

Review Article

# Beyond Glycaemic Control: The Expanding Role of GLP-1 Receptor Agonists in Obesity, Obstructive Sleep Apnoea, Cardiovascular Disease, and Steatohepatitis: A Narrative Review

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## ABSTRACT

**Background:** Obesity and its associated metabolic complications, including type 2 diabetes mellitus, cardiovascular disease, obstructive sleep apnoea, and steatotic liver disease, represent interconnected clinical challenges driven by overlapping mechanisms such as insulin resistance, adiposity, inflammation, endothelial dysfunction, and altered hepatic metabolism. Glucagon-like peptide-1 receptor agonists were originally developed for glycaemic control, but accumulating evidence suggests broader therapeutic effects across obesity-related multimorbidity. **Objective:** This narrative review aimed to synthesize contemporary clinical and mechanistic evidence on GLP-1 receptor agonists and related incretin-based therapies beyond glycaemic control, with emphasis on obesity, cardiovascular disease, obstructive sleep apnoea, and metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis. **Methods:** A focused narrative synthesis was undertaken using evidence from randomized controlled trials, cardiovascular outcome trials, phase 2 and phase 3 studies, and clinically relevant mechanistic and review literature. Priority was given to human clinical evidence evaluating liraglutide, semaglutide, dulaglutide, tirzepatide, and related incretin-based therapies in obesity-related cardiometabolic, respiratory, and hepatic disease contexts. Findings were organized thematically by disease domain and interpreted according to evidence maturity, agent specificity, clinical relevance, and safety considerations. **Results:** The strongest evidence supports clinically meaningful weight reduction with liraglutide, semaglutide, and tirzepatide, and cardiovascular risk reduction with selected GLP-1 receptor agonists in high-risk populations. Evidence in obstructive sleep apnoea is emerging, with improvements largely linked to weight reduction, particularly in tirzepatide trials. Hepatic evidence in MASLD/MASH is promising but heterogeneous, with benefits varying by agent, fibrosis stage, and histological endpoint. Gastrointestinal adverse effects remain the most frequent tolerability concern, while long-term safety and durability in non-diabetic populations require continued evaluation. **Conclusion:** GLP-1 receptor agonists and related incretin-based therapies are increasingly relevant beyond diabetes management, particularly in obesity-centered cardiometabolic care. Their use should be evidence-calibrated, agent-specific, and integrated within multidisciplinary treatment pathways while further research clarifies long-term outcomes, comparative effectiveness, access, and emerging indications. **Keywords:** GLP-1 receptor agonists; obesity; cardiovascular disease; obstructive sleep apnoea; MASLD; MASH; semaglutide; tirzepatide.

## INTRODUCTION

The global rise in obesity and its cardiometabolic complications has reshaped the therapeutic priorities of modern medicine. Obesity, type 2 diabetes mellitus, cardiovascular disease, obstructive sleep apnoea,

and metabolic dysfunction-associated steatotic liver disease represent overlapping clinical entities rather than isolated disorders, sharing common pathways such as insulin resistance, chronic low-grade inflammation, visceral adiposity, endothelial dysfunction, altered hepatic lipid metabolism, and neurohormonal dysregulation. Within this interconnected disease spectrum, glucagon-like peptide-1 receptor agonists have gained increasing clinical importance because their effects extend beyond glucose lowering to include appetite regulation, clinically meaningful weight reduction, improvement in cardiometabolic risk markers, and potential benefits in obesity-related respiratory and hepatic complications (1).

Glucagon-like peptide-1 receptor agonists were initially developed as antihyperglycaemic agents for patients with type 2 diabetes mellitus, primarily through glucose-dependent stimulation of insulin secretion, suppression of glucagon release, slowing of gastric emptying, and enhancement of satiety. However, subsequent clinical evidence has demonstrated that these agents exert broader metabolic effects that are especially relevant in patients with obesity and obesity-related multimorbidity. Liraglutide and semaglutide have shown efficacy in chronic weight management, including in populations without diabetes, while newer incretin-based therapies have further expanded the therapeutic landscape. This shift is clinically important because even moderate weight loss can improve blood pressure, lipid profile, glycaemic status, systemic inflammation, functional capacity, and obesity-associated disease burden (2,3).

The cardiovascular relevance of glucagon-like peptide-1 receptor agonists has been strengthened by large cardiovascular outcome trials demonstrating reductions in major adverse cardiovascular events among selected high-risk populations. Trials involving agents such as liraglutide, semaglutide, and dulaglutide have supported the role of this drug class in cardiometabolic risk reduction, particularly among patients with type 2 diabetes and established or elevated risk of atherosclerotic cardiovascular disease (4–6). More recent evidence has extended interest to patients with obesity without diabetes, indicating that the benefits of incretin-based therapies may not be limited to glycaemic control alone. Nevertheless, the magnitude and nature of benefit vary by agent, population, baseline cardiovascular risk, and outcome assessed; therefore, careful distinction is needed between class-level evidence, agent-specific findings, and emerging indications.

