REVIEW ARTICLE

The Dark Side of GLP-1 Receptor Agonists: Risks and Adverse Events

CL Nawal[1], Hazari Lal Saini[2], Govind Rankawat[3*], Radhey Shyam Chejara[4]

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as pivotal therapeutic agents in type 2 diabetes mellitus and obesity, demonstrating efficacy in enhancing glycemic regulation, facilitating weight loss, and reducing cardiovascular risk. Despite their favorable efficacy profile, these agents have been linked to diverse adverse outcomes that warrant careful consideration. The most frequently encountered complications arise from their actions on gastrointestinal motility, leading to nausea, emesis, gastrointestinal discomfort, constipation, and impaired gastric motility. Less common but clinically important effects include gallbladder dysfunction, pancreatitis, alterations in biliary flow, and enzyme elevation. Rarely, GLP-1 RAs have been linked to neuropsychiatric manifestations, aspiration pneumonia due to gastric stasis, sarcopenia associated with excessive weight loss, and potential long-term risks such as neoplastic changes. The underlying mechanisms of these events often reflect the widespread distribution due to the presence of GLP-1 receptors in the gastrointestinal system, pancreatic tissue, gallbladder, and central nervous system. Although many adverse events are transient or mild, the potential for severe outcomes underscores the importance of individualized patient selection, vigilant monitoring, and further research into long-term safety. A mechanism-based understanding of these adverse effects can guide clinicians in balancing therapeutic benefits with potential risks. Preventing GLP-1 RA-associated adverse effects requires a multifaceted strategy integrating personalized patient selection, careful titration, lifestyle counseling, pharmacological adjuncts, and vigilant monitoring.

Keywords: Gastrointestinal diseases, Glucagon-like peptide-1 receptor agonists, Mental disorders, Pancreatic diseases, Retinopathy, Sarcopenia.

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Introduction

The global prevalence of disturbances in carbohydrate metabolism, along with cardiovascular and renal complications, continues to rise at an alarming rate.[1] A wide range of pharmacological agents has been developed for the management of type 2 diabetes mellitus (T2DM) and its associated comorbidities, with substantial evidence supporting their clinical utility.[1] Among these, incretin-based therapies have been established as a clinically significant treatment category. Among these are GLP-1 receptor agonists (GLP-1 RAs) and DPP-4 inhibitors, which exert their therapeutic benefits by modulating the physiological actions of incretin hormones, thereby improving glucose homeostasis.[2]

Endogenously, glucagon-like peptide-1 (GLP-1) is released from intestinal L-cells following nutrient ingestion, where it enhances insulin secretion from pancreatic β-cells and concurrently inhibits glucagon release from α-cells.[3] Clinically, GLP-1 RAs, available in parenteral as well as oral dosage forms, have demonstrated exhibit significant potency in improving glycemic control and improving atherosclerosis-related parameters.[4] Their pharmacological effects differ according to duration of action: short-acting agents predominantly modulate gastric motility, thereby reducing postprandial excursions, whereas long-acting agents primarily exert insulinotropic and glucagonostatic effects, thereby targeting fasting glycemia.[5]

Despite these advantages, concerns from a safety perspective and tolerability of GLP-1 RAs remain doubtful. Semaglutide, in particular, has attracted widespread attention owing to its dual benefits on weight reduction and glycemic regulation; however, increasing reports of off-label use have raised questions about rare but serious adverse events.[6]

More recently, the therapeutic landscape has expanded with the introduction of tirzepatide, which simultaneously activates GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 receptors as a dual incretin agonist. Both semaglutide and tirzepatide have gained unprecedented global traction, not only for T2DM but also for obesity management. Their effectiveness in achieving significant, clinically relevant weight reduction marks a paradigm shift in metabolic medicine. In clinical trials, once-weekly semaglutide at 2.4 mg (STEP program) achieved average weight reductions of 10–15% of baseline body weight,[7] while tirzepatide demonstrated even greater reductions of 15–20% in the SURMOUNT-1 trial.[8] In addition to facilitating weight reduction, these agents enhance glycemic regulation, favorably influence cardiovascular risk markers, and overall metabolic homeostasis, reinforcing their value across the spectrum of diabetes and obesity management.[9]

The rapid adoption of these therapies has been accelerated by regulatory endorsements, rising public awareness, and extensive media coverage. Nevertheless, issues of accessibility, affordability, long-term safety, and equitable availability remain critical challenges, particularly in resource-limited regions. The growing popularity of semaglutide and tirzepatide not only underscores the recognition of obesity as a chronic, treatable condition but also highlights the transformative potential of incretin-based therapies in redefining modern metabolic care.

Adverse Outcomes and Safety Considerations of GLP-1 RA

While gastrointestinal disturbances remain the most frequently observed adverse reactions with GLP-1 RA, increasing evidence has highlighted a range of rare yet clinically significant complications. These include acute pancreatitis, gallbladder disease, aspiration pneumonia, sarcopenia, neuropsychiatric manifestations, and possible links to certain malignancies (Fig. 1 and Table 1). Although such events are uncommon, their potential severity, diagnostic complexity, and long-term

[1]Senior Professor; [2]Associate Professor; [3]Assistant Professor; [4]Professor, Department of General Medicine, SMS Medical College, Jaipur, Rajasthan, India; *Corresponding Author

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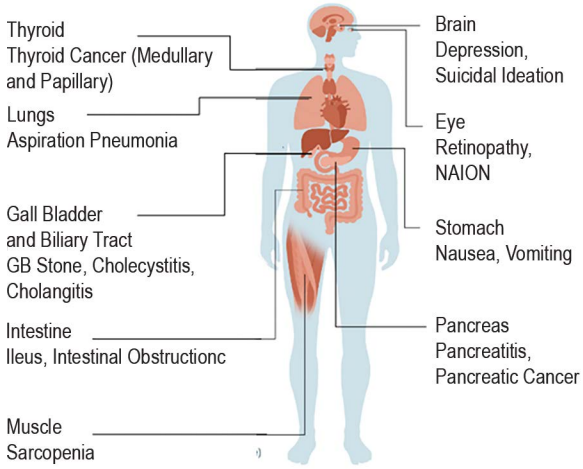

