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Gastrointestinal and Extra-Metabolic Effects of GLP-1-Based Therapies: A Narrative Review

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ABSTRACT

The GLP-1 receptor agonists (GLP-1RAs) have become important drugs for use in the management of type 2 diabetes mellitus and obesity. Their metabolic effects, such as glycemic control and weight loss, are widely recognized, however, the growing evidence reveals that these therapies have substantial gastrointestinal and extra-metabolic effects via intricate interactions amongst the gut–pancreas–brain axis. This review offers a physiological evaluation of the gastrointestinal actions and the systemic effects of GLP-1–based therapies. A thorough literature search has been carried out on PubMed, Google Scholar, MDPI and other databases, with the inclusion of English language studies from 2016 to 2026. Data from clinical trials, experimental studies and review articles were reviewed to determine the key mechanisms, therapeutic potential, side effects and new applications. GLP-1RAs control glucose homeostasis by stimulating glucose-dependent insulin secretion, inhibiting glucagon, slowing gastric emptying and inducing satiety. Gastrointestinal side effects are common, such as nausea, vomiting, diarrhea, constipation and slowed gastric emptying which could affect adherence to treatment. In addition to metabolic effects, GLP-1-based drugs exhibit hepatoprotective, cardioprotective, renoprotective, anti-inflammatory, and neuroprotective effects. However, additional evidence has emerged that suggests potential applications in metabolic-associated steatohepatitis, cardiovascular disease, neurodegenerative diseases and addiction-related diseases. There are some potential benefits, however, gastrointestinal tolerability, long-term safety, cost, and patient selection are potential problems. In summary, GLP-1-based drugs are a new class of therapeutic agents that have multiple systems of action and use, and their applications go far beyond glycemic control and weight management.

Keywords: Glucagon-Like Peptide 1 Receptor Agonists; Diabetes Mellitus, Type 2; Obesity; Gastrointestinal Tract; Gastric Emptying.

INTRODUCTION

The global prevalence of various metabolic disorders have risen significantly over the past few decades due to the modern, "obesogenic" environment brought by the increase in the Processed-Food Industry being more accessible as well as people's lifestyles have become more sedentary with less motor activities required. This results in excessive calorie intake without doing the required amount of exercise or movement to use them, affecting both developed and developing countries. Type 2 Diabetes Mellitus, closely associated with Obesity and Insulin Resistance, increases due to said lifestyles, has also created major health challenges as well as due to increase in economic challenges worldwide, the healthcare costs have risen significantly while the quality of life and lifestyle cannot improve as quickly. It can also be said for obesity which is a nutritional disorder but also a chronic inflammatory condition that causes metabolic dysfunction (1). As the number of diseases continues to escalate, therapeutic methods such as GLP-1-based therapies, which provides efficient glycemic control in recent years due to its ability to stimulate improved glycemic control, reduced body weight and lower cardiovascular risk factors.

GLP-1 is an incretin hormone functions to control the blood glucose which are secreted enteroendocrine L cells lining the small intestine, specifically distal ileum, and colon (2). It potentiates insulin secretion in beta cells while simultaneously inhibiting the glucagon secretion from alpha cells during eating. Several medications have been made which schedule dosage for each kind (3). GLP-1 receptor agonists (GLP-1 RAs) are synthetic medications that are engineered to mimic the function of a natural GLP-1 secreted by the ileum and colon. Unlike the body's hormone, which degrades in minutes, the GLP-1 therapies can resist enzyme breakdown to stay longer, which helps for people suffering with obesity and type 2 diabetes (4). Several medications such as semaglutide, have clinical benefits and are increasingly prescribed for both diabetes management as well as for obesity control for non-diabetic individuals.

Many existing reviews discussing either regarding the metabolic outcomes or the gastrointestinal effects of GLP-1 therapies results in limited understanding on how these mechanisms interact. As GLP-1 receptor agonists (GLP-1RAs) function to act on gut-pancreas-brain axis, a clearer and broader evaluation on both gastrointestinal and extra-metabolic effects is crucial to understand the overall therapeutic significance.

Therefore, this review evaluates the extra-metabolic effects of GLP-1 based therapies by examining the physiological mechanism of GLP-1 signaling and the gut-pancreas-brain axis. This review further explores the gastrointestinal actions such as gastric motility, appetite regulation, satiety and digestive functions, while also providing clinical implications. By doing so, it will provide more in-depth understanding on how these therapies can influence multiple physiological systems beyond the glycemic control and weight reduction, helping in managing metabolic disorders such as Type 2 Diabetes Mellitus, obesity and other related complications.