Obstructive sleep apnoea and steatotic liver disease are two additional obesity-linked conditions in which incretin-based therapies have generated growing interest. In obstructive sleep apnoea, weight reduction remains a central therapeutic target because excess adiposity contributes to upper-airway collapsibility, impaired ventilatory control, nocturnal hypoxaemia, and systemic inflammation. Recent evidence involving tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, suggests clinically relevant improvement in sleep apnoea severity among individuals with obesity, although this evidence should be interpreted as agent-specific and still developing rather than as a uniform effect of all glucagon-like peptide-1 receptor agonists (7). Similarly, in non-alcoholic fatty liver disease and its progressive inflammatory phenotype, historically termed non-alcoholic steatohepatitis and increasingly classified under metabolic dysfunction-associated steatohepatitis, glucagon-like peptide-1 receptor agonists and related incretin-based agents may improve hepatic steatosis, inflammatory activity, and selected histological outcomes through weight-dependent and weight-independent mechanisms (8).

Despite this expanding evidence base, the clinical interpretation of glucagon-like peptide-1 receptor agonists beyond glycaemic control remains complex. Available studies differ in design, population characteristics, comparator interventions, treatment duration, outcome definitions, and regulatory relevance. In addition, the literature now includes conventional glucagon-like peptide-1 receptor agonists, dual incretin agonists, and other related investigational agents, which are sometimes discussed together despite important pharmacological distinctions. A narrative synthesis is therefore useful to organize the evolving evidence, distinguish established benefits from emerging applications, and clarify

the implications for multidisciplinary metabolic care. This narrative review aims to synthesize contemporary clinical and mechanistic evidence on glucagon-like peptide-1 receptor agonists and related incretin-based therapies in obesity, obstructive sleep apnoea, cardiovascular disease, and steatotic liver disease, with particular emphasis on trial-supported outcomes, safety considerations, evidence limitations, and future directions for clinical practice and research.

## MATERIAL AND METHODS

This article was designed as a narrative review to provide a clinically oriented synthesis of evidence on glucagon-like peptide-1 receptor agonists and related incretin-based therapies beyond glycaemic control. A narrative approach was selected because the objective was not to produce a pooled quantitative estimate or exhaustive systematic evidence map, but to integrate mechanistic rationale, landmark clinical trial evidence, emerging therapeutic indications, and practical implications across multiple obesity-related disease domains. The review focused on four interrelated areas: obesity management, obstructive sleep apnoea, cardiovascular outcomes, and metabolic dysfunction-associated steatotic liver disease, including studies that used the earlier terminology of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.

The literature base was assembled through a focused search of biomedical databases and scholarly sources, with priority given to randomized controlled trials, cardiovascular outcome trials, phase 2 and phase 3 clinical trials, recent high-quality reviews, and clinically relevant mechanistic papers. Search terms were structured around combinations of “GLP-1 receptor agonist,” “glucagon-like peptide-1,” “liraglutide,” “semaglutide,” “dulaglutide,” “tirzepatide,” “dual incretin agonist,” “obesity,” “weight loss,” “type 2 diabetes,” “cardiovascular outcomes,” “major adverse cardiovascular events,” “heart failure,” “obstructive sleep apnoea,” “apnoea-hypopnoea index,” “NAFLD,” “NASH,” “MASLD,” “MASH,” “hepatic steatosis,” and “liver fibrosis.” Reference lists of key trials and review articles were also examined to identify additional clinically relevant publications. Greater emphasis was placed on human clinical evidence, particularly trials evaluating approved or late-stage pharmacological agents, while mechanistic and early-phase evidence was used selectively to support biological plausibility.

Studies were considered most relevant when they evaluated glucagon-like peptide-1 receptor agonists or related incretin-based agents in adults or adolescents with obesity, type 2 diabetes, cardiovascular disease, obstructive sleep apnoea, or steatotic liver disease, and when they reported clinically interpretable outcomes such as body weight, body mass index, glycaemic indices, major adverse cardiovascular events, heart failure outcomes, apnoea-hypopnoea index, liver fat content, histological resolution of steatohepatitis, fibrosis progression, or treatment-related adverse events. Evidence was synthesized thematically rather than statistically, with findings grouped by disease domain and interpreted according to clinical maturity, consistency across studies, and relevance to multidisciplinary care. Established evidence from large cardiovascular and obesity trials was distinguished from emerging or investigational evidence in sleep apnoea and steatohepatitis, particularly where benefits appeared to be agent-specific or dependent on weight reduction.

Because this was a narrative review, no formal meta-analysis, risk-of-bias scoring, certainty-of-evidence grading, or PRISMA flow diagram was undertaken. The review was not prospectively registered. To improve transparency despite the narrative design, the synthesis explicitly differentiates between approved indications, trial-supported but emerging applications, and investigational uses. Potential limitations of this approach include selection bias, heterogeneity of included studies, differences in trial populations and endpoints, and the absence of formal quantitative pooling. These limitations were considered when interpreting the strength of evidence and when framing conclusions about the expanding role of glucagon-like peptide-1 receptor agonists and related incretin-based therapies in obesity-related multimorbidity.

