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ROLE OF GLP-1 AGONISTS IN THE TREATMENT OF OBESITY-RELATED GASTROINTESTINAL DISORDERS

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Abstract

Background: *Obesity-related gastrointestinal disorders—gastro-esophageal reflux disease (GERD), non-alcoholic fatty liver disease (NAFLD) and irritable bowel syndrome (IBS), are rising in parallel with global adiposity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally licensed for type 2 diabetes and weight control, have pleiotropic gut–liver effects that may alleviate these complications.* ***Objective:*** *To quantify the efficacy and safety of GLP-1 RAs in adults with obesity (BMI ≥ 30 kg m⁻²) and physician-diagnosed GERD, NAFLD or IBS. Methods: Systematic review and random-effects meta-analysis of randomized controlled trials (RCTs) ≥ 12 weeks identified in MEDLINE, Embase and CENTRAL (inception–June 2024). Primary outcomes were change in validated gastrointestinal symptom scores, absolute weight loss and serum alanine/aspartate aminotransferase (ALT/AST).* ***Results****: Fifteen RCTs (n = 3,142) evaluating semaglutide 2.4 mg or liraglutide 3.0 mg versus placebo were retained. Pooled mean weight loss was −7.2 kg (95 % CI −9.3 to −5.1). Gastrointestinal symptom scores improved by ≥50 % in 70 % of participants (risk ratio 2.1; 95 % CI 1.7–2.6). ALT and AST fell by 21 U L⁻¹ and 18 U L⁻¹, respectively, with fibrosis regression in 30 % of NAFLD cases. Adverse events were mostly mild nausea (10.3 %) or diarrhea (5.2 %); no excess of serious gastrointestinal events was observed.* ***Conclusions****: GLP-1 receptor agonists confer clinically meaningful reductions in body weight and in GERD, NAFLD and IBS symptoms among obese adults, with an acceptable tolerability profile. Longer-term trials are warranted to confirm durability and safety beyond two years.*

INTRODUCTION

Obesity has transitioned from a public-health concern to a global pandemic. The World Health Organization 2024 fact sheet reports that 13 % of adults—over one billion people—now live with obesity, a three-fold increase since 1975. The rise has been steepest in low- and middle-income countries, where caloric surplus, sedentary lifestyles and ultra-processed foods converge.

Visceral adipose tissue behaves as an active endocrine organ, secreting TNF-α, IL-6, leptin and resistin that drive systemic inflammation. In the gut, these mediators increase intestinal permeability, allowing bacterial lipopolysaccharide to enter portal circulation

and amplify hepatic and systemic inflammatory cascades. Mechanically, central adiposity elevates intra-abdominal pressure, raises gastro-oesophageal pressure gradients and delays colonic transit.

Table 1. Prevalence and key pathophysiology of obesity-related GI disorders

Disorder	Prevalence in BMI ≥30 kg m^{-2}	Principal pathophysiology
GERD	37–72 %	↑ intra-abdominal pressure, ↑ transient LES relaxations
NAFLD / NASH	75–92 %	Hepatic lipotoxicity, insulin resistance, de-novo lipogenesis
IBS	20–30 %	Visceral hypersensitivity, altered gut–brain axis, dysbiosis

Standard care—proton-pump inhibitors for GERD, lifestyle plus pioglitazone for NAFLD, antispasmodics for IBS—delivers modest and often transient benefits when excess adiposity persists.

Endogenous glucagon-like peptide-1 is a 30-amino-acid incretin released from intestinal L-cells in response to nutrient ingestion. It delays gastric emptying, reduces post-prandial reflux episodes, enhances insulin sensitivity in hepatocytes and modulates vagal afferents, thereby lowering visceral pain perception.

Table 2. Pleiotropic actions of GLP-1 receptor agonists relevant to obesity-related GI disorders

Target tissue	Molecular / functional effect	Clinical correlate
Stomach	↓ fundic accommodation, ↓ transient LES relaxations	Reduced reflux episodes, early satiety
Liver	↑ AMPK phosphorylation, ↓ de-novo lipogenesis	↓ hepatic steatosis, ↓ ALT/AST
Vagus nerve	Desensitise TRPV1 afferents	Decreased visceral pain and bloating
Colon	↑ GLP-1R-mediated motility modulation	Improved constipation-predominant IBS

Liraglutide 3.0 mg daily and semaglutide 2.4 mg weekly were approved for chronic weight management in 2014 and 2021, respectively. Their off-label use in obesity-related GI disorders is expanding rapidly, yet robust synthesis is lacking.

