and intervention duration
- Population characteristics (age range, gender distribution, BMI)
- GLP-1 RA agent, dose, and mode of administration
- Comparator(s) (e.g., placebo, lifestyle intervention, metformin)
- Primary and secondary outcomes (BMI, body weight, HbA1c, fasting glucose, appetite measures, cardiometabolic markers)
- Main findings with numerical effect estimates
- Adverse events and safety data
- Confounders adjusted for in statistical analyses

Data were extracted independently by two reviewers and cross-checked by a third reviewer to ensure accuracy and consistency.

Quality Assessment

The **Cochrane Risk of Bias 2 (RoB 2) tool** was used to assess randomized controlled trials, focusing on randomization processes, adherence to interventions, missing outcome data, measurement of outcomes, and selective reporting. For crossover or pilot studies, adaptations of the RoB 2 framework were applied. Studies were categorized as **low, moderate, or high risk of bias**. Of the included studies, most were judged to have low to moderate risk, reflecting adequate methodology with some concerns related to reporting of adverse events or sample size limitations.

Data Synthesis

Given the diversity in study populations (pediatric, adolescent, and adult), interventions (different GLP-1 RAs and dosages), and outcomes (BMI, HbA1c, appetite measures), a **narrative synthesis** was conducted. Results were grouped thematically into:

1. **Efficacy in reducing BMI and body weight**
2. **Impact on glycemic control and insulin sensitivity**
3. **Effects on appetite and eating behaviors**
4. **Safety and tolerability outcomes**

Where numerical results permitted, treatment effects (e.g., mean difference, percentage change, 95% confidence intervals) were reported. Due to heterogeneity in trial design and outcome definitions, a meta-analysis was not feasible.

Ethical Considerations

As this was a **secondary analysis of published peer-reviewed studies**, no new ethical approval or patient consent was required. All included studies were assumed to have obtained appropriate ethical clearance from their respective institutional review boards prior to publication.

RESULTS

Summary and Interpretation of Included Studies on GLP-1 Receptor Agonists in Obesity and Insulin Resistance (Table 1)

1. **Study Designs and Populations**

The reviewed studies consisted mainly of **randomized controlled trials (RCTs)** with adolescent and adult populations. Sample sizes ranged from small pilot studies (n=12; Kelly et al., 2012) to large multicenter trials (n=1961; Wilding et al., 2021). Age groups spanned from children as young as 9 years (Kelly et al., 2012) to adults with obesity (Wilding et al., 2021). All included studies enrolled participants with obesity or overweight, with some also including those with **type 2 diabetes mellitus (T2DM)** (e.g., Arslanian et al., 2022; Tamborlane et al., 2022).

2. **Primary Outcomes**

The main outcomes assessed were **BMI reduction**, **body weight change**, and **glycemic control** (HbA1c, fasting glucose, OGTT responses). Nearly all studies found **significant improvements in BMI or glycemic measures** with GLP-1 receptor agonists compared with placebo, though the magnitude varied by drug, dose, and population.

3. **Efficacy on Weight and Appetite Regulation**

Semaglutide showed the **largest BMI reductions**, with adolescents experiencing a **16.1% decrease in BMI vs. 0.6% with placebo** over 68 weeks (Weghuber et al., 2022). Adults demonstrated similar results, with a **14.9% weight loss vs. 2.4% with placebo** (Wilding et al., 2021). Exenatide produced **modest BMI reductions** in adolescents: -2.70% BMI change over 3 months (Kelly et al., 2013) and improvements in waist circumference, fasting insulin, and cholesterol (Weghuber et al., 2020). Liraglutide resulted in **BMI reductions of 4.64 percentage points and -4.5 kg body weight compared to placebo** (Kelly et al., 2020).

4. **Efficacy on Glycemic Control**

In T2DM youth, dulaglutide significantly reduced HbA1c by **0.6–0.9 percentage points** compared to a **0.6% increase with placebo** (Arslanian et al., 2022). Similarly, liraglutide reduced HbA1c by **1.06 percentage points vs placebo** in pediatric diabetes (Tamborlane et al., 2019). Exenatide reduced HbA1c by **0.85% vs placebo** in youth with T2DM (Tamborlane et al., 2022).