METHODOLOGY

This is a narrative review study which explains gastrointestinal and extra-metabolic effects of GLP-1-based therapies. In this review we will discuss the existing evidence, regarding the mechanisms, actions, data, advantages and disadvantages and implications of GLP 1 receptor antagonists.

A comprehensive literature search was found by following databases such as PubMed, Google Scholar, MDPI etc and relevant articles published in English between 2015 till 2026. Additional studies were identified through manual screening of references list from selected articles.

This research involves combination of keywords and medical subject heading (MeSH) terms such as, GLP-1 receptor agonists, GLP-1 therapies, semaglutide, liraglutide, gastrointestinal effects, gastric emptying, hepatic effects, anti-inflammatory effects, cardiovascular protection and extra metabolic effects.

Studies were included in, if they discussed gastrointestinal outcomes or extra metabolic effects associated with GLP-1 therapies in humans or animal models. Observational studies, experimental studies and review articles were included. Articles unrelated to GLP-1 therapies, non-English

publications, conferences obstructed without full text access and studies with insufficient or unclear data were excluded from the review.

This Screening process involves reviewing article titles and abstracts to determine relevance. Full text versions of potentially eligible studies were then analyzed in detail, duplicate publications and unrelated articles were removed during the process.

Preferences were given to recent, high quality and clinically relevant studies to ensure the reliability and contemporary relevance of the findings. The selected articles were analyzed narratively to identify major themes, underlying mechanisms, clinical implications and current gaps in research regarding the gastrointestinal and extra metabolic effects of GLP 1 based therapies.

DISCUSSION

PHYSIOLOGY OF GLP-1 SIGNALING AND MECHANISMS

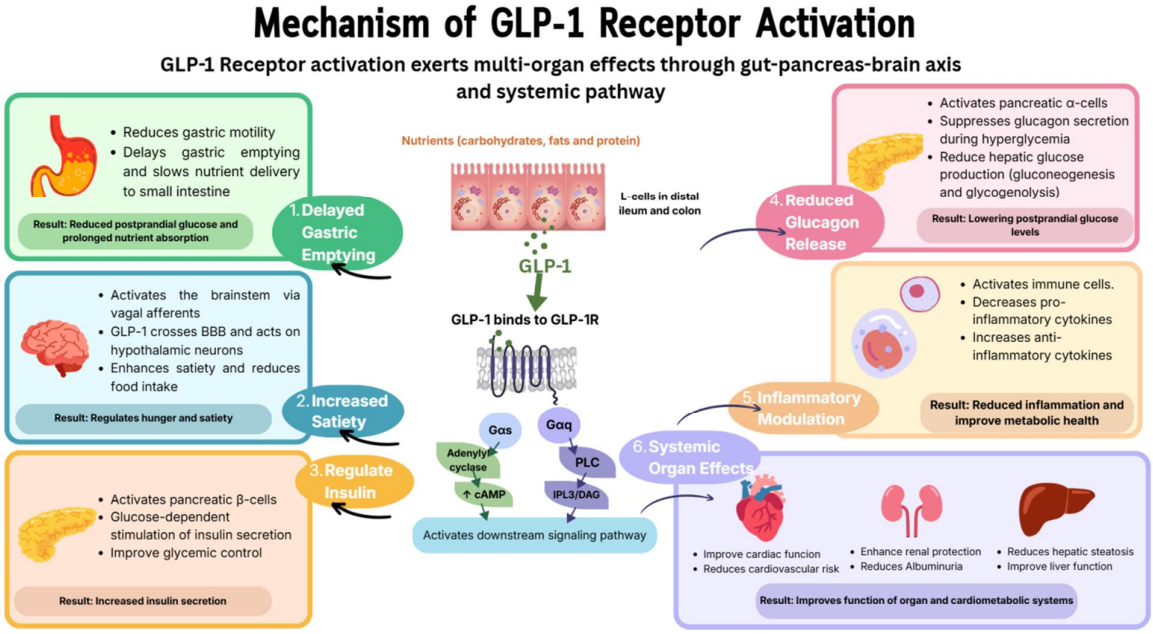
GLP-1 is released by enteroendocrine L-cells for digestion of nutrients such as carbohydrates and fats. After food intake, it is released and acted through gut-pancreas-brain axis to regulate postprandial metabolic responses. Although its lifespan is very short due to degradation by dipeptidyl peptidase-4, its physiological effects are still significant for digestion (5).