Fig. 1: GLP-1 RA and GIP/GLP-1 Co RA-associated affected systems and related adverse events

Table 1: GLP-1 RA-associated adverse effects, their proposed mechanism and clinical implications

Rare adverse effect	*Proposed mechanism*	*Clinical implication*
Pancreatitis	GLP-1R expression on ductal/acinar cells → proliferation and enzyme activation	Acute pancreatitis (rare but serious)
Pancreatic neoplasia (debated)	β-cell/ductal proliferation in animal models	Concern for pancreatic cancer (inconclusive in humans)
Gallbladder disease	↓ CCK-stimulated gallbladder contraction → gallstone formation	Cholelithiasis, cholecystitis
Aspiration pneumonia	Delayed gastric emptying → gastric stasis, reflux, vomiting	Aspiration during anesthesia/sedation
Intestinal obstruction (rare)	Marked slowing of GI transit	Bowel obstruction symptoms
Sarcopenia/muscle loss	Excessive weight loss → lean body mass reduction	Frailty, impaired physical function
Neuropsychiatric events	CNS GLP-1R activation; serotonin/dopamine modulation	Depression, anxiety, suicidal ideation (rare reports)
Acute kidney injury (AKI)	Dehydration from severe GI losses (nausea, vomiting, diarrhea)	Worsening renal function in susceptible pts
Hypersensitivity/anaphylaxis	Immune-mediated drug reaction	Angioedema, urticaria, systemic allergy
Medullary thyroid carcinoma (MTC)	GLP-1R stimulation of thyroid C-cells in rodents (not proven in humans)	Boxed warning in some GLP-1 RAs

therapeutic implications warrant careful consideration. Recognition of these rare outcomes is essential to enable clinicians to optimize the balance between therapeutic efficacy and patient safety through vigilant monitoring, early detection, and individualized risk–benefit assessment.

Gastrointestinal System Adverse Effects

Clinical trial data indicate that gastrointestinal adverse events are the predominant complications linked to GLP-1 RA therapy.[10] The most frequently observed adverse events are nausea and diarrhea (>10%), followed by vomiting, constipation, abdominal pain, and dyspepsia (1–10%) (Table 2). Such symptoms typically emerge during the early phases of therapy, affecting approximately 50–60% of patients.[11] Although often transient, their incidence is dose-dependent and represents a frequent cause of treatment discontinuation. The propensity of GLP-1 receptor agonists (GLP-1 RAs) to delay gastric emptying and gastroparesis has generated concerns about potential intestinal obstruction and an increased risk of aspiration during anesthesia or procedural sedation. Delayed gastric emptying, reduced gastric and intestinal motility, CNS-mediated nausea, gallbladder hypomotility, and gut microbiome alteration are major contributing mechanisms for gastrointestinal adverse effects.

Gastric emptying is governed by a coordinated interaction between gastric pacemaker cells, smooth muscle contractility, and neurohormonal regulatory pathways. The inhibitory action of GLP-1 RA on gastrointestinal motility occurs through multiple pathways, such as vagal afferent–mediated modulation of central GLP-1 receptor activity[12] and enteric nervous system signaling, including presynaptic modulation and nitric oxide-dependent mechanisms.[13] Patients with diabetes, particularly those affected by autonomic neuropathy and preexisting gastrointestinal disorders, may experience a more marked impact (Fig. 2). In clinical trials, the incidence of adverse events was significantly higher with semaglutide treatment than with placebo, affecting 74.2% and 47.9% of participants, respectively. Importantly, these events were generally mild to moderate in severity for most participants, transient in nature, and resolved without the need for permanent treatment discontinuation.

Gastroparesis

Gastroparesis has emerged as a clinically significant adverse event associated with incretin-based therapies comprising GLP-1 RA (e.g., semaglutide) and dual GIP/GLP-1 RA (e.g., tirzepatide). These agents contribute to glycemic control and weight reduction partly by delaying gastric emptying through mechanisms involving vagal modulation, reduced antral contractility, and increased pyloric tone, thereby enhancing satiety. While this pharmacological action underpins their therapeutic efficacy, it may precipitate drug-induced gastroparesis in susceptible individuals, presenting characterized by clinical features including early satiety, nausea, vomiting, bloating, and abdominal discomfort.

Clinical trial data, including the STEP (semaglutide) and SURMOUNT (tirzepatide) programs, have consistently reported gastrointestinal adverse events, with nausea and vomiting observed in up to 30% of participants; these events are typically mild to moderate in severity and often resolve with dose adjustment or treatment discontinuation.[14] Identified risk factors include preexisting diabetic autonomic neuropathy, rapid dose escalation, concomitant use of opioids or anticholinergic medications, and female sex, which carries a higher baseline prevalence of gastroparesis.[15]

Management approaches include dietary modification (small, frequent meals with reduced fat and fiber content), symptomatic therapy with antiemetics or prokinetic agents, and gradual dose titration. In

Table 2: GLP-1 RA-associated gastrointestinal adverse effects, their frequency, proposed mechanism, clinical implications, and management strategy