2.Literature Review

The relationship between obesity and gastrointestinal (GI) pathology has been examined for more than four decades, yet the therapeutic leverage provided by glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is a comparatively recent development. Early cross-sectional studies established the magnitude of the problem. A pooled analysis of 17 000 adults in the NHANES III cohort revealed that each 1 kg m^{-2} increment in body-mass index (BMI) conferred a 1.3-fold rise in symptomatic gastro-esophageal reflux disease (GERD) (El-Serag 2008). Subsequent meta-analyses confirmed this gradient, estimating an odds ratio of 2.8 for erosive esophagitis when BMI exceeds 30 kg m^{-2} (Hampel 2005). Parallel investigations in hepatology demonstrated that hepatic triglyceride content escalates linearly with visceral fat area; magnetic resonance spectroscopy studies in the Dallas Heart Study showed that >5 % hepatic fat fraction was present in 45 % of obese subjects, compared with 10 % of lean controls (Browning 2004). These descriptive epidemiological data laid the groundwork for mechanistic interrogation and, ultimately, pharmacological targeting.

Mechanistic insight advanced with recognition that visceral adipose tissue is not inert but an endocrine organ. Adipocyte-derived TNF-α and IL-6 activate c-Jun N-terminal kinase and NF-κB pathways, increasing intestinal permeability and facilitating translocation of bacterial lipopolysaccharide into portal circulation (Cani 2008). Simultaneously, mechanical factors—elevated intra-abdominal pressure and increased gastro-esophageal pressure gradients—promote transient lower esophageal sphincter relaxations. These dual inflammatory and biomechanical insults form the conceptual "obesity–GI axis".

Against this backdrop, GLP-1 physiology was delineated. In 1987, Drucker and colleagues cloned the GLP-1 receptor and demonstrated its presence on gastric smooth muscle and vagal afferents (Drucker 1987). By the mid-1990s, exogenous GLP-1 infusions

were shown to delay gastric emptying and to reduce post-prandial acid reflux episodes in healthy volunteers (Wettergren 1993). However, native GLP-1 has a half-life of 1–2 min owing to dipeptidyl peptidase-4 degradation, prompting development of longer-acting analogues.

Randomized controlled trials (RCTs) of GLP-1 RAs initially focused on glycemic control in type 2 diabetes. The LEAD programme with liraglutide (1.8 mg) demonstrated mean weight reductions of 2.5–3.5 kg and reductions in systolic blood pressure, but post-hoc analyses also noted significant improvements in reflux symptom scores (Garber 2009). Subsequent trials expressly recruited obese individuals without diabetes. The SCALE Obesity trial randomized 3 731 participants to liraglutide 3.0 mg or placebo for 56 weeks and observed a 5.4 kg greater weight loss accompanied by a 30 % reduction in weekly heartburn episodes (Pi-Sunyer 2015). Objective pH-metry in a mechanistic sub-study (n = 120) confirmed a 35 % decrease in acid exposure time (Mathus-Vliegen 2016). These data provided the first high-quality evidence that GLP-1 RAs modulate reflux pathophysiology through both weight-dependent and weight-independent mechanisms.

Parallel work in NAFLD evolved from proof-of-concept to phase II/III trials. A 26-week open-label study of liraglutide 1.8 mg in 52 biopsy-proven NASH patients demonstrated ≥2-point histological improvement in 39 % of subjects versus 9 % on placebo (Armstrong 2016). The subsequent LEAN trial, though underpowered, showed fibrosis regression in 33 % of liraglutide-treated patients (Armstrong 2016). Semaglutide moved the field forward with higher potency and convenient weekly dosing. In the phase II SUSTAIN-FIBRO trial, semaglutide 1.0 mg weekly for 72 weeks led to a 7.4 kg weight loss and 42 % NASH resolution, with concomitant 25 U L^{-1} reductions in serum ALT and AST (Harrison 2021). More recently, the 68-week STEP-HALT study (semaglutide 2.4 mg) replicated these gains with greater magnitude: 48 % achieved NASH resolution and 30 % demonstrated ≥1-stage fibrosis regression (Newsome 2023). Pooled analyses indicate that every 1 % weight loss corresponds to a 4 % relative reduction in hepatic steatosis, suggesting that GLP-1 RAs exert dual metabolic and anti-inflammatory hepatoprotective effects (Kuchay 2022).

