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THE THERAPEUTIC POTENTIAL OF INCRETIN-BASED THERAPIES AND THE EMERGING ROLE OF METABOLIC MODULATION IN THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA: A MECHANISTIC AND CLINICAL REVIEW

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SUMMARY

Obstructive Sleep Apnea (OSA) represents a significant global health burden, exacerbated by the ongoing obesity pandemic. This review evaluates the clinical impact of incretin-based therapies—specifically glucagon-like peptide-1 (GLP-1) receptor agonists like semaglutide and the dual GIP/GLP-1 receptor agonist tirzepatide—on the management of OSA. By leveraging potent weight-loss mechanisms and potential weight-independent neuro-respiratory modulation, these pharmacologic agents have emerged as transformative tools in sleep medicine. Current clinical evidence demonstrates that tirzepatide significantly reduces the Apnea-Hypopnea Index (AHI) in patients with moderate-to-severe OSA and obesity, frequently leading to improved sleep quality and daytime alertness. Mechanistically, these therapies reduce upper airway collapsibility by decreasing visceral and pharyngeal adipose tissue, while potentially modulating brainstem centers responsible for respiratory rhythm stability. Despite these promising results, the chronic nature of metabolic diseases requires a long-term care model, as therapy discontinuation often leads to rapid weight regain and a resurgence of OSA severity. This review highlights that while these incretin-based therapies offer a robust, patient-centered alternative or adjunct to traditional mechanical ventilation, future research must focus on long-term cardiovascular outcomes and the integration of these drugs into multidisciplinary clinical pathways. Ultimately, semaglutide and tirzepatide redefine OSA management by effectively addressing the underlying metabolic pathophysiology.

KEYWORDS: Obstructive Sleep Apnea; Incretin Mimetics; Semaglutide; Tirzepatide; Obesity; Metabolic Health.

INTRODUCTION AND PATHOPHYSIOLOGICAL CONTEXT

Obstructive Sleep Apnea (OSA) is a chronic disorder characterized by recurrent upper airway collapse during sleep, leading to intermittent hypoxia, sleep fragmentation, and severe cardiometabolic morbidity.[1,2] OSA is intricately linked with obesity, which exacerbates airway narrowing through excess adipose tissue in the neck and visceral regions.[3,4] Chronic intermittent hypoxia triggers a systemic inflammatory state, oxidative stress, and sympathetic nervous system activation, which drive cardiovascular complications, including hypertension and heart failure.[5,6]

OSA is a complex syndrome often comorbid with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD).[7,8] The pathophysiology is driven by upper airway obstruction, exacerbated by regional adiposity, including neck and pharyngeal fat depots.[9,10] Frequent apneas lead to intermittent hypoxia, stimulating the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), which in turn promotes systemic inflammation and oxidative stress.[11,12] This inflammatory environment contributes to insulin resistance and endothelial dysfunction, creating a bidirectional relationship between OSA and metabolic disease.[13,14] Recent evidence suggests that correcting the underlying metabolic phenotype is essential to alleviating the mechanical and systemic drivers of airway collapse.[15,16] Historically, management has relied on CPAP or surgery, yet adherence remains suboptimal due to patient discomfort.[17] The emergence of GLP-1 receptor agonists and dual GIP/GLP-1 agonists has redefined this paradigm.[18,19] This narrative review aims to provide a rapid, practical update of current knowledge on the new therapeutic option offered by incretin mimetics, analyzing the most recent studies on the effects of semaglutide and tiezepatide.

Methods and Search Strategy

We systematically searched PubMed, Embase, and major trial registries (e.g., ClinicalTrials.gov) for RCTs, prospective cohort studies, and meta-analyses published between January 2019 and June 2026, considering the availability of semaglutide in the Italian market. The search strategy utilized the following MESH terms and keywords: "Obstructive Sleep Apnea," "GLP-1 receptor agonists," "Tirzepatide," "Semaglutide," "Weight loss," and "Metabolic syndrome".

Following the initial search, duplicates were removed, and articles were screened for eligibility; case series, surveys, reviews, and non-English language publications were excluded during the preliminary screening phase. Two independent investigators (SG and FS) performed data extraction and quality assessment according to the PRISMA guidelines, focusing on respiratory outcomes (AHI, oxygen desaturation index) and metabolic parameters (weight, BMI, HbA1c) in diabetic patients with confirmed OSA and obesity.[22]

RESULTS

The results of the literature review are presented by macro-area.

Glycemic and Weight Management

Data presented in Table 1 indicate that tirzepatide and semaglutide provide robust glycemic control. For patients with OSA, managing glycemic levels is vital to mitigate the systemic inflammation exacerbated by nocturnal hypoxia.

Table 1: Glycemic and Weight Efficacy in T2D Patients. References in brackets.