Adverse effect	*Frequency (clinical trials)*	*Proposed mechanism*	*Clinical implications*	*Management strategies*
Nausea	Very common (≥1/10)	Central nervous system activation; delayed gastric emptying	Often occurs in 50–60% of patients during initiation; may reduce adherence	Gradual dose escalation, smaller meals, patient reassurance
Diarrhea	Very common (≥1/10)	Enhanced intestinal motility and secretion	Can cause dehydration, electrolyte imbalance if severe	Adequate hydration, dietary adjustment, dose reduction if persistent
Vomiting	Common (≥1/100 to <1/10)	Delayed gastric emptying; central nausea pathways	May lead to fluid loss and poor drug tolerance	Antiemetics if necessary; slow dose titration
Constipation	Common (≥1/100 to <1/10)	Altered gut motility; changes in water absorption	May cause discomfort, rare risk of fecal impaction	Increased dietary fiber, fluids, mild laxatives
Abdominal pain/dyspepsia	Common (≥1/100 to <1/10)	Delayed gastric emptying; increased gastric distension	Mimics dyspepsia; can complicate adherence	Symptomatic treatment; dose adjustment
Gastroparesis-like symptoms/intestinal obstruction	Rare; case reports	Marked delay in gastric emptying, particularly with long-acting GLP-1 RAs	Can mimic or exacerbate gastroparesis; raises perioperative aspiration risk	Avoid use in patients with severe gastroparesis; perioperative withholding of drug; preprocedural fasting protocols

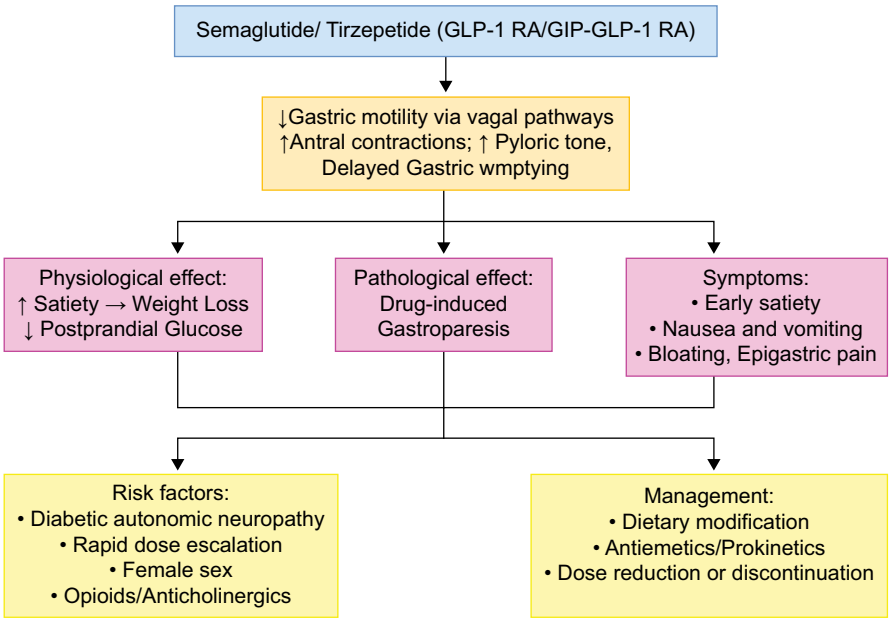

Fig. 2: GLP-1 RA and GIP/GLP-1 RA-associated gastrointestinal adverse effects

refractory cases, treatment discontinuation may be necessary. To balance efficacy with tolerability, patient selection, individualized titration, and regular monitoring are critical components of GLP-1 RA therapy.

Intestinal Obstruction

The European Medicines Agency (EMA) first raised concerns in 2013 regarding intestinal obstruction as a potential adverse effect of GLP-1 RAs, prompted by early case reports.[16] Pharmacovigilance data from VigiBase indicate that the incidence of reported intestinal obstructions is more than 4.5-fold higher in patients receiving incretin-based agents than in those treated with alternative antidiabetic therapies.[17]

Aspiration Pneumonia

Concerns have emerged regarding the periprocedural implications of GLP-1 RA-induced delayed gastric emptying, as several case reports have described aspiration during anesthesia among affected individuals.[18] Supporting this, several studies have demonstrated increased gastric residue in treated patients. There is a complex pathway of reflux and regurgitation during anesthesia and sedation (Fig. 3). Esophagogastroduodenoscopy findings revealed higher rates of retained gastric contents in patients treated with GLP-1 RAs compared with controls.[19] In a prospective ultrasound-based study of patients initiated on semaglutide, 70% exhibited retained solid gastric content after an overnight fast, compared with only 10% in the control group.[20] Similarly, in their analysis, Nersessian et al.[21] found that semaglutide exposure within 10 days before elective surgery was independently correlated with increased residual gastric content, detected in 40% of semaglutide users versus 3% of nonusers.

Given these findings, the American Society of Anesthesiologists has recommended withholding short-acting GLP-1 RAs for 24 hours and long-acting formulations for at least one week before elective surgery to mitigate aspiration risk.[22] However, the optimal discontinuation interval remains uncertain. A study involving 124 participants demonstrated that 56% of patients continued to exhibit elevated residual gastric content despite 7 days of cessation of GLP-1 RAs, thereby challenging the effectiveness of this approach.[23] In clinical practice, a more individualized strategy may be warranted. For patients with ongoing gastrointestinal symptoms, objective assessment of gastric emptying—via standardized gastric emptying studies or point-of-care gastric ultrasound—may assist in identifying patients at increased risk of aspiration.