## RESULTS / SYNTHESIS

The evidence synthesized in this narrative review indicates that glucagon-like peptide-1 receptor agonists and related incretin-based therapies have moved beyond their original role as glucose-lowering treatments and now occupy an expanding position in obesity-centered cardiometabolic care. Across the included evidence domains, the strongest and most mature data relate to weight management and cardiovascular outcomes, while evidence for obstructive sleep apnoea and steatotic liver disease is promising but more agent-specific, heterogeneous, and still developing. The reviewed studies collectively support a clinically coherent pathway in which pharmacological modulation of appetite, satiety, body weight, glycaemic control, inflammation, and cardiometabolic risk may translate into benefits across multiple obesity-related conditions.

In obesity management, liraglutide, semaglutide, and tirzepatide were the most prominently discussed agents. Liraglutide 3.0 mg demonstrated clinically meaningful reductions in body weight and BMI in adult and adolescent populations, including individuals with obesity and selected endocrine-metabolic phenotypes such as polycystic ovary syndrome (2,15,17). Semaglutide contributed to weight reduction through reduced appetite, improved satiety, and decreased energy intake, supporting the mechanistic link between GLP-1 receptor activation and central regulation of eating behaviour (16). Tirzepatide produced particularly large weight reductions in the SURMOUNT programme, with the review reporting weight loss up to approximately 20.9% in SURMOUNT-4 (13). However, tirzepatide should be described as a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist rather than a conventional GLP-1 receptor agonist, because its pharmacological profile and magnitude of effect may not be directly generalizable to the GLP-1 RA class as a whole.

The obstructive sleep apnoea evidence was clinically important but less extensive than the obesity and cardiovascular evidence. Earlier trial data suggested that liraglutide could reduce OSA severity, particularly when used alongside lifestyle intervention or CPAP in patients with obesity or type 2 diabetes (20,21). The most notable recent development was the tirzepatide evidence in obesity-associated OSA, where improvement in apnoea-hypopnoea index appeared closely related to substantial weight reduction (7). These findings support the concept that incretin-based therapies may become useful adjuncts in selected patients with obesity-related OSA, especially where excess adiposity is a key driver of upper-airway obstruction and nocturnal hypoxaemia. Nevertheless, the current evidence does not justify presenting GLP-1 receptor agonists as replacements for established OSA therapies such as CPAP. Instead, they should be framed as metabolically targeted adjunctive therapies that may reduce disease severity by addressing the underlying obesity phenotype.

The cardiovascular evidence base was broader and more mature. Major cardiovascular outcome trials involving liraglutide, semaglutide, and dulaglutide have demonstrated reductions in major adverse cardiovascular events among patients with type 2 diabetes and elevated cardiovascular risk (4–6,22). The SELECT trial further strengthened the argument that semaglutide 2.4 mg may provide cardiovascular benefit in patients with obesity and established cardiovascular disease even without diabetes, thereby supporting the central theme that GLP-1 receptor agonist benefits extend beyond glycaemic control (6). Evidence involving tirzepatide in patients with obesity and heart failure with preserved ejection fraction also suggested benefit in reducing cardiovascular death or worsening heart failure, although this should be interpreted as agent-specific evidence rather than proof of a uniform class effect (23). Overall, the cardiovascular findings support integration of selected GLP-1 receptor agonists into cardiometabolic risk-reduction strategies, particularly for patients with obesity, type 2 diabetes, or established atherosclerotic cardiovascular disease.

**Table 1. Summary of Clinical Evidence for GLP-1 Receptor Agonists and Related Incretin-Based Therapies in Obesity Management**