GLP-1 exerts its effect by first binding to the GLP-1 Receptor (GLP-1R), a member of the class B family of G protein-coupled receptors within glucagon superfamily. The C-terminal region of GLP-1 binds to the N-terminus of the GLP-1 receptor which then activates intracellular signaling pathways involving $G\alpha s$ and $G\alpha q$ proteins. This signaling cascades stimulation of cyclic AMP (cAMP) production and other downstream pathways responsible for insulin secretion, neural signaling and gastrointestinal regulation (6).

Incretin effect takes place when you consume glucose orally results with your body releasing insulin significantly more than when injecting the same amount of glucose intravenously. The incretin effect of GLP-1 is to enhance pancreatic insulin secretion when carbohydrates or fat are consumed. GLP-1 enhances glucose-dependent insulin secretion from pancreatic β-cells, along with this process, GLP-1 also suppresses glucagon release from pancreatic α-cells. This is because the glucagon is responsible for promoting hepatic glucose production, suppressing it helps reduce the risk of hyperglycemia by reducing the postprandial blood glucose level.

In individuals with Type 2 diabetes mellitus (T2DM), the insulinotropic response to GLP-1 is partially impaired called "GLP-1 resistance". This can result in loss of the incretin effect which leads to decrease in insulin secretion by the pancreatic β-cells and uncontrollable glucagon release causes the liver to release excess glucose into the bloodstream. It also leads to accelerated β-cell failure due to being under constant strain of high blood sugar (glucotoxicity), leading to accelerated apoptosis, which results in reduced capability of pancreas's insulin-producing capacity (7).

GLP-1 also affects several cells and tissues in the digestive system. In the stomach, it reduces gastric motility to help slow gastric emptying and transfer of nutrients into the small intestine. This helps in delaying glucose absorption and postprandial glucose spike (3). It also helps in promoting feeling fullness after meals by interacting with the vagal pathway to regulate gastrointestinal motility and digestive activity. This helps regulate appetite and satiety by GLP-1 receptors present in the hypothalamus and brainstem are responsible for controlling hunger and energy balance. In the brainstem pathway, when food enters small intestine, L-cells secrete GLP-1 which activates GLP-1R on adjacent vagal afferent nerve fibers that transmits signals to nucleus tractus solitarius (NTS) in brainstem, triggering feeling of fullness and satiation during a meal. In the Hypothalamus pathway, the GLP-1 circulates the bloodstream and enters via the blood-brain barrier of the brain at the arcuate nucleus (ARC) of hypothalamus. It can then stimulate specific neurons for feeling of satiety or hunger depending on the current necessity (8).



Mechanism of GLP-1 Receptor Activation : GLP-1 Receptor activation exerts multi-organ effects through gut-pancreas-brain axis and systemic pathway

OVERVIEW OF GLP-1-BASED THERAPIES

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), one of the evolving therapeutic groups for the treatment of metabolic diseases. They were initially created for the glycemic management of type 2 diabetes; however, some agents have demonstrated their additional benefits in reducing the risk of obesity and cardiovascular disease (9)

GLP-1 RAs improve satiety, prolong stomach emptying, reduce erroneous glucagon release, and improve glucose-dependent insulin secretion (10). FDA authorized semaglutide for the treatment of

obesity (11). Since then, the newest agents in the family, tirzepatide, have been approved for the treatment of type 2 diabetes, and long-term weight control, obstructive sleep apnea. Emerging evidence points to established indications for neurological, dermatological, respiratory conditions, and investigational roles in the treatment of addiction and immunological disorders. Though clinical evidence remains limited in most of those areas (9).

GLP-1 RAs are best described using a generational model, which indicates a substantial increase in duration of action and clinical potency. Exenatide and lixisenatide, first-generation short-acting agents administered once or twice daily, provided proof of concept for incretin-based treatment; However, their requirement for frequent injections limited their long-term clinical uptake in comparison to the later generations. Liraglutide, dulaglutide, and semaglutide are second-generation long-acting agents with high receptor affinity and prolonged half-lives, allowing for administration of Liraglutide once-daily, dulaglutide, and semaglutide once-a week enhancing glycemic management and weight loss effects. Tirzepatide, a third-generation dual GIP/GLP-1 receptor agonist, which clinically exhibit the highest potency within this class, with elevated HbA1c decrease (-2.01% vs. -1.86%) and greater weight loss (-10.3% vs. -6.9%) in the SURPASS-2 study compared to semaglutide 1mg (9). Studies have demonstrated potency differences amongst agents throughout the class. In terms of A1C reduction (10).