Hepatobiliary Adverse Effects

The precise biological pathways responsible for GLP-1 RA-associated biliary toxicity remain incompletely defined; current evidence suggests both weight-loss-dependent and independent pathways. Cholelithiasis is a widely acknowledged consequence of accelerated weight reduction, with new gallstone formation reported in over 30% of obese patients following

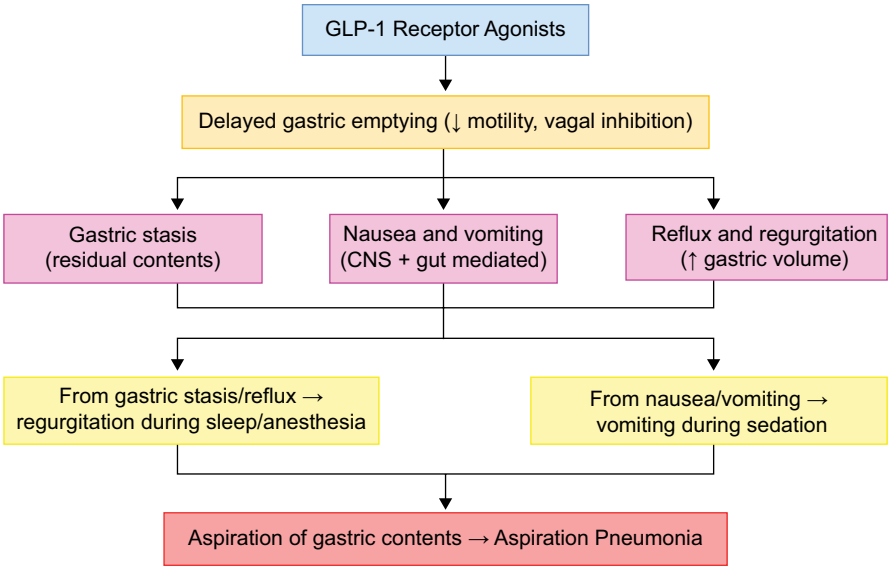

Fig. 3: GLP-1 RA-associated aspiration pneumonia, its proposed mechanism and clinical implications

Table 3: GLP-1 RA-associated pancreatic disorder, their pathophysiology and clinical consequences

Mechanism	*Pathophysiology*	*Clinical consequence*
Exocrine stimulation	GLP-1 receptors on acinar and ductal cells → proliferation, ductal hyperplasia, enzyme activation	Acute pancreatitis, pancreatic inflammation
Endocrine effects	Promotes β-cell proliferation, inhibits apoptosis; animal models show α/ductal proliferation	Concern for neoplasia / pancreatic intraepithelial changes (uncertain in humans)
Enzyme elevation	Increased serum amylase and lipase levels due to pancreatic stimulation	Asymptomatic hyperenzymemia or pancreatitis
Biliary–pancreatic interaction	Impaired gallbladder emptying → gallstone formation → duct obstruction	Gallstone-induced pancreatitis
Immune-mediated inflammation	Altered cytokine response, possible immune activation in pancreatic tissue	Exacerbation of inflammation/ pancreatitis

gastric bypass surgery.[24] Weight loss induces cholesterol supersaturation of bile, thereby predisposing to gallstone development.[24]

In addition to weight-related mechanisms, GLP-1 RAs may directly impair gallbladder motility. By suppressing cholecystokinin secretion, these agents delay gallbladder contraction and prolong bile stasis, promoting sludge accumulation and gallstone formation.[25] The LEADER study demonstrated a significantly higher incidence of acute gallstone disease among liraglutide-treated patients (3.1%) compared with those given placebo (1.9%; $p < 0.001$).[26] Evidence from a meta-analysis of 76 RCTs corroborated these results, demonstrating that GLP-1 receptor agonists significantly increased the risk of gallbladder and biliary complications.[27] The elevated risk was particularly evident when GLP-1 receptor agonists were administered for weight-loss purposes rather than for diabetes management ($p < 0.001$), at higher dosages ($p = 0.006$), and with prolonged treatment duration ($p = 0.030$).

In clinical practice, careful enhanced clinical vigilance is required in individuals with previous gallbladder or biliary disease. Providers should maintain vigilance for symptoms such as right upper quadrant pain, jaundice, or dyspepsia, and consider early diagnostic imaging when clinically indicated.[28]

Pancreatic Adverse Effects

Acute pancreatitis associated with GLP-1 receptor agonists (GLP-1 RAs) has been recognized since the early postmarketing period. Between 2004 and 2009, pharmacovigilance data analyses demonstrated that use of the initial incretin-based therapies approved in the United States—sitagliptin, a DPP-4 inhibitor, and exenatide, a GLP-1 mimetic—was linked to a sixfold escalation in reported pancreatitis cases.[29] The same report also identified a higher incidence of pancreatic cancer with these agents, with risks elevated 2.9-fold for exenatide and 2.7-fold for sitagliptin relative to patients receiving different oral glucose-lowering therapies.[29] Between 2004 and 2020, an evaluation of the FDA's adverse event reporting system identified a notable pharmacovigilance signal for malignant pancreatic neoplasms associated with GLP-1 RA use (PRR = 9.86).[30]

While the biological plausibility of GLP-1 RA–associated pancreatic toxicity is supported by evidence of Pancreatic localization of GLP-1 receptor expression and animal studies suggesting proliferative changes, definitive causality remains controversial. Given these uncertainties, clinicians are advised to monitor patients on GLP-1 RAs for unexplained abdominal pain, nausea, or vomiting and to discontinue therapy promptly if pancreatitis is suspected (Table 3).

The assessment of GLP-1 RA–associated pancreatitis is challenged by the fact that most randomized controlled trials exclude high-risk individuals, such as those with chronic alcohol consumption or prior pancreatic disease. In a diabetic rat study prompted by an FDA inquiry, short-term administration of exenatide and liraglutide resulted in pancreatic changes, including acinar-to-ductal metaplasia and ductal hyperplasia; notably, one exenatide-treated rat developed fatal pancreatic necrosis.[31] These findings support a hypothesis that persistent GLP-1 receptor activation in exocrine pancreatic cells could drive hyperplasia, dysplastic transformation, and pancreatitis.[32]

From a clinical standpoint, comprehensive risk assessment is recommended before initiating GLP-1 RA therapy, particularly in underlying events of pancreatitis, gallstone disease, or other established risk factors. If pancreatitis is suspected during treatment, discontinuation of the drug and appropriate management should be promptly undertaken.[33]

The safety of semaglutide has received particular scrutiny due to early preclinical and pharmacovigilance reports linking GLP-1 RAs to elevated pancreatic enzyme activity and ductal proliferation.[34] Concerns regarding pancreatic malignancy initially arose from rodent models and early clinical datasets. However, major cardiovascular outcome studies (SUSTAIN-6 and PIONEER 6) failed to demonstrate a statistically significant excess of pancreatic cancer relative to placebo.[35]

Ongoing long-term postapproval pharmacovigilance and well-designed prospective future investigations will play a key role in delineating the true risk profile of semaglutide and related agents with respect to pancreatic safety.