Study / First Author	Year Study Design	Population / Clinical Context	Intervention and Comparator	Main Outcome Domain	Key Finding Reported in the Review	Evidence Interpretation
Pi-Sunyer et al.	2015 Randomized controlled trial	Adults with obesity or overweight requiring chronic weight management	Liraglutide 3.0 mg versus placebo	Body weight and metabolic risk	Liraglutide demonstrated clinically meaningful weight reduction compared with placebo (2).	Established evidence supporting GLP-1 receptor agonist use in obesity management.
Kelly et al.	2020 Randomized, double-blind controlled trial	Adolescents with obesity	Liraglutide 3.0 mg versus placebo	Body mass index and weight-related outcomes	Liraglutide significantly reduced BMI in adolescents with obesity (17).	Supports use in selected younger populations, with age-specific safety and monitoring considerations.
Gibbons et al.	2021 Randomized, double-blind controlled trial	Patients with type 2 diabetes and obesity-related appetite dysregulation	Semaglutide versus placebo	Appetite, satiety, energy intake, and body weight	Semaglutide reduced appetite and increased satiety, contributing to weight reduction (16).	Supports biological plausibility for weight loss through central appetite and satiety pathways.
Elkind-Hirsch et al.	2022 Randomized, double-blind controlled trial	Patients with obesity associated with polycystic ovary syndrome	Liraglutide 3.0 mg versus placebo	BMI and obesity-related reproductive-metabolic phenotype	Liraglutide reduced BMI in patients with obesity related to PCOS (15).	Evidence supports benefit in selected endocrine-obesity phenotypes.
Aronne et al. / SURMOUNT-4	2024 Randomized, double-blind withdrawal trial	Adults with obesity or overweight	Continued tirzepatide versus withdrawal/placebo	Weight maintenance and further weight reduction	Continued tirzepatide maintained and extended weight reduction, with reported weight loss reaching approximately 20.9% in the review (13).	Strong agent-specific evidence for tirzepatide as a dual GLP/GLP-1 receptor agonist; should not be presented as a conventional GLP-1 RA class effect.
Malhotra et al.	2024 Randomized, double-blind controlled trial	Adults with obesity and obstructive sleep apnoea	Tirzepatide versus placebo	Body weight and OSA-related outcomes	Tirzepatide reduced body weight and contributed to improvement in OSA severity (7).	Best interpreted as dual-domain evidence linking weight reduction with sleep apnoea improvement.

**Table 2. Summary of Evidence for GLP-1 Receptor Agonists and Related Incretin-Based Therapies in Obstructive Sleep Apnoea**

Study / First Author	Year Study Design	Population / Clinical Context	Intervention and Comparator	Main Outcome Domain	Key Finding Reported in the Review	Evidence Interpretation
Blackman et al. / SCALE Sleep Apnoea	2016 Randomized, double-blind controlled trial	Adults with obesity and moderate-to-severe obstructive sleep apnoea without diabetes	Liraglutide 3.0 mg plus lifestyle intervention versus placebo plus lifestyle intervention	Apnoea-hypopnoea index and weight-related outcomes	Liraglutide reduced OSA severity in association with weight reduction (21).	Early trial evidence suggests benefit, but effects are closely linked to weight loss.
Jiang et al.	2023 Prospective randomized controlled trial	Patients with type 2 diabetes and severe obstructive sleep apnoea receiving CPAP	Liraglutide plus CPAP versus CPAP alone	AHI, oxygenation, and sleep-related outcomes	Liraglutide used alongside CPAP improved AHI scores and oxygenation compared with CPAP alone (20).	Supports possible adjunctive use in metabolically complicated OSA, but not replacement of CPAP.
Malhotra et al. / SURMOUNT-OSA	2024 Randomized, double-blind controlled trial	Adults with obesity and obstructive sleep apnoea	Tirzepatide versus placebo	AHI, body weight, and sleep-related quality outcomes	Tirzepatide reduced AHI primarily through substantial weight reduction and improved OSA-related outcomes (7).	Strong emerging evidence for tirzepatide in obesity-associated OSA; effect should be described as agent-specific and not generalized to all GLP-1 RAs.
Malhotra et al. / SURMOUNT-OSA design report	2023 Phase 3 trial design report	Adults with obesity and OSA, including populations with and without positive airway pressure use	Tirzepatide versus placebo	Planned assessment of OSA severity and weight-related endpoints	Trial design established the rationale for evaluating tirzepatide in OSA (19).	Supports methodological context but should not be treated as outcome evidence.

**Table 3. Summary of Cardiovascular Outcome Evidence for GLP-1 Receptor Agonists and Related Incretin-Based Therapies**

Study / Trial	Year	Study Design	Population / Clinical Context	Intervention and Comparator	Main Outcome Domain	Key Finding Reported in the Review	Evidence Interpretation
LEADER	Noted in review	Cardiovascular outcome trial	Patients with type 2 diabetes and high cardiovascular risk	Liraglutide versus placebo	Major adverse cardiovascular events	Liraglutide contributed to cardiovascular risk reduction in high-risk patients (4).	Established cardiovascular outcome evidence for selected GLP-1 receptor agonists.