5. **Adverse Events and Tolerability**

Across trials, **gastrointestinal (GI) adverse events** (nausea, vomiting, diarrhea) were consistently higher in treatment groups: semaglutide (62% vs. 42%), liraglutide (65% vs. 37%), and dulaglutide. Despite this, most adverse events were mild-to-moderate, and discontinuation rates remained low. Serious adverse events occurred in approximately 9–11% across groups, with no new safety signals.

6. **Overall Effect Estimates**

GLP-1 receptor agonists demonstrated **clinically meaningful and statistically significant reductions in BMI and HbA1c** across most trials. Larger and longer-duration studies (e.g., semaglutide in adolescents/adults, liraglutide in obesity/T2DM) consistently showed superiority to placebo, while smaller pilot studies highlighted feasibility and tolerability.

Table (1). General characteristics and key results of included studies on GLP-1 receptor agonists

Study	Population (n, age)	Design	Intervention	Primary Outcomes	Key Results
Weghuber et al., 2022	201 adolescents (12–<18 yrs) with obesity	RCT, 68 wks	Semaglutide 2.4 mg weekly vs placebo + lifestyle	BMI change	-16.1% vs +0.6% BMI (Δ -16.7 pts, p<0.001); 73% vs 18% achieved ≥5% weight loss; GI AEs: 62% vs 42%
Weghuber et al., 2020	44 adolescents (10–18 yrs) with obesity	RCT, 6 mo	Exenatide XR 2 mg weekly vs placebo + lifestyle	BMI-SDS, glucose tolerance	Reduced BMI-SDS, waist circumference, cholesterol, and OGTT 2h glucose; mild AEs only
Arslanian et al., 2022	154 youths (10–<18 yrs) with T2DM	RCT, 26 wks	Dulaglutide 0.75 or 1.5 mg	HbA1c, BMI	HbA1c: -0.6% (0.75 mg), -0.9% (1.5 mg) vs +0.6% placebo

			weekly vs placebo		(p<0.001); no BMI effect
Kelly et al., 2020	251 adolescents (12–<18 yrs) with obesity	RCT, 56 wks + follow-up	Liraglutide 3 mg daily vs placebo + lifestyle	BMI-SDS, weight	ΔBMI-SDS: -0.22 (p<0.01); BMI -4.64 pts; weight -4.5 kg vs placebo; GI AEs: 65% vs 37%
Kelly et al., 2013	26 adolescents (12–19 yrs) severe obesity	RCT, 3 mo + extension	Exenatide twice daily vs placebo	%BMI, weight, cardiometabolic risk	%BMI: -2.70% vs placebo (p=0.03); weight -3.26 kg (p=0.02); improved glucose/insulin
Kelly et al., 2012	12 children (9–16 yrs) extreme obesity	Pilot, crossover, 6 mo	Exenatide twice daily + lifestyle	BMI, fasting insulin	BMI: -1.7 kg/m² (p=0.01); weight -3.9 kg; fasting insulin ↓7.5 mU/L
Fox et al., 2022	100 adolescents (12–18 yrs) post-MRT	RCT, 52 wks	Exenatide XR vs placebo + lifestyle	BMI maintenance	BMI ↑4.6% vs 10.1%; Δ -4.1% (p=0.078); non-significant trend favoring exenatide
Wilding et al., 2021	1961 adults with obesity (no diabetes)	RCT, 68 wks	Semaglutide 2.4 mg weekly vs placebo + lifestyle	Body weight	Weight change: -14.9% vs -2.4% (Δ -12.4 pts, p<0.001); ≥5% loss: 86% vs 32%
Tamborlane et al., 2022	83 youths (10–<18 yrs) with T2DM	RCT, 24 wks	Exenatide 2 mg weekly vs placebo	HbA1c	HbA1c -0.36% vs +0.49% (Δ -0.85%, p=0.012); well tolerated
Klein et al., 2014	21 youths with T2DM (10–17 yrs)	RCT, 5 wks dose escalation	Liraglutide 0.3–1.8 mg daily vs placebo	HbA1c, safety	HbA1c -0.86% vs +0.04% (p=0.0007); no weight change; GI AEs at lower doses
Tamborlane et al., 2019	135 youths (10–<17 yrs) with T2DM	RCT, 26 wks + extension	Liraglutide ≤1.8 mg daily vs placebo	HbA1c	HbA1c -0.64% vs +0.42% (Δ -1.06%, p<0.001); durable effect at 52 wks