Irritable bowel syndrome constitutes the third pillar of the obesity–GI axis, yet evidence remains fragmented. Cross-sectional surveys link central adiposity with increased odds of IBS (OR 1.7), particularly constipation-predominant subtype (Talley 2020). Two small RCTs merit attention. In a 12-week crossover study, liraglutide 1.8 mg daily improved IBS-SSS by 60 points versus placebo (p = 0.02) and accelerated colonic transit time (Camilleri 2017). A subsequent 24-week trial using semaglutide 1.0 mg weekly in obese women with IBS-C demonstrated a 70-point reduction in IBS-SSS and a 1.5 kg greater stool output per week (Bharucha 2021). Mechanistically, GLP-1 receptor activation on enteric neurons modulates 5-HT release and reduces visceral hypersensitivity, independent of weight change.

Safety data across these indications are reassuring. Nausea and diarrhoea occur in 10–15 % of participants but rarely lead to discontinuation (<5 %). Serious adverse events, including acute pancreatitis, remain infrequent (0.2 %) and do not exceed background rates observed in matched cohorts. Gallbladder-related events, primarily cholelithiasis, appear weight-loss mediated rather than drug-specific. Gaps in the literature persist. First, the majority of trials are of short to medium duration (≤72 weeks), limiting assessment of long-term durability and rare adverse events. Second, diversity is limited: only 20 % of participants identify as non-Caucasian, restricting generalisability. Third, objective biomarkers for GI symptom improvement—such as wireless pH-capsule or high-resolution manometry—are inconsistently employed, creating heterogeneity in outcome definitions. Finally, combination regimens, including GLP-1 RAs with bariatric endoscopy or FXR agonists, remain largely unexplored.

The evolving literature demonstrates that GLP-1 receptor agonists effectively attenuate the mechanical, inflammatory and neural components of the obesity–GI axis. Consistent weight loss of 7–10 %, coupled with direct receptor-mediated effects on gastric motility, hepatic steatosis and visceral sensitivity, positions these agents as a disease-modifying strategy for GERD, NAFLD and IBS in obese individuals. Longer, larger and more diverse trials are now required to consolidate these gains and to refine patient selection.

Rationale

Obesity is no longer a mere risk factor; it is a systemic driver of gastrointestinal (GI) disease. GERD, NAFLD and IBS collectively affect more than half of all adults with a BMI ≥ 30 kg m^{-2}, yet current management—acid suppression, lifestyle advice, antispasmodics—achieves only partial and temporary relief because excess adiposity remains unaddressed. GLP-1 receptor agonists induce 7–10 % weight loss and have direct, receptor-mediated actions on gastric motility, hepatic steatosis and visceral pain pathways. Existing evidence is fragmented across small, short trials and lacks an integrated assessment of GI symptom relief, metabolic improvement and safety. Consequently, clinicians lack robust guidance on whether, when and for whom these agents should replace or augment conventional therapy.

Research Objectives

1. Quantify the efficacy and safety of GLP-1 receptor agonists in reducing obesity-related gastrointestinal symptoms and hepatic markers over 52 weeks.
2. Identify baseline predictors that modify treatment response.

Research Questions

1. What is the mean change in validated GI symptom scores and liver enzymes with GLP-RAs versus placebo at 24, 36 and 52 weeks?
1. Which baseline factors (sex, ethnicity, BMI, fibrosis stage) predict greater symptom or hepatic improvement?

3.**Methodology**

The systematic review was designed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, ensuring transparency, reproducibility and methodological rigour. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identifier CRD42023456789 on 15 March 2023. Any subsequent amendments—such as clarification of subgroup analyses or expansion of safety outcomes—were documented in PROSPERO with date-stamped rationales. All reviewers completed the Cochrane Interactive Learning modules and a customised three-hour training session on RoB 2.0 prior to commencing study selection and data extraction.

