Int. J. Sci. R. Tech., 2026 3(8)
A Multidisciplinary peer-reviewed Journal
www.ijsrtjournal.com [ISSN: 2394-7063]

Original Article

GLP- 1 Receptor Agonists In Type 2 Diabetes And Obesity: Review Article

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ABSTRACT

Glucagon-Like Peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L-cells in response to nutrient intake. It regulates glucose homeostasis, appetite,and energy metabolism. GLP-1 receptor agonists mimic these physiological actions by stimulating glucose-dependent insulin secretion, suppressing glucagone release, delaying gastric emptying ,and promoting satiety. These mechanisms improve glycemic control and support significant weight reduction. This review highlights the therapeutic relevance of agents such as Semaglutide, Liraglutide, Dulaglutide, Exenatide, and Tirzepatide. Beyond glycemic control, these drugs demonstrate cardiovascular protection, improved lipid metabolism, and reduced systemic inflammation. Trizepatide, a dual GIP and GLP-1 receptor agonist, shows superior efficacy in both glucose lowering and weight reduction. Inhibition of dipeptidyl peptidase-4 (DPP-4) further prolongs incretin activity, enhancing outcomes. Overall, GLP-1 receptor agonists represent a physiologically based, highly effective strategy for managing type 2 diabetes and obesity.

Keywords: GLP-1, Incretin, DPP-4

INTRODUCTION

Glucagon-Like Peptide-1 (GLP-1) is released after meals and acts on multiple organs including the pancreas, stomach, brain, heart, and liver. Its major physiological functions include :

- Stiulating insulin secretion in a glucose-dependent manner
- Suppressing glucagon release
- Delaying gastric emptying
- Promoting satiety and reducing appetite

In type 2 diabetes and obesity, the natural incretin response is impaired. GLP-1 receptor agonists and dual incretin drugs restore this pathway, improving both blood glucose control and body weight regulation.[1]

LITERATURE REVIEW

The literature review provides a comprehensive and scholarly examination of glucagon-like peptide-1 receptor (GLP-1R) agonists, tracing their evolution from glycemic control agents in diabetes mellitus (DM) to multifaceted therapeutics with expanding indications in cardiovascular, renal, and metabolic health. We explore the underlying biological mechanisms, summarize clinical trial evidence, and highlight emerging applications in non-diabetic populations. Recent developments underscore the relevance of GLP-1R agonists in addressing the complex interplay of cardiovascular-kidney-metabolic (CKM) syndrome, microvascular dysfunction, and metabolic-associated steatohepatitis (MASH). We also discuss combination therapies and strategies to mitigate muscle mass loss during treatment and calls for targeted research, improved clinical education, and policy reforms to optimize the

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

translational potential of GLP-1R agonists in both individualized care and population health.[2]

Another study states that Glucagon-like peptide-1 (GLP-1) receptor agonists are incretin analogues that promote glucose-mediated insulin release and are used to treat type 2 diabetes mellitus and obesity. GLP-1 receptor agonists and GLP-1 and glucose-dependent insulinotropic peptide agonists have several mechanisms of action, including reduction in gastric emptying, inhibition of glucagon secretion, beneficial changes in the intestinal microbiome, and direct action on hypothalamic nuclei to enhance satiety (which promotes weight loss). Beyond the impressive effects of GLP-1 receptor agonists on blood glucose levels and body weight, large-scale randomized, controlled trials have shown that GLP-1 receptor agonists reduce cardiovascular risk and slow progression to renal failure in persons at high risk and those with type 2 diabetes. Adverse side effects from GLP-1 receptor agonists are mostly gastrointestinal but may also include loss of muscle and bone mass. Questions remain about long-term adherence, weight regain after discontinuation of treatment, and the functional implications of the loss of muscle and bone mass. Recent and ongoing targeted studies suggest the possibility of additional uses for GLP-1 receptor agonists.[3]

GLP-1 receptor agonists Action

1. **Semaglutide**

Mechanism of action

- Mimics the natural GLP-1 hormone

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- Stimulates insulin release only when glucose is high
- Suppresses glucagon secretion
- Delays gastric emptying
- Acts on hypothalamus to reduce appetite

Effect in Type 2 Diabetes

- Lowers HbA1c significantly
- Improves insulin sensitivity
- Reduces fasting and postprandial glucose

Effect in Obesity

- Strong appetite suppression
- Reduced calorie intake
- Significant visceral fat reduction
- Produces major weight loss

Additional Benefits

- Cardiovascular protection
- Reduced inflammation
- Fatty liver improvement

2. **Liraglutide**

Mechanism of action

- Daily GLP-1 analogue
- Enhances glucose – dependent insuline secretion
- Slows stomach emptying
- Increase satiety
- In Diabetes
- Controls blood glucose
- Low risk of hypoglycaemia
- Improves β-cell function