Study / Trial	Year	Study Design	Population / Clinical Context	Intervention and Comparator	Main Outcome Domain	Key Finding Reported in the Review	Evidence Interpretation
<b>SUSTAIN-6</b>	Noted in review	Cardiovascular outcome trial	Patients with type 2 diabetes and elevated cardiovascular risk	Semaglutide versus placebo	Major adverse cardiovascular events	Semaglutide reduced major adverse cardiovascular events in high-risk patients (4).	Established agent-specific cardiovascular benefit.
<b>REWIND</b>	2019 / 2023 analysis cited	Randomized placebo-controlled cardiovascular outcome trial	Patients with type 2 diabetes with or without established cardiovascular disease	Dulaglutide versus placebo	Major adverse cardiovascular events and biomarker changes	Dulaglutide reduced cardiovascular outcomes and was associated with favourable biomarker changes (5,22).	Strong evidence supporting cardiovascular benefit in broad type 2 diabetes populations.
<b>SELECT</b>	2024	Randomized cardiovascular outcome trial	Adults with obesity or overweight and cardiovascular disease without diabetes	Semaglutide 2.4 mg versus placebo	Cardiovascular outcomes and obesity-related risk	Semaglutide improved cardiovascular outcomes in patients with obesity or metabolic disease without type 2 diabetes (6).	Important evidence extending benefit beyond glycaemic control.
<b>Packer et al.</b>	2025	Randomized, double-blind placebo-controlled trial	Patients with obesity and heart failure with preserved ejection fraction	Tirzepatide versus placebo	Cardiovascular death or worsening heart failure	Tirzepatide lowered the risk of cardiovascular death or worsening heart failure compared with placebo (23).	Agent-specific evidence for tirzepatide; should not be generalized to the entire GLP-1 RA class.
<b>McGuire et al.</b>	2025	Randomized, double-blind placebo-controlled trial	Patients over 50 years with type 2 diabetes and atherosclerotic cardiovascular disease	Oral semaglutide versus placebo	Major cardiovascular events	Oral semaglutide reduced major cardiovascular event risk in high-risk patients.	Potentially important but requires full citation verification before final submission.
<b>Lincoff et al.</b>	2023	Randomized, double-blind placebo-controlled trial	Patients with obesity or metabolic disease without type 2 diabetes	Semaglutide 2.4 mg versus placebo	Cardiovascular outcomes	Semaglutide improved cardiovascular outcomes in non-diabetic patients with obesity or metabolic disease.	Important evidence for cardiometabolic benefit beyond diabetes; citation details should be completed.

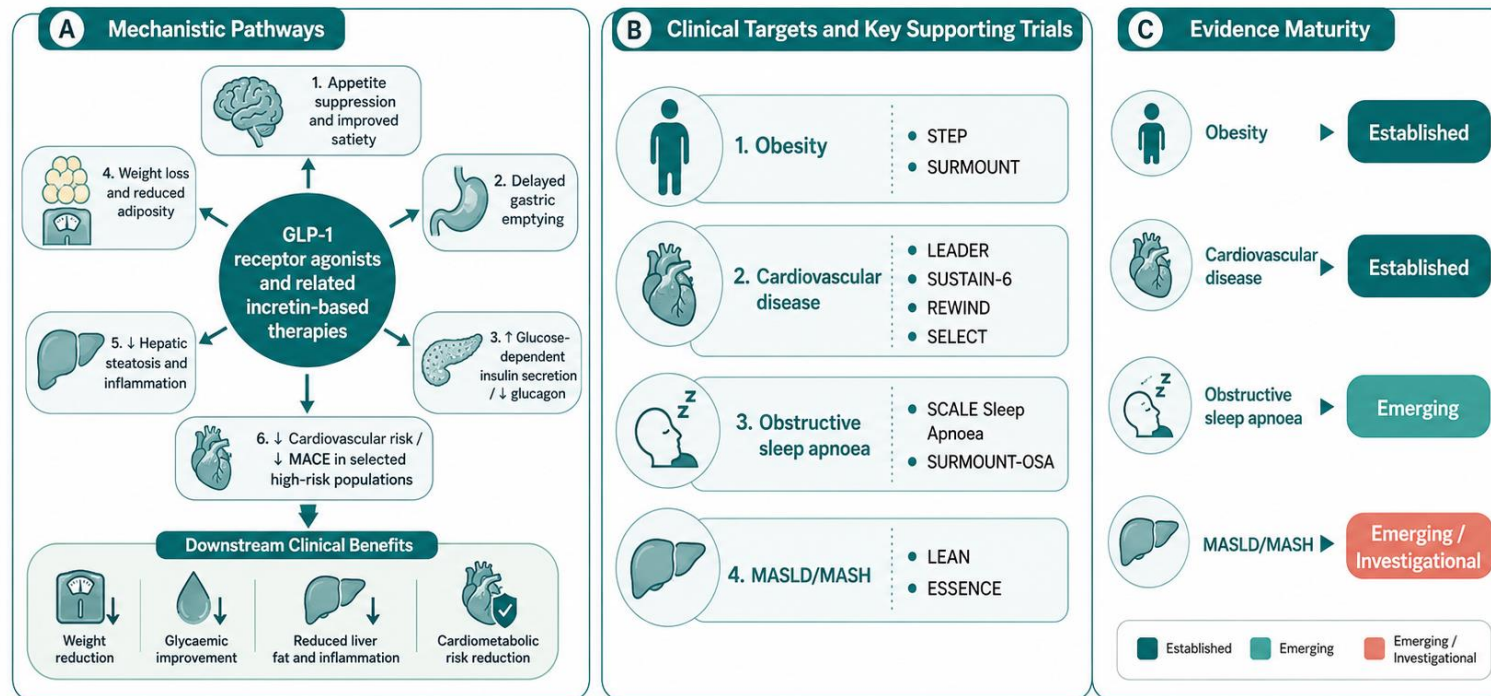
**Table 4. Summary of Evidence for GLP-1 Receptor Agonists and Related Incretin-Based Therapies in NAFLD, NASH, MASLD, and MASH**