Gastrointestinal side effects are the most common associated limitation due to the delayed stomach emptying mechanism and central GLP-1 receptor activation. The most frequently reported GLP-1 RA-induced gastrointestinal adverse event was nausea (42.23%), followed by diarrhea (21.93%) and vomiting (21.90%). Semaglutide showed the highest risk of nausea (ROR 7.41), vomiting (ROR 6.67), diarrhea (ROR 3.55), and constipation (ROR 6.17), whereas liraglutide had the strongest signals for upper abdominal pain (ROR 4.63) and pancreatitis (12). Additionally, Meta-analysis data suggest that tirzepatide has the greatest risk of causing nausea and diarrhea, while dulaglutide and lixisenatide have the lowest risks (11).

Short-acting GLP-1 RAs may pass more easily through the blood-brain barrier, activating central GLP-1 receptors which lead to exacerbating the symptoms including nausea and anorexia. Long-acting agents, such as semaglutide and dulaglutide, have longer circulation half-lives, ensuring continuous GLP-1 receptor activation and increasing intestinal motility, which raises the risk of diarrhea (11).

In terms of severity, liraglutide had the greatest risk of severe gastrointestinal adverse effect (23.31%), while dulaglutide had the lowest (12.29%), with the majority of gastrointestinal symptoms occurring within 30 days after onset of therapy (12). Despite these tolerance differences, overall discontinuation rates owing to adverse effects are less than 10% (10). These discrepancies highlight the need for an individualized approach to prescribing.

Delayed Gastric Emptying

GLP-1 receptor agonists cause delayed gastric emptying through modulatory effects on gastrointestinal motility mediated by vagus nerve, including proximal stomach relaxation, antral peristalsis suppression, and tonic contraction of the pyloric sphincter (13). In terms of pharmacology, acute intravenous GLP-1 infusion decreases stomach emptying significantly and dose-dependently. This is accompanied by elevated pyloric tone, relaxation of the gastric fundus, improved gastric compliance, and inhibition of antral contractility (14). Dose-response tests on healthy volunteers given graded intravenous GLP-1 infusions demonstrated a linear connection between systemic drug concentrations and the duration of delayed solid stomach emptying (13).

Gastric emptying is currently recognized as the key indicator of postprandial glycemic excursions in both healthy and diabetic individuals, accounting for around one-third of the variation in the first rise in glucose following oral challenge. In terms of satiety, the lack of a relationship between energy intake and changes in gastric emptying and intragastric distribution in lixisenatide-treated individuals lends credence to the idea that appetite effects are primarily centrally mediated, possibly through direct or indirect interaction with neurons in the hypothalamus, rather than a secondary consequence of slower gastric emptying. Linear regression analysis revealed no indication of a decline in the effects of short-acting GLP-1 RAs on stomach emptying with time; however, long-acting GLP-1 RAs appear to reduce the degree of slowing with time. This tachyphylaxis distinction has notable therapeutic consequences because the fact that effect sizes are greater for short-acting vs long-acting GLP-1 RAs might be related to the incidence of tachyphylaxis with long-acting formulations but not with short-acting formulations (14). Long-acting formulations, such as once-weekly semaglutide or tirzepatide, have a more significant effect than their nominal pharmacokinetic half-lives due to increased receptor occupancy and delayed downstream activation (13).

According to meta-analyses, there is a five- to six-fold increase in the risk of clinically significant remaining stomach content above 1.5 mL/kg before elective diagnostic procedures (13). Symptoms cannot consistently predict this in the absence of symptoms, stomach emptying can be severely delayed, but in some individuals with strong symptoms, gastric emptying can be normal or accelerated. Another explanation for retained contents during extended fasting is because exogenous GLP-1 suppresses the migrating motor complex, including phase 3 activity, even at near-physiological intact GLP-1 concentrations (14). Nonetheless, despite the substantial pathophysiological signal, clinically significant pulmonary aspiration is rare, with the largest known series indicating just a little and statistically insignificant increase (13).

Nausea and Vomiting

GLP-1 RA therapy's most common gastrointestinal side effects are nausea and vomiting, which can be difficult to manage in both diabetic and non-diabetic patients. According to the clinical trial literature, gastrointestinal side effects affect 40-70% of treated patients, however they have occasionally documented up to 85% of individuals (15). The risk has a significant dose-dependence connection; increasing the dosage of GLP-1 RAs were linked with an increase in nausea, which climbed quicker at lower dosages and plateaued at higher levels. All GLP-1 RAs investigated in non-diabetic patients who are overweight or obesity were associated with a significantly increased risk of nausea, with orforglipron having the highest risk, followed by exenatide, tirzepatide, semaglutide, and liraglutide (16).