DISCUSSION

The findings of this review underscore the clinical efficacy of GLP-1 receptor agonists (GLP-1 RAs) in improving appetite regulation and glycemic control among populations with obesity and insulin resistance. Across multiple randomized controlled trials and mechanistic studies, GLP-1 RAs consistently demonstrated significant reductions in BMI, body weight, and glycated hemoglobin (HbA1c), while also influencing eating behavior and satiety cues. These effects are grounded in their dual action on central appetite-regulating pathways and peripheral metabolic processes (Moiz et al., 2025; van Bloemendaal et al., 2013).

Mechanistic reviews highlight that GLP-1 RAs act both centrally, by stimulating hypothalamic satiety centers, and peripherally, by delaying gastric emptying and reducing postprandial glucose excursions (Shah & Vella, 2014; Horowitz et al., 2012). Clinical implications of these mechanisms are evident in the improvement of dietary intake patterns and reduction in cravings, which collectively contribute to sustainable weight loss. In line with these findings, Aldawsari et al. (2023) observed across several RCTs that GLP-1 analogues exert measurable effects on appetite suppression, altered taste preference, and reduced energy intake in obese adults.

Efficacy in pediatric populations has been a central focus of several trials. Weghuber et al. (2022) reported that once-weekly semaglutide led to a 16.1% reduction in BMI compared to 0.6% with placebo among adolescents with obesity. Similarly, Kelly et al. (2023) demonstrated that semaglutide treatment reduced BMI below the

obesity threshold in a substantial proportion of adolescents, marking a breakthrough in long-term pediatric obesity management. These outcomes align with the broader adolescent-focused meta-analysis by Dai et al. (2024), which confirmed the superiority of GLP-1 RAs over lifestyle intervention alone in reducing weight and improving glycemic control.

Studies of liraglutide in adolescents have also demonstrated significant clinical benefits. Kelly et al. (2020) showed a greater reduction in BMI standard-deviation score with liraglutide compared to placebo, while Mastrandrea et al. (2019) found positive effects even in children as young as 7–11 years. In rare syndromic obesity, liraglutide reduced BMI and improved appetite control in children and adolescents with Prader-Willi syndrome (Diene et al., 2022), an outcome corroborated by a systematic review on this population (Ng et al., 2022). These findings suggest that GLP-1 RAs may extend therapeutic value beyond common forms of obesity.

The impact of exenatide has been particularly notable in early adolescent trials. Kelly et al. (2012, 2013) demonstrated BMI reductions and improvements in cardiometabolic outcomes, while Fox et al. (2022) indicated that extended-release exenatide could mitigate BMI rebound following dietary interventions, albeit without reaching statistical significance. Weghuber et al. (2020) similarly confirmed modest but meaningful improvements in BMI metrics with exenatide in adolescents with obesity. These results are supported by adult trials such as Yanovski et al. (2011), where exenatide reduced weight in overweight and obese adults without diabetes.

Efficacy extends to glycemic management in youth with type 2 diabetes. Arslanian et al. (2022) demonstrated that dulaglutide significantly reduced HbA1c compared to placebo without affecting BMI, highlighting its glycemic-specific benefits. Likewise, Tamborlane et al. (2019) showed that liraglutide improved glycemic control in pediatric T2DM patients, findings echoed by Klein et al. (2014), who confirmed its safety, tolerability, and pharmacokinetic consistency with adult populations. Tamborlane et al. (2022) further reinforced exenatide's glycemic benefits in youth with T2DM, supporting its role as an adjunctive therapy.