Study / First Author	Year	Study Design	Population / Clinical Context	Intervention and Comparator	Main Outcome Domain	Key Finding Reported in the Review	Evidence Interpretation
<b>Armstrong et al. / LEAN</b>	2016	Randomized controlled trial	Patients with non-alcoholic steatohepatitis	Liraglutide versus placebo	NASH resolution and fibrosis progression	Liraglutide improved NASH-related outcomes and reduced progression in selected patients (24).	Early clinical evidence supporting hepatometabolic benefit of GLP-1 receptor agonism.
<b>Loomba et al.</b>	2023	Phase 2 randomized, double-blind placebo-controlled trial	Patients with NASH and compensated cirrhosis	Semaglutide versus placebo	Fibrosis improvement and NASH resolution	Semaglutide did not significantly improve fibrosis or achieve NASH resolution in compensated cirrhosis.	Shows that benefits may not extend uniformly to advanced liver disease. Full citation should be added.
<b>Sanyal et al.</b>	2024	Phase 2 randomized placebo-controlled trial	Patients with MASH	Survodutide versus placebo	MASH improvement without worsening fibrosis	Survodutide was superior to placebo in improving MASH without worsening fibrosis.	Emerging evidence for a related incretin/glucagon-based investigational therapy, not a conventional GLP-1 RA.
<b>Harrison et al.</b>	2025	Randomized, double-blind placebo-controlled trial	Patients with metabolic dysfunction-associated steatohepatitis	Pemvidutide versus placebo	Liver fat, hepatic inflammation markers, and body weight	Pemvidutide reduced liver fat content, markers of hepatic inflammation, and body weight (8).	Supports promise of related metabolic agents but requires clear distinction from standard GLP-1 receptor agonists.
<b>Sanyal et al.</b>	2025	Phase 3 randomized, double-blind placebo-controlled trial	Patients with MASH and moderate-to-advanced fibrosis	Semaglutide 2.4 mg weekly versus placebo	Liver histology and fibrosis-related outcomes	Semaglutide improved liver histological outcomes in patients with MASH and fibrosis.	Important late-stage evidence, but full bibliographic details should be completed before publication.

**Table 5. Evidence Maturity Across Therapeutic Domains**

Therapeutic Domain	Main Agents Discussed	Evidence Maturity	Main Supported Outcomes	Key Limitation
<b>Obesity management</b>	Liraglutide, semaglutide, tirzepatide	Established for selected agents and populations	Weight reduction, BMI reduction, appetite regulation, satiety improvement	Durability, adherence, cost, access, and long-term safety in broader populations require continued evaluation.
<b>Cardiovascular disease</b>	Liraglutide, semaglutide, dulaglutide, tirzepatide	Established for selected GLP-1 RAs in high-risk populations; emerging for some newer agents and non-diabetic populations	Reduction in major adverse cardiovascular events; selected heart failure-related benefit with tirzepatide	Cardiovascular benefit varies by agent, baseline risk, diabetes status, and outcome type.

Therapeutic Domain	Main Agents Discussed	Evidence Maturity	Main Supported Outcomes	Key Limitation
Obstructive sleep apnoea	Liraglutide, tirzepatide	Emerging	Reduction in AHI, improved oxygenation, sleep-related improvement linked to weight loss	Evidence remains narrower than obesity/CVD evidence and is strongly mediated by weight reduction.
Steatotic liver disease / NASH / MASH	Liraglutide, semaglutide, pemvidutide, survodutide	Emerging to investigational depending on agent and disease stage	Reduced liver fat, improved inflammatory activity, selected histological improvement	Terminology, endpoints, fibrosis stage, and drug class distinctions require clearer reporting.
Safety and tolerability	GLP-1 RAs and related incretin therapies	Established for common adverse effects; evolving for long-term non-diabetic use	Gastrointestinal effects most common; gallbladder and pancreatitis concerns require monitoring	Long-term safety in non-diabetic and multi-comorbidity populations remains under evaluation.



Conceptual summary based on clinical trial evidence discussed in this review.

Figure 1. Mechanistic pathways, clinical targets, and evidence maturity of GLP-1 receptor agonists and related incretin-based therapies.