The underlying mechanism includes both peripheral and central pathways. GLP-1 receptor agonism slows gastric emptying and suppresses small intestinal motility; Essentially GLP-1RAs interacts directly with GLP-1 receptors in brainstem regions such as the area postrema and nucleus tractus solitarii, which are not protected by the blood-brain barrier and are commonly involved in medication-induced nausea (9). These symptoms have serious implications for treatment persistence. The most common reason for disconnection was nausea, followed by vomiting and diarrhea. According to clinical trial programs, permanent discontinuations occur in 1.6-6% of treated patients, as opposed to less than 1% of placebo patients. Symptoms, on the other hand, are frequently self-limiting, appearing during the dosage-escalation phase, subsiding shortly after reaching the maintenance dose, and ranging in intensity from mild to moderate (15).

Intestinal Motility and Bowel Effects

GLP-1 receptor agonists have multimodal effects on bowel function, which could lead to diarrhea or constipation depending on the medication administered. These gastrointestinal side effects attributed to GLP-1 RAs' inhibitory influence on gastric emptying delay and neural circuit activation. Diarrhea is the most established gastrointestinal side effect. GLP-1RAs are considered to cause diarrhea via altering intestinal motility, which is regulated by the vagus nerve. This effect is due to the prolonged circulating half-lives of long-acting and ultra-long-acting GLP-1RAs, such as semaglutide (via fatty acid acylation) and dulaglutide (via Fc fragment fusion), which maintain sustained GLP-1 receptor stimulation and leads to hypermotility, increasing the risk of diarrhea. Short-acting GLP-1RAs, such as lixisenatide, necessitate more frequent dosage since their half-lives are shorter, leading to intermittent receptor activation, which may lower the risk of diarrhea (11). Constipation, while less often discussed, poses a clinically significant bowel complication. With an overall incidence of 7.92%, estimated at 8% for semaglutide, 7% for liraglutide, and 6% for dulaglutide, with tirzepatide having the lowest incidence at just 0.14%, indicating that it has negligible constipation risk (11). The FAERS database's real-world pharmacovigilance data verifies and expands these tendencies across agents. Semaglutide is a new generation of long-acting GLP-1 RA with a longer half-life than liraglutide after subcutaneous administration (183 vs 11-15 hours), suggesting that it’s effects on gastrointestinal

motility and neural circuitry may be more significant than those of other GLP-1 RAs used. As a result, semaglutide had the highest risk of diarrhea (ROR 3.55; 95% CI 3.35-3.77) and constipation (ROR 6.17; 95% CI 5.72-6.66) of all of the agents studied. Agents vary in their onset timings and clinical severity. The median time-to-onset for semaglutide was 4 days (IQR 0-40), while lixisenatide had the shortest at 0 days (IQR 0-11), with 77.44% of all gastrointestinal adverse effects occurring within 30 days of agent start. Liraglutide had the most serious gastrointestinal side effects (23.31%), whereas dulaglutide had the least (12.29%) (12).

Gut-Brain Axis

GLP-1 regulates appetite, satiety, and energy balance via the gut-brain axis. GLP-1 receptor agonists (GLP-1RA) are intended to imitate GLP-1's peripheral functions, but it is now well established that their efficacy in the treatment of obesity is contingent on decreasing energy intake via central nervous system activity. Appetite signaling is initiated peripherally by enteroendocrine L cells. Rapid signaling between the stomach and the brain regarding recently consumed nutrients impacts metabolism and eating behavior, both of which are required to maintain body weight. This happens through a variety of processes, including the nutrient-mediated release of a repertory of peptide hormones from a little part of enteroendocrine cells in the gastrointestinal epithelium. The transmission of GLP-1 signals from the stomach to the brain is influenced by vagal pathways. GLP-1R is expressed on a large population of stomach-innervating vagal afferent neurons that detect GI stretch and transmit this information to the nucleus of the solitary tract (NTS), and GLP-1R signaling in these neurons is required for the slow gastric emptying induced by native GLP-1 and GLP-1RAs (17).

Furthermore, peripheral GLP-1 may send a signal to the brain through a neuroendocrine signaling mechanism without entering the brain, mediated by GLP-1R expressed on the portal vein, which is heavily innervated by the vagal afferent nerve, with the signal further sent to the nodose ganglion and subsequently to the nucleus tractus solitarius in the brainstem (18). In terms of CNS involvement in satiety, GLP-1R is expressed in numerous neural populations throughout the CNS, including the arcuate nucleus, paraventricular nucleus, lateral hypothalamus, and dorsomedial hypothalamus, as well as regions involved in motivated behavior and reward, such as the ventral tegmental area and nucleus accumbens (17). Stimulation of NTS GLP-1R neurons leads to non-aversive satiation, most likely via projections to the paraventricular nucleus, and this circuit was preferentially induced by nutrients rather than non-nutritive aversive stimuli. Meanwhile, the disagreeable gastrointestinal side effects of GLP-1RAs are likewise CNS-mediated, with GLP-1R deletion from the postrema region but not NTS reducing GLP-1RA-induced taste avoidance, which is formed by projections to the parabrachial nucleus (17)