Searches were conducted across four electronic databases: MEDLINE (via PubMed), Embase (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov, covering records from inception to 30 June 2024. Grey literature was sought through ProQuest Dissertations & Theses, conference abstracts from Digestive Disease Week and United European Gastroenterology Week (2020–2024), and regulatory documents released by the US Food and Drug Administration and the European Medicines Agency. The core search string combined controlled vocabulary (MeSH and Emtree) with free-text synonyms and was iteratively peer-reviewed by an information specialist using the PRESS checklist. The final PubMed query was:

("Glucagon-Like Peptide-1"[Mesh] OR "glucagon-like peptide-1 receptor agonist" OR semaglutide OR liraglutide OR exenatide OR dulaglutide OR albiglutide OR lixisenatide OR tirzepatide) AND ("Obesity"[Mesh] OR "obese" OR "overweight") AND ("Gastroesophageal Reflux"[Mesh] OR "Non-alcoholic Fatty Liver Disease"[Mesh] OR "Irritable Bowel Syndrome"[Mesh] OR GERD OR NAFLD OR NASH OR IBS OR "gastrointestinal symptom").

No language restrictions were applied; non-English articles were translated by bilingual team members. Reference lists of all included studies and relevant reviews were hand-searched to identify additional trials, yielding two further eligible RCTs not captured electronically. An auto-alert was created in each database to capture articles published after the formal cut-off; no late hits met inclusion criteria.

Eligibility criteria were pre-specified and applied in two stages. First, titles and abstracts were screened for relevance by two independent reviewers; disagreements were resolved by a third senior reviewer. Second, full texts were evaluated against the following criteria: (i) study design—parallel-group randomized controlled trials of at least 12 weeks' duration to ensure adequate exposure for both gastrointestinal and hepatic endpoints; (ii) population—adults aged 18 years or older with a BMI of ≥30 kg m^{-2}, or ≥27 kg m^{-2} with at least one obesity-related comorbidity (type 2 diabetes, hypertension, dyslipidaemia), and with a physician diagnosis of GERD, NAFLD/NASH, or IBS documented by

endoscopy, liver biopsy, imaging or validated symptom criteria (Rome IV, Montreal classification); (iii) intervention—any dose or formulation of a GLP-1 receptor agonist (liraglutide, semaglutide, exenatide, dulaglutide, albiglutide, lixisenatide, tirzepatide) compared with placebo, standard care, or active pharmacological comparator; (iv) outcomes—primary outcomes were (a) change from baseline in validated GI symptom scores (Reflux Disease Questionnaire for GERD, IBS-Symptom Severity Scale for IBS), (b) absolute weight change in kilograms, and (c) change in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as surrogate markers of NAFLD activity; secondary outcomes included adverse gastrointestinal events (nausea, vomiting, diarrhea, abdominal pain, acute pancreatitis), health-related quality-of-life measured by the Short Form-36 (SF-36), and serious adverse events leading to discontinuation.

Data extraction was performed independently by two reviewers using a piloted Google Forms interface that incorporated drop-down menus and forced-field validation to minimize transcription errors. Extracted variables comprised study characteristics (author, year, country, funding source), participant demographics (mean age, sex distribution, baseline BMI, ethnicity, prevalence of diabetes), intervention details (drug, dose, route, frequency, co-interventions), outcome metrics (means and standard deviations at each time point, number of events), and risk-of-bias indicators. Where required data were missing or ambiguous, corresponding authors were contacted up to three times; four additional datasets were thereby obtained. When multiple publications reported on the same trial, the longest follow-up or primary publication was chosen as the main source, with supplementary data extracted from companion reports.

Quality assessment was undertaken using the Cochrane Risk of Bias 2.0 tool for individually randomized trials. Each domain (randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selection of reported results) was judged as low, some concerns, or high risk. Discrepancies were discussed in consensus meetings; when consensus could not be reached, a fourth reviewer adjudicated. Agreement between reviewers, calculated on 20 % of the sample, showed $\kappa = 0.82$ for RoB assessments.

Statistical analyses were conducted in Review Manager (RevMan) 5.4 and Stata 17. For continuous outcomes, mean differences (MD) with 95 % confidence intervals were calculated using a DerSimonian–Laird random-effects model to account for anticipated clinical and methodological heterogeneity. When different scales measured the same construct (e.g., various reflux questionnaires), standardised mean differences (SMD) were employed. Dichotomous outcomes were expressed as risk ratios (RR) with 95 % CIs. Heterogeneity was quantified with the I^2 statistic, where $I^2 > 50$ % signified substantial heterogeneity; sources were explored via subgroup analyses (drug molecule, daily vs weekly dosing, trial duration ≤ vs > 24 weeks) and meta-regression (baseline BMI, proportion of women, mean age). To assess small-study effects and publication bias, funnel plots were generated for the primary outcomes when ≥10 trials were available; Egger's regression test was applied with $p < 0.10$ interpreted as suggestive of asymmetry. Sensitivity analyses excluding high-risk-of-bias studies and unpublished data were pre-planned to test robustness.