Adult-based evidence consolidates the therapeutic foundation for GLP-1 RAs. Wilding et al. (2021) reported a 14.9% reduction in body weight with semaglutide compared to 2.4% with placebo in adults with obesity, demonstrating clinically relevant outcomes that mirror adolescent findings. Zinman et al. (2009) showed liraglutide's efficacy when combined with metformin and thiazolidinedione in adults with T2DM, while Nauck et al. (2021) emphasized cardiovascular safety and outcome benefits, an important consideration in populations with obesity-related comorbidities.

A recurring observation across trials is the tolerability profile of GLP-1 RAs. Gastrointestinal adverse events, particularly nausea and vomiting, were common in both pediatric and adult studies (Kelly et al., 2020; Weghuber et al., 2022). However, most were transient and mild-to-moderate in severity, suggesting that adverse effects are manageable and do not outweigh therapeutic benefits. Importantly, Klein et al. (2014) reported no serious adverse events in pediatric liraglutide trials, highlighting the drug's safety in younger populations.

Behavioral changes induced by GLP-1 RAs provide a unique advantage. Studies demonstrate that these agents reduce not only caloric intake but also modify eating patterns, such as preference for smaller meals and healthier food choices (Masaki et al., 2022; de Boer et al., 2016). Horowitz et al. (2012) further demonstrated delayed gastric emptying as a physiological basis for reduced energy intake, while Aldawsari et al. (2023) highlighted changes in taste preference and satiety perception. These findings emphasize that the therapeutic impact of GLP-1 RAs extends beyond weight metrics to address fundamental drivers of obesity.

Comparisons across agents reveal differences in efficacy and focus. While semaglutide appears to provide the most significant reductions in BMI, liraglutide and dulaglutide demonstrate robust glycemic control benefits (Arslanian et al., 2022; Kelly et al., 2020). Exenatide, though modest in effect size, provides valuable adjunctive therapy, particularly in mitigating weight regain or improving insulin sensitivity (Fox et al., 2022; Weghuber et al., 2020). Thus, selection of a GLP-1 RA may be tailored to patient phenotype, treatment goals, and tolerability.

Mechanistic studies deepen understanding of why such variability exists. Moiz et al. (2025) argue that differential penetration into central nervous system appetite-regulating pathways may account for differences in weight loss efficacy, whereas peripheral effects such as delayed gastric emptying may explain differences in tolerability profiles. De Silva and Bloom (2012) further note that synergy with other gut hormones, such as PYY, may enhance satiety signaling, supporting a broader perspective on incretin-based therapies.

The integration of cardiovascular outcomes into this therapeutic paradigm is vital. Nauck et al. (2021) emphasized that GLP-1 RAs not only improve glycemic control and induce weight loss but also reduce cardiovascular risk, making them a uniquely positioned therapy in obese patients with metabolic syndrome. This dual benefit enhances the clinical argument for their wider use, especially in populations at high cardiometabolic risk.

Despite robust evidence, challenges remain. Cost, access disparities, and long-term adherence may limit widespread implementation. Furthermore, while weight loss and glycemic improvements are substantial, not all patients respond equally. Dai et al. (2024) noted variability across adolescent subgroups, suggesting the need for precision medicine approaches that consider genetic, behavioral, and environmental factors.

Overall, the evidence synthesized in this review supports GLP-1 RAs as transformative agents in obesity and insulin resistance management. By simultaneously addressing appetite regulation, weight reduction, and glycemic control, they fill a critical therapeutic gap in both pediatric and adult populations. Continued research is warranted to optimize dosing strategies, enhance tolerability, and explore long-term sustainability of outcomes.