Microbiome and Emerging GI Research

GLP-1 receptor agonists (GLP-1 RAs) exhibit a bidirectional interaction with the gut microbiota, with dietary patterns and weight loss being the dominant factors contributing to alterations in the gut microbiota, rather than the GLP-1 RAs themselves. Animal models confirm that GLP-1 RAs, such as liraglutide, dulaglutide and semaglutide, consistently improve good microbiota, especially Akkermansia muciniphila, linked to improvements in metabolic health and gut barrier function (19).

Human data remain sparse, as semaglutide failed to induce important modifications in microbial abundance in patients with type 2 diabetes mellitus (T2DM), even if baseline microbial composition was associated with glycemic response (HbA1c) and could be employed to stratify patients (20). The combination of semaglutide and A. muciniphila (Akk11) demonstrated additive effects on metabolic outcomes in rodent models. Also, GLP-1 RAs might pose an elevated risk for small intestinal bacterial overgrowth due to their known influence on gastric motility and slowed gastric emptying (21).

Table 1:

Major Gastrointestinal Effects of GLP-1 Therapies

GI Effect	Mechanism	Clinical Significance	Citations
Delayed Gastric Emptying	Proximal stomach relaxation, antral peristalsis suppression, and tonic pyloric sphincter contraction mediated by vagally driven neurohumoral pathways	Accounts for ~one-third of variation in postprandial glucose excursions; five- to sixfold increase in risk of retained gastric content before elective procedures	(14)
Nausea	Direct activation of GLP-1 receptors in brainstem regions — area postrema and nucleus tractus solitarii — not protected by the blood-brain barrier	Most prevalent GI side effect affecting 40–70% of patients; most common reason for treatment discontinuation; dose-dependent relationship confirmed	(16)
Vomiting	Central GLP-1 receptor activation in brainstem emetic centres compounded by delayed gastric emptying	Permanent discontinuation in 1.6–6% of treated patients; symptoms typically self-limiting during dose-escalation phase	(16)

Diarrhea	Sustained GLP-1 receptor stimulation improving intestinal motility, particularly with long-acting agents such as semaglutide and dulaglutide via prolonged circulating half-lives	Semaglutide carries highest real-world risk (ROR 3.55); 77.44% of all GI adverse effects occur within 30 days of drug initiation	(12)
Constipation	Inhibitory influence on gastric emptying and neural circuit activation	Overall incidence 7.92%; semaglutide highest risk (ROR 6.17); tirzepatide lowest incidence (0.14%).	(11)
Microbiome Alteration	Indirect modulation predominantly via weight reduction and improved glycemic control rather than direct pharmacological action on microbial communities	Baseline microbiome composition may predict glycemic response to therapy; direct clinical significance not yet established in prospective human studies	(19,20)

EXTRA-METABOLIC EFFECTS

GLP-1 receptor agonists (GLP-1RAs) and dual GIP/GLP-1 agonists were created for both weight loss and glycemic control but many studies demonstrated broader effects on hepatic, cardiovascular, renal, anti-inflammatory and neuroprotective health.

Hepatic Effects

Demonstrating hepatoprotective effects, GLP-1RAs are currently under broad studies for steatohepatitis and metabolic-associated fatty liver disease (22) (23). Within NASH, liraglutide enhanced liver histology, raised the resolution of NASH which slows the rate of progression to fibrosis in many patients who are overweight and obese (24). An umbrella/meta-analytic overview indicated that GLP-1RAs lead to improvement in Liver fibrosis and MASH. (25). Benefits in insulin resistance are potentially indirect, GLP-1RAs lower weight, postprandial lipemia and glycemia, factors which likely help in boosting insulin resistance as well as reducing hepatic fat. (26). Clinical and preclinical data illustrated that GLP-1RAs minimize liver inflammation and hepatocyte injury in NASH models and humans, however, direct hepatic GLP-1 receptor expression remains unclear which suggest mechanisms involving systemic metabolic and inflammatory shifts instead of direct hepatocyte

signaling (26). For patients with cirrhosis/MASLD, GLP-1RA use was linked to decreased risks of hepatic decompensation, hepatocellular carcinoma, liver failure and portal hypertension, though these observational findings require further confirmation (9).