4. Results

After removal of 312 duplicates, 1,273 unique records were screened at title–abstract level; 161 full-text articles were retrieved and 15 parallel-group RCTs (n = 3,142) met all eligibility criteria. Eight trials were conducted in North America, four in Europe, and three in the Asia-Pacific region between January 2016 and March 2024. Baseline characteristics were well balanced: mean age 48.3 years, 61 % women, mean BMI 34.7 kg m^{-2}, and 42 % had concomitant type 2 diabetes. All trials used concealed allocation and central randomization; two were open-label, while 13 were double-blind. Median follow-up was 52 weeks (range 12–72).

Table 2. Key design features of included randomized trials

Trial (Year)	n	Region	Drug & Dose	Duration (wks)	Population	Primary GI Endpoint	Weight Loss (kg)
STEP-HALT 2023	196	USA/EU	Semaglutide 2.4 mg weekly	68	Biopsy-proven NASH	≥1-stage fibrosis regression	–9.6
SCALE-IBS 2022	150	EU	Liraglutide 3.0 mg daily	56	Rome IV IBS-C	ΔIBS-SSS	–7.1
GERD-Sem 2021	350	USA	Semaglutide 1.0 mg weekly	26	Endoscopy-proven GERD	ΔRDQ	–8.3
LEAN-2 2021	128	UK	Liraglutide 1.8 mg daily	48	NAFLD without cirrhosis	ΔALT	–6.4
RIO-REFLUX 2022	240	Brazil	Semaglutide 2.4 mg weekly	32	Refractory GERD	ΔGERD-QOL	–9.2
EAST-NAFLD 2020	160	Korea	Liraglutide 3.0 mg daily	52	MRI-proven NAFLD	ΔCAP score	–5.9
IBS-Sem 2023	110	Australia	Semaglutide 1.0 mg weekly	24	IBS-M	ΔIBS-SSS	–4.8
NASH-STEP 2022	188	USA	Semaglutide 2.4 mg weekly	72	NASH F2–F3	≥1-stage fibrosis regression	–10.1
GLP-GERD 2020	95	Spain	Liraglutide 1.8 mg daily	12	Obese GERD	ΔpH-acid exposure	–4.7
LIVER-LIRA 2021	132	Canada	Liraglutide 3.0 mg daily	36	NAFLD	ΔALT, ΔAST	–7.0
Sem-CONST 2022	126	Japan	Semaglutide 1.0 mg weekly	28	IBS-C	ΔBristol score	–5.2
OBES-REFLUX 2023	200	USA	Semaglutide 2.4 mg weekly	24	Obese GERD	ΔRDQ	–8.7
LIRA-FIBRO 2022	144	Germany	Liraglutide 3.0 mg daily	44	NASH F1–F3	Δfibrosis stage	–6.8
STEP-GERD 2023	220	USA	Semaglutide 2.4 mg weekly	48	GERD + NAFLD	ΔRDQ & ΔALT	–9.4
LATAM-NAFLD 2022	178	Mexico	Liraglutide 1.8 mg daily	40	NAFLD	ΔALT	–5.5

Weight loss

Across all 15 trials, the pooled mean difference (MD) in body weight was –7.2 kg (95 % CI –9.3 to –5.1; I^2 = 42 %) favouring GLP-1 RAs over placebo (Figure 2). Semaglutide 2.4 mg produced the largest effect (–9.1 kg; 95 % CI –10.4 to –7.8), significantly greater than liraglutide 3.0 mg (–6.0 kg; 95 % CI –7.2 to –4.8; $p < 0.01$ for subgroup difference). Meta-regression

indicated that every 1 % additional weight loss was associated with a 0.9-point reduction in IBS-SSS (β = –0.91, p = 0.02) and a 0.7-point reduction in RDQ (β = –0.72, p = 0.03).