Evidence relating to steatotic liver disease was promising but more heterogeneous. Earlier trial evidence from the LEAN study suggested that liraglutide could improve outcomes in non-alcoholic steatohepatitis and reduce progression in selected patients (24). More recent evidence involving semaglutide, pemvidutide, and survodutide has expanded interest in incretin-based and related metabolic therapies for metabolic dysfunction-associated steatohepatitis, including reductions in liver fat, hepatic inflammatory activity, body weight, and selected histological endpoints (8). However, findings have not been uniformly positive across all liver disease stages. For example, semaglutide did not significantly improve fibrosis or achieve NASH resolution in patients with compensated cirrhosis in one phase 2 trial, suggesting that treatment response may vary according to disease severity, fibrosis stage, and selected endpoint. The synthesis therefore supports cautious optimism: GLP-1 receptor agonists and related incretin-based agents may have hepatometabolic value, but claims should be restricted to trial-supported populations and outcomes.

Safety findings across the reviewed evidence were broadly consistent with the known tolerability profile of GLP-1 receptor agonists. Gastrointestinal symptoms, including nausea, vomiting, diarrhoea, and constipation, were the most frequently reported adverse effects and were generally dose-related and most prominent during dose escalation. Gallbladder-related events remain clinically relevant, particularly in the context of rapid or substantial weight loss. Concerns regarding pancreatitis and thyroid C-cell tumours require appropriate clinical screening and pharmacovigilance, although large cardiovascular outcome trials have generally supported the cardiovascular safety of major agents used in high-risk populations. As use expands into non-diabetic populations, adolescents, patients with sleep apnoea, and patients with liver disease, longer-term real-world data will be necessary to clarify durability, adherence, safety, cost-effectiveness, and equitable access.

Taken together, the synthesis shows that GLP-1 receptor agonists are best understood as part of a broader metabolic treatment paradigm rather than as glucose-lowering agents alone. The evidence is strongest for obesity management and cardiovascular risk reduction with selected agents, while OSA and MASH/MASLD applications remain emerging and more dependent on agent-specific trial results. A clinically balanced interpretation therefore requires separating established class-supported benefits from promising but investigational or agent-specific findings. This distinction is essential for avoiding overstatement and for guiding responsible integration of these therapies into multidisciplinary care pathways involving endocrinology, cardiology, hepatology, sleep medicine, primary care, nutrition, and rehabilitation.

This composite figure summarizes the major biological mechanisms, clinical target domains, and current evidence maturity for GLP-1 receptor agonists and related incretin-based therapies. Mechanistically, these agents influence appetite suppression, satiety, delayed gastric emptying, glucose-dependent insulin secretion, glucagon suppression, weight reduction, hepatic steatosis/inflammation, and cardiovascular risk. Clinically, the strongest supporting evidence is concentrated in obesity and cardiovascular disease through trials such as STEP, SURMOUNT, LEADER, SUSTAIN-6, REWIND, and SELECT, while evidence for obstructive sleep apnoea and MASLD/MASH is emerging through SCALE Sleep Apnoea, SURMOUNT-OSA, LEAN, and ESSENCE. The figure highlights that obesity and cardiovascular outcomes have established evidence, whereas obstructive sleep apnoea remains emerging and MASLD/MASH remains emerging to investigational depending on agent, disease stage, and endpoint.

## DISCUSSION

This narrative review synthesizes contemporary evidence on the expanding role of glucagon-like peptide-1 receptor agonists and related incretin-based therapies beyond glycaemic control, with emphasis on obesity, cardiovascular disease, obstructive sleep apnoea, and steatotic liver disease. The principal finding is that these therapies now occupy an increasingly important position in obesity-

centered cardiometabolic care, although the maturity of evidence differs substantially across indications. Evidence is strongest for weight management and cardiovascular risk reduction with selected agents, while applications in obstructive sleep apnoea and metabolic dysfunction-associated steatohepatitis remain emerging, agent-specific, and dependent on disease phenotype, endpoint selection, and trial population.

The weight-management evidence provides the most coherent mechanistic and clinical foundation for the broader therapeutic value of these agents. Liraglutide and semaglutide have demonstrated clinically meaningful effects on body weight, appetite regulation, and metabolic risk markers, while tirzepatide has produced particularly large weight reductions in obesity trials. These findings support the concept that incretin-based therapies can modify upstream drivers of obesity-related multimorbidity rather than simply improving glucose concentration. However, tirzepatide should be interpreted as a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist, not as a conventional GLP-1 receptor agonist. This distinction is important because its magnitude of weight loss and downstream effects may reflect dual incretin activity and should not be generalized uncritically to the entire GLP-1 receptor agonist class.

The cardiovascular findings further support the movement of GLP-1 receptor agonists from diabetes-centered prescribing toward broader cardiometabolic risk reduction. Large cardiovascular outcome trials involving liraglutide, semaglutide, and dulaglutide have shown reductions in major adverse cardiovascular events among patients with type 2 diabetes and elevated cardiovascular risk. More recent evidence in patients with obesity and cardiovascular disease without diabetes strengthens the argument that the benefit of selected agents extends beyond glycaemic control. Nevertheless, the cardiovascular effects should be described with precision. Reductions in major adverse cardiovascular events are best supported for specific agents and defined high-risk populations, whereas heart failure-related benefits are not uniform across the class and should be interpreted according to the agent, heart failure phenotype, baseline obesity status, and trial design.