Cardiovascular Effects

Extensive cardiovascular outcome trials indicated that GLP-1RAs decrease major adverse cardiovascular events (MACE) or maintain cardiac safety in type 2 diabetes (22). Focused outcomes studies confirm lower instances of myocardial infractions, cardiovascular death and stroke (26). The mechanisms involved are multifactorial, factors such as weight loss, glucose lowering blood-pressure reduction and lipid improvement likely play a role (22). Direct vascular/cardiac effects: GLP-1 receptors within endothelial cells and cardiomyocytes promote vasodilatory, anti-inflammatory as well as anti-atherosclerotic effects. These include enhanced endothelial functioning, decreased vascular smooth-muscle proliferation and anti-inflammatory effects directly on macrophages. GLP-1RAs might also enhance myocardial insulin sensitivity and energy metabolism, shifting away from fatty-acid oxidation to glucose oxidation (23).

Renal Effects

Cardiovascular-renal meta-analyses and systematic reviews indicate that kidney benefits with GLP-1RAs alongside cardiovascular gains, such as favorable “kidney outcomes” in patients with type 2 diabetes (24). Pharmacokinetic review also highlights recognized hepatoprotective effects alongside renoprotective effects. However, compared to the heart, details surrounding the mechanisms are less clearly defined. Potential factors include an improved metabolic milieu (glycemia, weight, blood pressure, lipids) and perhaps shifts in volume of distribution and glomerular filtration rate with therapy; however, drug-drug interaction effects through renal clearance are still poorly understood and require more study (22).

Anti-Inflammatory and Systemic Effects

Beyond glucose control, GLP-1 based therapies demonstrate immunomodulatory and anti-inflammatory actions. One review emphasizes "anti-inflammatory effects of GLP-1-based therapies beyond glucose control". In many preclinical neurodegenerative models, GLP-1 receptor activation in the brain exhibits anti-inflammatory properties (27). On a systemic level, GLP-1 actions include the management of cardiovascular pathophysiology and inflammation. Additionally, glucagon and GLP-1 are characterized as “novel anti-inflammatory and immune-modulatory compounds”._Through the integration of weight loss, appetite reduction, delayed gastric emptying, glucagon suppression and insulin secretion, GLP-1RAs organize metabolic regulations affecting the entire body, which probably supports numerous extra-metabolic organ benefits (23).

Neuroprotective and Emerging Effects

Produced within the brain, GLP-2 serves an important function in inflammation and neuroprotection through GLP-1 receptor pathways. Activation of the GLP-1R lowers neuroinflammatory responses in many neurodegenerative disease models, which makes those agents possible treatments for neuroinflammatory and neurodegenerative disorders (27). GLP-1 and dual GIP/GLP-1 agonists regulate neurotransmitter systems (dopamine, serotonin, glutamate, GABA), enhance neuronal insulin sensitivity, reduce neuroinflammation, encourage neuroplasticity, and restrict pathological protein aggregation, showing wide neuroprotective potential (28). They are also being investigated in addiction, where GLP-1R activation in reward-related regions (VTA, NAc, PFC) regulates relapse-like and craving through neuroinflammatory mechanisms and shifts in glutamatergic and dopaminergic signaling (29). However, even with encouraging early clinical signals and preclinical data, long-term central safety, confirmed efficacy for neurodegenerative disease, and specific neuroprotective mechanisms, particularly for dual agonists, are still not fully explained and require high-quality trials (23,28).

Table 2:

Extra-Metabolic Effects of GLP-1 Therapies

Organ/System	Proposed Effect	Current Evidence	Citations
Liver	Decreased Steatosis, enhanced MASH/MASH fibrosis	Meta-analyses and RCTs demonstrate better NASH histology and fibrosis; these gains are mostly indirect through metabolic and weight improvements	(27)
Cardiovascular	Lowered MACE, better HFpEF symptoms	Major outcome trials indicate decreased CV death, stroke and MI. HFpEF trial illustrates improvements in symptoms	(22,23)
Kidney	Reduced rate of kidney disease progression	Kidney outcomes are reported as favorable alongside CV benefits in meta-analyses	(24)

Systemic inflammation	Anti-inflammatory and immunomodulatory effects	Inflammatory responses across many tissues are diminished by signaling of GLP-1	(27)
Brain	Neuroprotection, neuropsychiatric modulation	Many preclinical and rising clinical data showed long-term impacts, however the mechanisms remain under investigation	(27,28)

CLINICAL IMPLICATIONS AND CHALLENGES

While dual GLP-1/GIP agonists and GLP-1 receptor agonists are remarkably potent for obesity and type 2 diabetes, their application is restricted by factors like costs, gastrointestinal side effects, the need for individualized prescribing and some uncertain long-term risks. GLP-1 based drugs can achieve near-normal glycemia, lower body weight by approximately 25% and markedly reduce cardiovascular risk, providing benefits in comparison to bariatric surgery (30). Gastrointestinal adverse events occur frequently and are dose-dependent, while high doses can enhance glycemic and weight outcomes, they are constrained by vomiting, diarrhea and nausea (22,23). An important strategy involves slow dose titration (23,30).