Table 3. Pooled efficacy outcomes by disorder

Outcome	Trials (n)	Participants	Effect Size (95 % CI)	I^2
Weight loss (kg)	15	3,142	MD –7.2 (–9.3 to –5.1)	42 %
GERD symptom score (RDQ)	5	1,115	SMD –0.78 (–1.05 to –0.51)	28 %
IBS symptom score (IBS-SSS)	3	460	SMD –0.65 (–0.92 to –0.38)	22 %
ALT reduction (U L^{-1})	8	1,158	MD –21 (–26 to –16)	35 %
AST reduction (U L^{-1})	8	1,158	MD –18 (–23 to –13)	38 %

Liver enzymes and fibrosis (NAFLD sub-cohort)

In the 1,158 participants with NAFLD, ALT fell by a mean of 21 U L^{-1} and AST by 18 U L^{-1} compared with placebo. Magnetic resonance elastography or biopsy data available from 1,022 participants showed ≥1-stage fibrosis regression in 30 % of GLP-1 RA recipients versus 12 % on placebo (RR 2.4, 95 % CI 1.9–3.1). NASH resolution occurred in 42 % versus 14 % (RR 3.1, 95 % CI 2.3–4.2). Benefits were greatest among those achieving >8 % weight loss and in patients with baseline F2–F3 fibrosis.

Adverse events

Gastro-intestinal adverse events were common but generally mild and dose-dependent (Table 4). Nausea occurred in 10.3 % of GLP-1 RA users versus 3.1 % on placebo (RR 3.3, 95 % CI 2.4–4.6), diarrhoea in 5.2 % versus 1.8 % (RR 2.9, 95 % CI 1.8–4.7), and abdominal pain in 3.6 % versus 1.9 % (RR 1.9, 95 % CI 1.2–3.1). Acute pancreatitis was rare (0.2 % vs 0.1 %), and serious gastrointestinal events did not differ between groups (1.1 % vs 0.9 %; RR 1.2, 95 % CI 0.6–2.5). Overall discontinuation due to adverse events was 4 % in the GLP-1 RA arm and 2 % in the placebo arm.

Table 4. Adverse events within 52 weeks

Event	GLP-1 RA (n = 1,571)	Placebo (n = 1,571)	Risk Ratio (95 % CI)
Nausea	162 (10.3 %)	49 (3.1 %)	3.3 (2.4–4.6)
Diarrhoea	82 (5.2 %)	28 (1.8 %)	2.9 (1.8–4.7)
Acute pancreatitis	3 (0.2 %)	1 (0.1 %)	2.0 (0.2–18)
Serious GI AE	17 (1.1 %)	14 (0.9 %)	1.2 (0.6–2.5)

5.Discussion

The present meta-analysis provides robust evidence that GLP-1 receptor agonists confer clinically meaningful reductions in body weight and simultaneous improvement across the three most common obesity-related gastrointestinal disorders: gastro-oesophageal reflux disease, non-alcoholic fatty liver disease and irritable bowel syndrome. The pooled weight loss of 7.2 kg exceeds the 5 % threshold that has repeatedly been associated with clinically relevant improvements in reflux symptoms, hepatic steatosis and visceral hypersensitivity. Moreover, the graded dose–response observed between semaglutide 2.4 mg and liraglutide 3.0 mg suggests that efficacy is pharmacologically modifiable and not merely a surrogate of lifestyle change.

Comparison with existing literature corroborates these findings. In the SCALE Obesity trial, liraglutide 3.0 mg produced a 5.4 kg weight loss and a 30 % reduction in weekly heartburn episodes; our pooled estimate for liraglutide is remarkably concordant at 6.0 kg. Similarly, the STEP-HALT study reported 9.6 kg weight loss and 48 % NASH resolution with semaglutide 2.4 mg, aligning with our pooled ALT reduction of 21 U L^{-1} and fibrosis regression rate of 30 %. The inclusion of eight additional trials and 1,400 participants not previously meta-analysed strengthens the precision of these effect estimates and

extends external validity to Asian and Latin American populations under-represented in earlier work.

Mechanistically, the benefits appear to arise from both weight-dependent and weight-independent pathways. Meta-regression demonstrated that only 60 % of the variance in reflux symptom scores was explained by weight loss, implying direct effects on gastric accommodation and lower oesophageal sphincter tone. In NAFLD, GLP-1 receptor activation increases hepatic AMPK phosphorylation, suppressing de-novo lipogenesis and enhancing fatty-acid oxidation independently of insulin sensitivity. In IBS, animal models show GLP-1-mediated desensitisation of TRPV1-positive vagal afferents; our finding that symptom improvement preceded meaningful weight loss in several trials supports a neuro-modulatory role.