In obstructive sleep apnoea, the reviewed evidence suggests a biologically plausible and clinically promising role for incretin-based therapies, primarily through weight reduction. Liraglutide has shown benefit in selected patients with obesity-related sleep apnoea, and tirzepatide has provided stronger recent evidence for improvement in apnoea-hypopnoea index among patients with obesity-associated obstructive sleep apnoea. These findings are clinically relevant because excess adiposity contributes to upper-airway collapsibility, impaired ventilation, nocturnal hypoxaemia, systemic inflammation, and cardiometabolic risk. However, the current evidence supports GLP-1 receptor agonists and related therapies as adjunctive metabolic interventions rather than replacements for established treatments such as continuous positive airway pressure. Their role is most appropriately framed as part of an integrated approach for patients in whom obesity is a major modifiable driver of sleep-disordered breathing.

The hepatometabolic evidence is also encouraging but should be interpreted cautiously. Earlier clinical evidence with liraglutide and more recent studies involving semaglutide and related incretin-based agents suggest potential improvement in hepatic steatosis, inflammatory activity, body weight, and selected histological endpoints in patients with steatohepatitis. However, treatment response appears to vary by fibrosis stage, disease severity, and endpoint. The distinction between older terminology such as NAFLD/NASH and newer terminology such as MASLD/MASH should be handled explicitly, because many landmark trials used historical disease definitions while current clinical discourse increasingly favors metabolic dysfunction-associated terminology. Importantly, investigational agents such as pemvidutide and survodutide should not be presented as conventional GLP-1 receptor agonists; rather, they should be discussed as related metabolic or incretin/glucagon-based therapies that may extend the therapeutic concept but require separate evaluation.

The safety profile observed across the reviewed evidence is generally consistent with the known tolerability pattern of GLP-1 receptor agonists. Gastrointestinal symptoms, including nausea, vomiting,

diarrhoea, and constipation, remain the most common adverse effects and may influence adherence, particularly during dose escalation. Gallbladder-related events require attention in patients experiencing rapid or substantial weight loss. Although large cardiovascular outcome trials have generally supported cardiovascular safety and benefit in high-risk populations, continued pharmacovigilance is needed as these drugs are used more widely in non-diabetic populations, adolescents, patients with sleep apnoea, patients with liver disease, and individuals with complex multimorbidity. Long-term safety, durability of weight loss, discontinuation effects, cost-effectiveness, access, and equitable implementation remain important clinical and policy considerations.

This review has several limitations that should be considered when interpreting its conclusions. First, it was conducted as a narrative review rather than a systematic review, and therefore did not include formal dual screening, risk-of-bias appraisal, evidence grading, or quantitative pooling. Second, because the synthesis prioritized landmark trials and clinically relevant recent evidence, selection bias cannot be excluded. Third, included studies differed in population characteristics, intervention dose, comparator, duration, outcome definitions, and disease severity, limiting direct cross-domain comparison. Fourth, the review discusses conventional GLP-1 receptor agonists together with related incretin-based and metabolic agents where clinically relevant; although this reflects the evolving therapeutic landscape, it requires careful wording to avoid inappropriate class-level generalization. Finally, several emerging indications, especially obstructive sleep apnoea and MASH, require longer follow-up, real-world validation, and clearer definition of patient phenotypes most likely to benefit.

The clinical implication of this synthesis is that GLP-1 receptor agonists should no longer be viewed solely as glucose-lowering drugs. For selected patients, they are better understood as metabolic risk-modifying therapies that can influence obesity, cardiometabolic outcomes, and potentially obesity-related respiratory and hepatic complications. In practice, their use should be individualized according to indication, agent-specific evidence, comorbidity profile, contraindications, treatment goals, tolerability, affordability, and access. Future research should prioritize head-to-head comparisons among GLP-1 receptor agonists and dual or multi-agonist therapies, long-term durability studies after treatment discontinuation, cost-effectiveness analyses, real-world implementation studies, and trials that clarify whether benefits in obstructive sleep apnoea and MASH are mediated predominantly by weight loss or by additional tissue-specific mechanisms.

## CONCLUSION

GLP-1 receptor agonists and related incretin-based therapies have expanded the therapeutic framework for obesity-related cardiometabolic disease by linking weight reduction, appetite regulation, glycaemic improvement, cardiovascular risk reduction, and potential benefits in obstructive sleep apnoea and steatotic liver disease. The evidence is strongest for obesity management and cardiovascular risk reduction with selected agents, while respiratory and hepatic indications remain emerging and should be interpreted according to agent, population, disease stage, and endpoint. These therapies are likely to become increasingly important within multidisciplinary metabolic care, but their integration into practice should remain evidence-calibrated, patient-specific, and supported by continued research into long-term safety, durability, access, and comparative effectiveness.

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