Psychiatric Adverse Effects

Individuals with obesity demonstrate an increased occurrence of neuropsychiatric comorbidities, including depression and

suicidal ideation.[36] The use of pharmacological weight-loss agents has raised further concerns, as suicidal thoughts have been reported with several medications indicated for weight reduction.[37] For example, SSRIs and naltrexone/bupropion combinations are connected to mood disturbances and increased suicidal ideation.[38] The European Medicines Agency (EMA) previously withdrew Rimonabant, a CB1 receptor blocker, on account of its association with depression and suicidality.[39]

The relationship between obesity, weight loss, drug therapy, and suicidality appears multifactorial. In addition, accelerated weight reduction or difficulty adjusting to altered body image may trigger physiological and psychological stress mechanisms, potentially influencing the emergence of suicidality. CNS penetration and receptor activation, neurotransmitter modulation, HPA axis deviation, neuroinflammation, indirect metabolic effects, and sleep and circadian rhythm changes are the major contributing mechanisms to GLP-1 RA-associated neuropsychiatric effects.

Glucagon-like peptide-1 receptors are widely expressed in the central nervous system and are involved in emotional regulation, including the hypothalamus, hippocampus, and amygdala, as well as in peripheral tissues such as the pancreas. This distribution suggests that GLP-1 RAs could modulate both central and peripheral pathways affecting mood and behavior.[6] In addition, GLP-1 receptor activity influences critical neurotransmitter pathways, such as those involving serotonin, dopamine, and glutamate, which play central roles in mood stabilization and psychiatric health.[40] Overall, current evidence highlights a dual potential of GLP-1 RAs—while mechanistic plausibility exists for beneficial neuroprotective effects, the possibility of adverse psychiatric outcomes, including mood alterations and suicidality, cannot be excluded. Rigorous longitudinal studies are required to delineate these complex interactions and establish the true neuropsychiatric safety profile of GLP-1–based therapies.

In July 2023, the European Medicines Agency (EMA) initiated a formal review following approximately 150 spontaneous reports suggesting a possible association between GLP-1 receptor agonists (GLP-1 RAs) and suicidal ideation or self-harm.[41] Similarly, McIntyre et al.[42] examined the FDA adverse event reporting system (FAERS) database from 2005 to October 2023, noting reports of suicidal ideation and depression linked to both semaglutide and liraglutide.

A *post hoc* pooled analysis of the STEP 1, 2, 3, and 5 trials evaluating semaglutide 2.4 mg in individuals with obesity reported no excess risk of depressive symptoms or suicidal ideation compared with placebo, while even showing a statistically significant but clinically negligible reduction in depressive symptom scores.[43] However, these findings warrant cautious interpretation, as the trials were not powered to detect rare psychiatric events such as suicidal ideation or self-injurious behavior. Moreover, participants with preexisting psychiatric disorders—a group at highest clinical risk—were systematically excluded, limiting external validity. Comprehensive prospective studies with longer follow-up durations and structured psychiatric evaluations are required to better characterize potential risks. Updated US Food and Drug Administration (FDA) labeling for liraglutide and semaglutide recommends active monitoring for depressive symptoms and suicidal thoughts, with discontinuation of therapy if such adverse effects emerge.[44]

Ocular Adverse Effects

While GLP-1 RAs provide robust diabetes regulation and cardiometabolic benefits, their involvement in the advancement of diabetic retinopathy (DR) remains incompletely defined. Concerns were first raised in 2016 during the SUSTAIN-6 study, semaglutide treatment (0.5 or 1.0 mg) over a 104-week period was associated with an elevated risk of diabetic retinopathy events, including vitreous hemorrhage, visual impairment, and ocular interventions, relative to placebo.[45] Findings from the LEADER study indicated a higher, albeit non-significant, rate of diabetic retinopathy complications in the liraglutide group relative to placebo.[26]

One leading hypothesis attributes the phenomenon of retinopathy worsening has been linked to the rapid improvement in glycemic control, which alters osmotic gradients and may induce retinal hypoxia rather than reflecting a direct drug-related retinal toxicity.[46] Hypoxic conditions could secondarily influence vascular endothelial growth factor (VEGF) signaling, thereby modulating angiogenic pathways.[47] Further, preclinical studies propose that GLP-1 may upregulate VEGF expression and stimulate proliferation of endothelial progenitor cells, raising the possibility that angiogenesis could exacerbate retinal pathology.[48] Preclinical models have revealed that GLP-1 signaling can attenuate retinal neurodegeneration and suppress proinflammatory cascades, which may mitigate DR progression.

Evidence from a meta-analysis of 13 RCTs indicated that GLP-1 receptor agonist therapy was associated with a 23% higher risk of rapid worsening of diabetic retinopathy, with prolonged treatment duration further elevating risk.[49] *Post hoc* analyses of SUSTAIN-6 further highlighted that patients with pre-existing DR, particularly those treated with concomitant insulin, experienced the greatest risk, consistent with the phenomenon of acute retinopathy progression following rapid HbA1c reduction.[46] Analysis of the TriNeX database in a retrospective cohort study demonstrated that patients receiving GLP-1 RA with insulin exhibited greater risks of diabetic retinopathy and diabetic macular edema relative to those treated with SGLT-2 inhibitors plus insulin.[50] These findings reinforce the relevance of individualized patient selection, baseline retinal status, and rate of glycemic improvement as critical factors influencing DR outcomes during GLP-1 RA therapy.