In Obesity

- Reduces hunger and emotional eating
- Helps gradual sustained weight loss

Special Point

- One of the first GLP-1 drugs approved for obesity management

3. **Dulaglutide**

Mechanism of action

- Long-acting weekly GLP-1 agonist
- Improves insulin release

- Decreases glucagon levels

In Diabetes

- Excellent HbA1c reduction
- Stable glucose control over 1 week

In Obesity

- Moderate weight loss effect
- Reduces appetite

Additional Benefit

- Strong evidence for cardiovascular risk reduction

4. Exenatide

Mechanism of action[7,8]

- Synthetic exendin-4 peptide
- Resistant to rapid enzymatic breakdown
- Enhances incretin action

In Diabetes

- Reduces post-meal glucose spikes
- Improves insulin secretion

In Obesity

- Mild to moderate weight reduction
- Earlier GLP-1 drug with shorter action duration

Limitation

- More gastrointestinal side effects in some patients

5. Tirzepatide

Mechanism of action

Acts on two incretin receptors:

1. GLP-1 receptor
2. GIP receptor

This dual action creates stronger metabolic effects.

In Diabetes

- Very powerful HbA1c reduction
- Improved insulin sensitivity
- Better glucose utilization

In Obesity

- Marked appetite suppression
- Greater fat mass reduction
- Highest weight loss among current peptide therapies

Metabolic Shift

- Enhances energy metabolism
- Improves lipid profile
- Reduces visceral and ectopic fat.

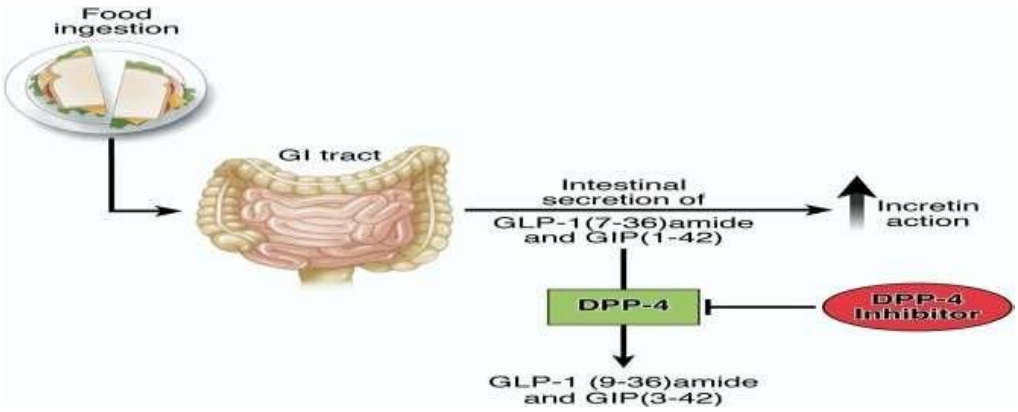

Figure : Bioactive GLP-1 and GIP are released from the small intestine after meal ingestion and enhance glucose stimulated insulin secretion (incretin action)[9]

Summary Of Metabolic Effects[4]

Drug	Main Action	Weight Loss	Diabetes Control
Semaglutide	GLP-1 agonist	Very high	Excellent
Liraglutide	GLP-1 agonist	Moderate–high	Excellent
Dulaglutide	Long-acting GLP-1	Moderate	Excellent
Exenatide	Early GLP-1 agonist	Mild–moderate	Good
Tirzepatide	GLP-1 + GIP dual agonist	Highest	Most powerful

Core Physiological Changes Produced

These agents collectively cause:

- Increased insulin secretion
- Reduced glucagon release
- Delayed gastric emptying
- Reduced appetite
- Increased satiety
- Fat mass reduction
- Improved insulin sensitivity
- Reduced systemic inflammation
- Better cardiovascular and renal outcome[9]

Simplified concept

- In Type 2 Diabetes
- They help the body
- Use insulin better
- produce insulin when needed,
- and reduce excess glucose production.

In Obesity

- They help the brain and stomach:
- feel full earlier,
- reduce cravings,
- and decrease calorie intake.[5,6]

CONCLUSION

This review focuses on regulating the mechanism of Glucagon-Like Peptide -1 which is an incretin hormones released rapidly after food intake the help regulate glucose metabolism and energy balance. Both hormones stimulate glucose-dependent insulin secretion through specific receptors on pancreatic beta-cell growth and reducing apoptosis GIP mainly supports energy storage by acting on adipose tissue and also promotes bone formation by stimulating osteoblast activity. In contrast, GLP-1 regulate blood glucose by slowing gastric emptying, suppressing glucagon secretion, and increasing satiety, leading to weight loss. Both incretins are rapidly degraded by the enzyme Dipeptidyl peptidase-4 (DPP-4). This led to the development of GLP-1 receptor agonists and DPP-4 inhibitors for treating Type 2 Diabetes. These therapies effectively lower HbA1c with minimal risk of weight gain and represent important physiologic approaches in modern diabetes management.

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HOW TO CITE: Sheeba Anitha Rani[1]*, Yerni Jyothi Kolli[2], Anusuyadevi V.[3], Prathima Prakasam[4], GLP- 1 Receptor Agonists In Type 2 Diabetes And Obesity: Review Article, Int. J. Sci. R. Tech., 2026, 3 (8), 361-365. https://doi.org/10.5281/zenodo.21872967