Meta-analyses indicate significantly higher frequencies of diarrhea, vomiting and nausea compared to placebo, which are typically mild but can affect adherence (25,31). These GI side effects contribute to a much lower persistence on therapy in real-world settings (9). By slowing gastric emptying, GLP-1 agents can cause demonstrated transit delays and higher luminal residue (32). Which leads to a recognized clinical aspiration risk during endoscopy or anesthesia, requiring individualized perioperative protocols (9,33). Although long-term trials largely dismissed concerns regarding pancreatitis and pancreatic cancer, potential gallbladder/biliary and thyroid cancer risks are still under investigation (9,25). Favorable renal and cardiovascular profiles support their use in individuals with cardiometabolic diseases (23,26). Patient selection should account for pregnancy, renal function, cardiovascular status and tolerability (23).

To encourage wider adoption, reimbursement policies and economic evaluations are prioritized , reflecting persistent access and cost barriers (23). GLP-1 based therapies are increasingly categorized as muti-system agents, with evidence of anti-inflammatory, neuroprotective, renal, cardiovascular and potential respiratory benefits that go beyond weight loss and glycemic control (25–27).

FUTURE DIRECTIONS

The trajectory for GLP-1 based drugs involves a shift toward multi-agonists, precision therapies, and a deeper grasp of safety and mechanisms of actions, especially within gastrointestinal disease. Offering better weight and glucose reduction compared to traditional GLP-1RAs, dual GIP/GLP-1 agonists like tirzepatide are leading a new movement of multi-receptor agonists. Research reviews point to “recent advances in the development of other dual and triple receptor agonists” and advocate for moving these unimolecular multi-agonists into clinical settings (23).

Although data is in the early stages, triple GLP-1/GIP/glucagon agonists already exhibit neuroprotective qualities in preclinical Alzheimer models, which suggests expanded organ targets (27). In regard to personalised therapies, current advice highlights the need to choose between dual agonists and GLP-1RAs based on administration route, renal function, cardiovascular status and tolerability (23). New emerging studies should evaluate dual agonists in special groups like in pregnancy, severe obesity and type 1 diabetes, while clarifying the long-term efficacy and safety of new multi-agonists. In particular, extensive trials are required to confirm long-term safety across various populations, including in pregnancy (23). Another important consideration is potential GI application, this is because GLP-1RAs significantly inhibit upper GI motility (32) and delay gastric emptying, they function as an "ileal brake” hormone that controls motility and secretion (30). There is a need for improved perioperative protocols to address aspiration risk and delayed gastric emptying (33)

With systematic reviews indicating more biliary disease and GI adverse events, a key future goal is determining the best use of these medications in GI-vulnerable patients (25,31). Primary unknowns involve the neuroprotective mechanism of GLP-1/GIP agonists, reason for weight gain and non response, and the drivers of drug-drug interactions and pharmacokinetic shifts beyond gastric emptying (22,23,34).Future research explicitly prioritizes focused studies on mechanisms related to CNS signaling and neurodegeneration (23).

CONCLUSION

GLP 1 based therapies have important rule in modern medicine, extending far beyond their original role in glucose regulation also in diabetes management. For improving glycemic control these agents demonstrate significant gastrointestinal and extra metabolic effect that contributes to the growing clinical importance. Their action is reflected in the effect on gastric motility and the gut-brain axis, showing the complexity of interaction between metabolic and non-metabolic pathways.

GLP 1 receptor agonists such as semaglutide and tirzepatide have been showing beneficial systemic effects, such as weight reduction, cardiovascular protection, anti-inflammatory activity and potential improvements liver disorders such as non-alcoholic fatty liver disease.

The mechanism of GLP 1 therapies is highly interconnected and involve multiple organ systems. At the same time gastrointestinal adverse effects include nausea, vomiting, abdominal discomfort or

diarrhea and delayed gastric emptying remain clinically relevant and can affect treatment adherence in some patients. Therefore, understanding both the therapeutic advantage and potential complication of these medications is essential for improving patient care.

These therapeutic benefits highlight just how far reaching GLP 1 based therapies truly are, rather than action on a single pathway or organ. Their mechanisms are deeply interconnected, influencing multiple systems across the body simultaneously, from the pancreas and liver to the heart, kidneys and brain.

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