Nonarteritic Anterior Ischemic Optic Neuropathy

The condition represents the leading acute optic neuropathy in adults and is marked by ischemic insult to the optic nerve head, producing sudden and painless visual loss. Despite its clinical relevance, the pathophysiology of nonarteritic anterior ischemic optic neuropathy (NAION) remains poorly understood.[51] Recent evidence has suggested a possible link between GLP-1 RAs, particularly semaglutide, and NAION. Although the mechanistic basis of this association is uncertain, several pathways may be implicated. GLP-1 signaling influences vascular homeostasis, endothelial function, and neuroprotection, each of which could theoretically modify susceptibility to optic nerve ischemia. Similar to the ambiguous findings regarding GLP-1 RAs and diabetic retinopathy, the biological plausibility of NAION risk requires further elucidation through mechanistic and clinical research.

To address these uncertainties, the dedicated ophthalmic FOCUS trial (NCT03811561) is currently underway. This study is designed to investigate the prolonged effects of semaglutide on the progression of diabetic retinopathy and may also provide insights into broader ocular safety, thereby refining the overall risk-benefit assessment of GLP-1 RAs among individuals with T2DM or overweight.[52] Tirzepatide appears comparable to semaglutide in ocular safety based on limited data, with no heightened risk specifically observed. Both drugs warrant caution—monitor vision changes, especially

Table 4: The comparative differences between semaglutide versus tirzepatide-related adverse events

Feature	*Semaglutide*	*Tirzepatide*
Mechanism-related	Pure GLP-1 receptor agonist → strong effect on gastric emptying and satiety	Dual GIP + GLP-1 receptor agonist → broader incretin action, somewhat less gastric delay
Gastrointestinal (most common AEs)	Nausea, vomiting, diarrhea, constipation, abdominal pain. GI events occur in 20–30% of patients, usually transient.	Similar profile (nausea, vomiting, diarrhea), but some trials (SURPASS, SURMOUNT) suggest slightly lower GI intolerance than semaglutide at equivalent weight loss levels.
Gastroparesis	Well-documented; delayed gastric emptying can progress to drug-induced gastroparesis in susceptible patients.	Reported but possibly less pronounced, as GIP component may mitigate gastric stasis (data still emerging).
Injection-site reactions	Rare (mild erythema, pain, swelling).	Similar frequency, generally mild.
Hypoglycemia	Rare, unless combined with insulin or sulfonylurea.	Same risk, but greater HbA1c reduction may predispose to more frequent mild hypoglycemia when combined with other agents.
Weight loss–related AEs	Cholelithiasis, cholecystitis due to rapid weight reduction.	Same risk, possibly higher due to greater average weight loss (15–20%).
Pancreatitis	Rare but reported; caution in history of pancreatitis.	Rare; similar concern as semaglutide.
Cardiovascular effects	CV benefit established in SUSTAIN-6 and SELECT trials.	CV outcome trial (SURPASS-CVOT) ongoing; early signals suggest potential benefit but not yet confirmed.
Other systemic AEs	Headache, dizziness, fatigue, mild increases in amylase/lipase.	Similar, but some reports of mild hair loss and reduced appetite being more pronounced.
Overall tolerability	High, but GI intolerance is the main discontinuation cause.	Appears better tolerated at equivalent efficacy, but long-term real-world safety still being studied.

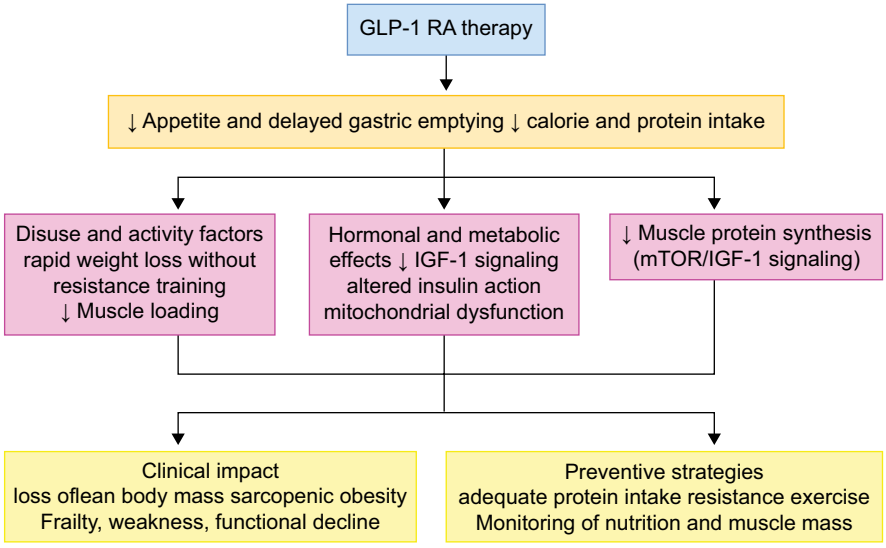

Fig. 4: GLP-1 RA-associated proposed mechanism of sarcopenia

in patients with preexisting ocular conditions or risk factors (Table 4).

While uniform recommendations for pretreatment retinopathy or optic nerve screening cannot yet be justified due to conflicting data, clinicians should carefully weigh the individual risk-benefit profile, especially among individuals with preexisting ocular disease. Patient counseling regarding possible visual side effects, coupled with regular ophthalmologic evaluations, represents a prudent strategy until more definitive evidence becomes available.

Sarcopenia

Glucagon-like peptide-1 RAs, particularly semaglutide, have revolutionized the management of T2DM and overweight by inducing clinically meaningful weight reduction and improving cardiometabolic outcomes. However, alongside pronounced fat mass reduction, emerging body-composition analyses indicate concurrent declines in fat-free mass (FFM), leading to apprehension over treatment-emergent sarcopenia—particularly among older adults and individuals with limited baseline muscle reserve.