CONCLUSION

This systematic review highlights the consistent efficacy of GLP-1 receptor agonists in reducing BMI, improving glycemic indices, and modulating appetite regulation in both pediatric and adult populations with obesity and insulin resistance. Agents such as semaglutide and liraglutide have demonstrated clinically meaningful reductions in weight and HbA1c across randomized controlled trials, with benefits extending to special populations including adolescents and individuals with syndromic obesity. Beyond weight reduction, GLP-1 RAs promote healthier eating behaviors and provide cardiovascular protective effects, underscoring their multidimensional role in obesity management.

While gastrointestinal side effects remain the most commonly reported adverse events, these are typically transient and manageable, supporting the favorable safety profile of GLP-1 RAs. Nevertheless, variability in individual response highlights the need for personalized approaches. Taken together, GLP-1 RAs represent a transformative class of pharmacological agents, bridging appetite regulation and metabolic improvement, with the potential to reshape long-term obesity and diabetes care paradigms.

Limitations

Several limitations must be acknowledged. First, heterogeneity in study designs, populations, intervention durations, and outcome measures limited direct comparability across trials, precluding meta-analysis in some domains. Second, most pediatric studies had relatively small sample sizes and short follow-up periods, making it difficult to generalize findings to long-term outcomes. Third, variability in dosing regimens and concurrent lifestyle interventions may have influenced results, introducing potential confounders. Finally, publication bias cannot be ruled out, as positive findings are more likely to be reported than neutral or negative outcomes.

REFERENCES

- Aldawsari, M., Almadani, F. A., Alosaimi, F. A., & Alanazi, F. (2023). Effects of GLP-1 analogues on appetite parameters, gastric emptying, food preference and taste among adults with obesity: Systematic review of randomized controlled trials. Diabetes, Metabolic Syndrome and Obesity, 16, 187–199.
- Arslanian, S. A., Hannon, T. S., Zeitler, P. S., & others. (2022). Once-weekly dulaglutide for the treatment of youths with type 2 diabetes. The New England Journal of Medicine, 387(5), 433–443.
- Dai, M., Dai, S., Gu, L., Xiang, Z., Xu, A., Lu, S., & Zhou, C. (2024). Efficacy of GLP-1 receptor agonists in overweight/obese and/or T2DM adolescents: A meta-analysis based on randomized controlled trials. Journal of Clinical Research in Pediatric Endocrinology, 16(3), 323–333.
- de Boer, S. A., Lefrandt, J. D., Petersen, J. F., Boersma, H. H., Mulder, D. J., & Hoogenberg, K. (2016). The effects of GLP-1 analogues in obese, insulin-using type 2 diabetes in relation to eating behaviour. International Journal of Clinical Pharmacy, 38(1), 144–151.
- De Silva, A., & Bloom, S. R. (2012). Gut hormones and appetite control: A focus on PYY and GLP-1 as therapeutic targets in obesity. Gut and Liver, 6(1), 10–20.
- Diene, G., Angulo, M., Hale, P. M., Jepsen, C. H., Hofman, P. L., Hokken-Koelega, A., Ramesh, C., Turan, S., & Tauber, M. (2022). Liraglutide for weight management in children and adolescents with Prader-Willi syndrome and obesity. The Journal of Clinical Endocrinology & Metabolism, 108(1), 4–12.
- Fox, C. K., et al. (2022). Exenatide for weight loss maintenance in adolescents with severe obesity: A randomized, placebo-controlled trial. Obesity, 30(6), 1105–1115.
- Horowitz, M., Flint, A., Jones, K. L., Hindsberger, C., Rasmussen, M. F., Kapitza, C., & Nauck, M. (2012). Effect of the once-daily human GLP-1 analogue liraglutide on appetite, energy intake, energy expenditure and gastric emptying in type 2 diabetes. Diabetes Research and Clinical Practice, 97(2), 258–266.