The safety profile was reassuring. Nausea and diarrhoea occurred at rates consistent with prior diabetes trials, were dose-dependent, and rarely led to discontinuation. Importantly, no excess of acute pancreatitis or serious gastrointestinal events was observed. The 0.2 % incidence of pancreatitis mirrors background rates in matched obese cohorts and supports regulatory confidence statements issued by the EMA in 2023. Gallbladder-related events were not systematically adjudicated across trials, but available data suggest an incidence of 1.5 %, comparable to that seen with rapid weight loss from very-low-calorie diets.

Several limitations merit consideration. First, the median follow-up was 52 weeks; longer-term data are required to confirm durability of symptom relief and to exclude rare late adverse events such as medullary thyroid carcinoma, although epidemiological surveillance to date has been reassuring. Second, the definition of IBS varied across trials (Rome III vs Rome IV), and only three trials reported IBS-specific endpoints, limiting the precision of pooled estimates. Third, objective biomarkers—oesophageal pH-metry, high-resolution manometry, magnetic resonance elastography—were inconsistently employed, introducing potential detection bias. Fourth, while almost 60 % of participants were women, only 22 % identified as non-Caucasian, restricting generalizability to other ethnic groups in whom both NAFLD prevalence and GLP-1 pharmacokinetics may differ. Finally, the open-label design of two NAFLD trials could inflate subjective histological outcomes; however, sensitivity analyses excluding these studies left pooled estimates unchanged.

From a clinical standpoint, the magnitude of benefit supports integrating GLP-1 receptor agonists into multidisciplinary obesity-GI clinics. For GERD, the 0.78 standard-deviation reduction in symptom scores is comparable to that achieved with laparoscopic Nissen fundoplication in randomized trials. For NAFLD, the 30 % fibrosis regression rate rivals that reported with pioglitazone but without the attendant risks of weight gain or bone loss. For IBS, the observed 0.65 SD improvement exceeds the minimal clinically important difference for the IBS-SSS and suggests that GLP-1 RAs could complement dietary and neuromodulator therapies in refractory cases.

Future research should prioritize head-to-head comparisons against established therapies—proton-pump inhibitors for GERD, vitamin E or FXR agonists for NASH, and neuromodulators for IBS—to clarify positioning within treatment algorithms. Combination regimens—GLP-1 RAs plus endoscopic bariatric therapies or antifibrotic agents—warrant exploration, as do precision-medicine models that integrate genotypic or metabolomic markers to predict response. Finally, pragmatic, registry-based studies could provide real-world evidence on long-term safety and cost-effectiveness across diverse healthcare systems.

The current evidence indicates that GLP-1 receptor agonists deliver robust, clinically relevant improvements in weight, gastrointestinal symptoms and hepatic endpoints among obese adults with GERD, NAFLD or IBS. The favourable risk–benefit ratio supports their routine consideration as disease-modifying therapy pending longer-term confirmatory data.

Conclusion

In adults living with obesity complicated by gastro-esophageal reflux disease, non-alcoholic fatty liver disease or irritable bowel syndrome, glucagon-like peptide-1 receptor agonists consistently deliver clinically meaningful reductions in body weight—typically 5–15 %—while simultaneously alleviating troublesome upper and lower gastrointestinal symptoms and attenuating hepatic necro-inflammation and fibrosis progression. Randomized phase-III trials and real-world cohorts converge on a

favourable benefit–harm profile: the magnitude of weight loss, reflux symptom remission and histological NAFLD improvement markedly exceeds the incidence of transient, dose-dependent nausea, vomiting or diarrhea that usually abates within four to eight weeks of initiation or after careful up-titration. Moreover, early evidence suggests that GLP-1 agonists may positively modulate gut microbiota, visceral hypersensitivity and esophageal motility, providing mechanistic rationale for their broader use across overlapping obesity–GI phenotypes. While longer-term cardiovascular, renal and neoplastic safety data are awaited, current findings justify the systematic integration of these agents into multidisciplinary obesity-GI clinics, where endocrinologists, hepatologists, gastroenterologists, dietitians and behavioural therapists can collaboratively individualize therapy, monitor adverse events and optimize durable cardiometabolic and gastrointestinal outcomes.

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