In the STEP-1 trial and its dual-energy X-ray absorptiometry (DXA) substudy, semaglutide produced greater absolute reductions in fat mass compared with lean tissue; nonetheless, the proportion of total weight loss attributable to FFM was substantial, prompting debate regarding the qualitative aspects of weight loss.[7] Subsequent analyses and reviews suggest that approximately 25–40% of weight lost with GLP-1 RAs may be FFM, a range consistent with other rapid weight-loss interventions, but clinically significant in individuals at risk for sarcopenia.[53]

Semaglutide's appetite-suppressive effects and gastrointestinal adverse events can limit both total caloric and protein intake. In addition, rapid negative energy balance, diminished mechanical loading due to weight loss, reduced physical activity, and age-related anabolic resistance may further predispose to muscle catabolism. Importantly, observational and interventional evidence indicates that structured resistance training combined with adequate dietary protein intake can attenuate or prevent excessive FFM loss during GLP-1 RA therapy (Fig. 4). Indeed, multimodal strategies integrating pharmacotherapy with lifestyle interventions appear more effective for preserving musculoskeletal health than either approach alone.[54]

High-risk populations—including older adults, individuals with sarcopenic obesity, chronic comorbidities, or low habitual physical

Table 5: The comparative differences between injectable vs oral semaglutide-related adverse events

Feature	*Injectable semaglutide*	*Oral semaglutide*
Route-specific issues	Injection-site reactions (erythema, swelling, pain, pruritus)–mild and self-limiting	GI irritation due to tablet formulation; requires an empty stomach + water (30 min fasting) → adherence issue
Gastrointestinal adverse effects	Very common: nausea, vomiting, diarrhea, constipation, abdominal pain. Usually dose-dependent and transient.	Higher rates of nausea, dyspepsia, abdominal discomfort compared to injectable, likely due to variable absorption and local gastric irritation
Gastroparesis risk	Reported (delayed gastric emptying leading to drug-induced gastroparesis); usually after dose escalation	Reported as well, but some studies suggest slightly higher upper GI intolerance due to prolonged gastric presence of the tablet
Hypoglycemia	Rare (mostly when combined with sulfonylurea/insulin)	Similar risk profile
Systemic adverse effects	Headache, fatigue, nasopharyngitis	Headache, dizziness, fatigue reported, but less prominent
Cardiovascular safety	Established cardiovascular benefit in injectable semaglutide (SUSTAIN-6, STEP trials)	Cardiovascular outcomes for oral semaglutide less robust, ongoing trials
Other concerns	Possible risk of gallbladder disease (cholelithiasis, cholecystitis), pancreatitis (rare), medullary thyroid carcinoma risk in rodents	Similar risks, but fewer long-term real-world safety data compared to injectable
Tolerability	Better long-term tolerability; GI events often resolve after initial weeks	Slightly lower tolerability due to persistent GI upset and strict administration requirements

activity—may warrant proactive screening for muscle health during treatment.

Proposed Mechanisms of GLP-1 RA-associated Sarcopenia

Calorie Restriction and Rapid Weight Loss

- Glucagon-like peptide-1 RAs reduce appetite, delay gastric emptying, and promote satiety. This leads to a negative energy balance, in which not only fat mass but also lean body mass (LBM) is reduced. Rapid or excessive weight loss disproportionately increases loss of skeletal muscle mass.

Reduced Protein Intake

- Appetite suppression may decrease overall dietary protein consumption, impairing muscle protein synthesis.

Altered Muscle Protein Turnover

- Glucagon-like peptide-1 may influence mTOR signaling pathways indirectly, potentially suppressing protein synthesis under catabolic conditions. Increased fat oxidation and decreased glucose utilization could shift energy balance away from supporting muscle growth.

Mitochondrial Dysfunction in Muscle

- Some studies suggest GLP-1 RAs may alter mitochondrial biogenesis or efficiency, possibly reducing skeletal muscle endurance and repair capacity.

Hormonal and Myokine Changes

- Weight loss is often accompanied by reduced insulin and IGF-1 signaling, which are anabolic for muscle. Changes in adipokines and myokines (e.g., irisin, myostatin) may further promote catabolism.

Physical Inactivity during Treatment

- Patients on GLP-1 RAs may not adequately increase resistance or strength exercise while losing weight. This accelerates muscle loss relative to fat loss, contributing to sarcopenia.

In the SUSTAIN 8 trial, individuals with type 2 diabetes experienced an average reduction of 2.3 kg in lean mass out of a total 5.3 kg weight loss, corresponding to 43.4% of overall weight reduction. Ongoing clinical investigation is addressing this issue more directly; for instance, a randomized, multicenter trial (NCT05616013) is actively investigating the safety and therapeutic efficacy of bimagrumab—an activin type II receptor inhibitor—administered alone or in combination with subcutaneous semaglutide to assess effects on sarcopenia risk.[55]

Future investigations of GLP-1–based therapies must prioritize rigorous assessment of muscle mass, composition, and functional endpoints to better understand their influence on musculoskeletal health. Early identification of at-risk populations, coupled with preventive strategies such as resistance training and optimized protein intake, is essential—particularly for older adults and frail individuals.

Other Cancers

Emerging evidence has drawn attention to a potential link between GLP-1 RAs and various neoplasms, including thyroid, breast, and cholangiocarcinoma.[56] In a 2020 clinical investigation in a cohort of patients with nonalcoholic steatohepatitis, tumors—whether benign, malignant, or unspecified—were observed in 15% (35/239) of participants treated among those receiving semaglutide vs 8% (6/80) in the control cohort.[57]

Pharmacovigilance analyses have provided additional signals. Evaluation of the FAERS between 2004 and 2020 demonstrated notable disproportionality signals for several cancers, including medullary thyroid carcinoma (PRR 27.43), papillary thyroid carcinoma (PRR 8.68), malignant pancreatic tumors (PRR 9.86), and pancreatic neuroendocrine neoplasms (PRR 2.86).[30] The FDA has previously issued advisories highlighting the potential for medullary thyroid carcinoma with GLP-1 RA therapy. However, such advisories may increase the likelihood of thyroid ultrasound screening in treated patients, potentially inflating tumor detection rates.