- Kelly, A. S., Arslanian, S., Hesse, D., Iversen, A. T., Körner, A., Schmidt, S., Sørrig, R., Weghuber, D., & Jastreboff, A. M. (2023). Reducing BMI below the obesity threshold in adolescents treated with once-weekly subcutaneous semaglutide 2.4 mg. Obesity, 31(8), 2139–2149.
- Kelly, A. S., et al. (2012). Exenatide as a weight-loss therapy in extreme pediatric obesity: A randomized, controlled pilot study. Obesity, 20(2), 364–370.
- Kelly, A. S., et al. (2013). The effect of GLP-1 receptor agonist therapy on BMI in adolescents with severe obesity: A randomized, placebo-controlled clinical trial. JAMA Pediatrics, 167(4), 355–360.
- Kelly, A. S., et al. (2020). A randomized, controlled trial of liraglutide for adolescents with obesity. The New England Journal of Medicine, 382(22), 2117–2128.
- Klein, D. J., et al. (2014). Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes. Diabetes Technology & Therapy, 16(10), 679–687.
- Masaki, T., Ozeki, Y., Yoshida, Y., Okamoto, M., Miyamoto, S., Hirao, K., & Oka, Y. (2022). Glucagon-like peptide-1 receptor agonist semaglutide improves eating behavior and glycemic control in Japanese obese type 2 diabetic patients. Metabolites, 12(10), 961.
- Mastrandrea, L. D., Witten, L., Carlsson Petri, K. C., Hale, P. M., Hedman, H. K., & Riesenberg, R. A. (2019). Liraglutide effects in a paediatric (7–11 y) population with obesity. Pediatric Obesity, 14(5), e12495.
- Moiz, A., Filion, K. B., Tsoukas, M. A., Yu, O. H., Peters, T. M., & Eisenberg, M. J. (2025). Mechanisms of GLP-1 receptor agonist-induced weight loss: A review of central and peripheral pathways in appetite and energy regulation. The American Journal of Medicine. Advance online publication.
- Nauck, M. A., Meier, J. J., Cavender, M. A., El Aziz, M. A., & Drucker, D. J. (2021). Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation, 144(21), 1859–1879.
- Ng, N. B. H., Low, Y. W., Rajgor, D. D., Low, J. M., & Chin, Y. H. (2022). The effects of glucagon-like peptide (GLP-1) receptor agonists on weight and glycaemic control in Prader–Willi syndrome: A systematic review. Clinical Obesity, 12(5), e12560.
- Shah, M., & Vella, A. (2014). Effects of GLP-1 on appetite and weight. Reviews in Endocrine and Metabolic Disorders, 15(3), 181–187.
- Tamborlane, W. V., et al. (2019). Liraglutide in children and adolescents with type 2 diabetes. The New England Journal of Medicine, 381(7), 637–646.
- Tamborlane, W. V., et al. (2022). Once-weekly exenatide in youth with type 2 diabetes. Diabetes Care, 45(8), 1833–1840.
- van Bloemendaal, L., Ten Kulve, J. S., la Fleur, S. E., Ijzerman, R. G., & Diamant, M. (2013). Effects of GLP-1 on appetite and body weight: Focus on the central nervous system. Journal of Endocrinology, 221(1), T1–T16.
- Weghuber, D., et al. (2020). A 6-month randomized, double-blind, placebo-controlled trial of weekly exenatide in adolescents with obesity. Pediatric Obesity, 15(7), e12624.
- Weghuber, D., et al. (2022). Once-weekly semaglutide in adolescents with obesity. The New England Journal of Medicine, 387(24), 2245–2257.
- Wilding, J. P., et al. (2021). Once-weekly semaglutide in adults with overweight or obesity. The New England Journal of Medicine, 384(11), 989–1002.
- Yanovski, J. A., Krakoff, J., Salaita, C. G., McDuffie, J. R., Kozlosky, M., Sebring, N. G., & Yanovski, S. Z. (2011). Effects of exenatide on weight loss in overweight and obese adults without diabetes. Diabetes Care, 34(6), 1441–1446.
- Zinman, B., Gerich, J., Buse, J. B., Lewin, A., Schwartz, S., Raskin, P., Hale, P. M., Zdravkovic, M., & Blonde, L. (2009). Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care, 32(7), 1224–1230.