Despite these associations, important caveats exist. Many spontaneous reports lack confirmation by healthcare professionals, and critical contextual data—including comorbidities, family history, and lifestyle factors such as alcohol and tobacco use—are often missing. Consequently, FAERS-based findings are susceptible to reporting bias and cannot establish causality.

At present, the oncogenic potential of GLP-1 RAs remains unresolved. Future prospective, long-term studies with rigorous cancer endpoints are essential to determine whether observed associations reflect true biological risk or detection bias. Until such evidence emerges, GLP-1 RAs should not be withheld solely due to cancer concerns. Nevertheless, clinicians should remain vigilant, particularly in patients with preexisting oncologic risk factors, and incorporate careful surveillance into routine practice.

Semaglutide, whether injectable or oral, commonly causes gastrointestinal side effects such as nausea, vomiting, and diarrhea. Injectable forms may lead to injection-site reactions and have more reported ocular complications, while oral formulations can cause gastric irritation if not taken properly. Both carry rare risks of pancreatitis, gallbladder disease, and retinopathy, though injectable semaglutide shows stronger weight loss efficacy, and oral semaglutide offers greater convenience and acceptability (Table 5).

Prevention of GLP-1 RA-associated Adverse Effects

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are now widely recognized for their efficacy in glycemic control, weight reduction, and cardiovascular protection. Despite these benefits, their clinical utility is often constrained by adverse effects, most notably gastrointestinal (GI) intolerance, gallbladder disorders, and rare but clinically significant complications such as pancreatitis and thyroid C-cell hyperplasia. A preventive framework, rooted in patient selection, dose optimization, and proactive management, is essential for maximizing therapeutic benefit while minimizing risks.

Patient Selection and Baseline Evaluation

Individualized risk stratification should precede GLP-1 RA initiation, including assessment of prior GI motility disorders, gallstone disease, pancreatitis, and family history of medullary thyroid carcinoma. Renal function evaluation is critical, as nausea, vomiting, and dehydration may exacerbate renal impairment. Special caution is warranted in older adults and frail patients, where weight loss may be detrimental.

Dose Titration and Formulation Strategies

Initiation at the lowest available dose, with gradual escalation every 2–4 weeks, substantially reduces GI side effects. Long-acting formulations (e.g., once-weekly semaglutide, dulaglutide) may offer superior tolerability compared to short-acting preparations. Avoid rapid up-titration in patients with heightened susceptibility to nausea or vomiting.

Dietary and Lifestyle Modifications

Patients should be counseled to consume smaller, more frequent meals and avoid high-fat or spicy foods during dose escalation. Adequate hydration is crucial to mitigate nausea and prevent renal complications. Alcohol moderation may reduce risks of pancreatitis and hepatobiliary complications.

Adjunctive Pharmacological Measures

Short-term use of antiemetic agents (e.g., ondansetron) or prokinetics (e.g., domperidone, metoclopramide) may be considered for refractory GI symptoms. Fiber supplementation and stool softeners can alleviate GLP-1 RA-induced constipation. Monitoring of concomitant therapies (e.g., insulin, sulfonylureas) is recommended to minimize hypoglycemia risk.

Monitoring and Early Detection of Serious Adverse Effects

Patients should be educated to promptly report persistent abdominal pain, vomiting, or jaundice, which may herald pancreatitis or gallbladder disease. Periodic liver function and pancreatic enzyme assessments may be prudent in high-risk individuals. Thyroid monitoring should be individualized, especially in those with nodular thyroid disease or family history of medullary thyroid carcinoma.

Patient Education and Shared Decision-making

Structured patient counseling programs improve adherence and tolerability by setting expectations regarding transient GI adverse effects. Shared decision-making, emphasizing both benefits and risks, ensures informed therapeutic choices and fosters long-term persistence.

Future Directions

Emerging evidence suggests that dual or triple agonists (e.g., GLP-1/GIP or GLP-1/glucagon co-agonists) may retain efficacy with an improved safety profile. Furthermore, the development of oral formulations with modified-release kinetics may help attenuate GI intolerance.

Conclusion

Glucagon-like peptide-1 RAs have become important therapeutic options for T2DM and obesity, providing benefits that go beyond glycemic control to include weight reduction and cardiovascular risk mitigation. Despite their efficacy, clinical use of GLP-1 RAs is linked to various adverse events, most commonly gastrointestinal symptoms related to delayed gastric emptying, but also less frequent complications such as pancreatitis, gallbladder disease, aspiration pneumonia, neuropsychiatric manifestations, and rare musculoskeletal or neoplastic outcomes. While many of these effects are transient and manageable, the possibility of severe or long-term complications highlights the need for individualized risk assessment, patient education, and ongoing monitoring. A mechanism-based understanding of these adverse effects can aid in early recognition, timely intervention, and informed decision-making. Preventing GLP-1 RA–associated adverse effects requires a multifaceted strategy integrating personalized patient selection, careful titration, lifestyle counseling, pharmacological adjuncts, and vigilant monitoring. Future research should continue to clarify the long-term safety profile of GLP-1 RAs to optimize their therapeutic potential while minimizing harm.

Author Contributions

Dr C Nawal and Dr H Saini contributed to the concept and design of this expert opinion document. The manuscript draft was developed by Dr G Rankawat and critically reviewed by all the authors. The manuscript was edited and modified by Dr G Rankawat and Dr R Chejara. The manuscript's final draft received approval from all contributing authors.

Orcid

Govind Rankawat https://orcid.org/0000-0003-3708-3068

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