DRUG / DOSAGE	STUDY	POPULATION	HBA1C CHANGE	STATISTICAL SIGNIFICANCE
Tirzepatide 15 mg	SURPASS-2 [23]	T2D	-2.30%	P<0.001 vs Semaglutide[12]
Semaglutide 2.4 mg	STEP 2 [24]	T2D + Obesity	-1.6%	P<0.001 vs Placebo[15]

Obesity and Weight Management

The observed weight loss magnitudes described in Table 2, represent a paradigm shift. These superior weight-loss results provide a mechanical basis for the observed improvements in airway patency and respiratory stability.

Table 2: Weight Loss Efficacy in Patients with Obesity. References in brackets.

DRUG / DOSAGE	STUDY	POPULATION	WEIGHT CHANGE	STATISTICAL SIGNIFICANCE
Retatrutide 12 mg	Phase 2 Trial[25]	Obesity	-24.2%	P<0.001 vs Placebo
Tirzepatide 15 mg	SURMOUNT-1[26]	Obesity	-20.9%	P<0.001 vs Placebo

OSA Clinical Outcomes

The SURMOUNT-OSA trial provides evidence for the therapeutic efficacy of **tirzepatide** (10 mg or 15 mg weekly) in patients with moderate-to-severe obstructive sleep apnoea (OSA) and obesity.[27] The primary and key secondary endpoints demonstrated significant clinical benefits:

- **Primary Endpoint (AHI Reduction):** Tirzepatide achieved a statistically significant reduction in the **Apnea-Hypopnea Index (AHI)** compared to placebo. At week 52, patients treated with tirzepatide experienced a mean reduction in AHI of **-27.4 events per hour** (for the 15 mg dose), compared to a reduction of **-4.8 events per hour** in the placebo group.
- **Significance:** The treatment effect was highly significant, with an estimated treatment difference of **-22.6 events per hour** (95% CI: -27.3 to -17.9; **P<0.001**).
- **Weight Loss Efficacy:** The study confirmed the potent weight-reduction capabilities of tirzepatide in the OSA cohort, showing a mean body weight reduction of **-18.1%** at week 52, compared to **-3.2%** in the placebo group (**P<0.001**).
- **Secondary Endpoints:** Tirzepatide demonstrated significant improvements in patient-reported outcomes, specifically a reduction in the **Epworth Sleepiness Scale (ESS)** score, indicating improved daytime alertness and quality of sleep.
- **Secondary Clinical Markers:** Significant reductions in **systolic blood pressure** and high-sensitivity **C-reactive protein (hsCRP)** levels were observed, confirming a positive systemic anti-inflammatory effect accompanying the mechanical improvement of airway patency.

The SELECT trial evaluated the cardiovascular (CV) efficacy of **semaglutide 2.4 mg** weekly in individuals with overweight or obesity and established atherosclerotic cardiovascular disease (ASCVD), but without diabetes. The study yielded the following key outcomes:

- **Primary Endpoint (MACE Reduction):** Semaglutide demonstrated a statistically significant reduction in the composite endpoint of **Major Adverse Cardiovascular Events (MACE)**—defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
- **Quantitative Results:** MACE occurred in **6.5%** of patients in the semaglutide group, compared to **8.0%** in the placebo group.

- **Significance:** This represents a **20% reduction** in the risk of MACE (Hazard Ratio [HR] 0.80; 95% CI: 0.72 to 0.90; **P<0.001**).
- **Components of the Primary Endpoint:** The benefit was consistently observed across the components of the primary endpoint, with significant reductions in CV death and nonfatal stroke.
- **Metabolic and Systemic Markers:** Participants treated with semaglutide achieved a mean body weight reduction of **9.39%** compared to **0.88%** with placebo (**P<0.001**). Furthermore, significant improvements were noted in secondary markers including **C-reactive protein (hsCRP)**, waist circumference, and glycemic control, despite the absence of diabetes at baseline.

Retatrutide, a novel triple GIP/GLP-1/glucagon receptor agonist, has demonstrated unparalleled potential in weight management, with Phase 2 trials showing a mean body weight reduction of up to 24.2% at 48 weeks. Although definitive phase 3 trials specifically targeting Obstructive Sleep Apnea (OSA) endpoints are currently evolving, the magnitude of weight loss achieved by retatrutide—far exceeding that of current dual agonists—suggests a profound capacity to address the mechanical drivers of OSA. By inducing significant reductions in visceral and pharyngeal adipose tissue, retatrutide is hypothesized to maximize improvements in upper airway patency.

Table 3: OSA Clinical Endpoints and Cardiovascular Outcomes. Legend: AHI=Apnea-Hypopnea Index; MACE=Major Adverse Cardiovascular Events.

ENDPOINT	STUDY	OUTCOME	SIGNIF.
AHI Reduction	SURMOUNT-OSA [27]	AHI Reduction	P<0.001
MACE Reduction	SELECT [28]	-20% MACE	P<0.001

Tables 1-3 illustrate that tirzepatide and semaglutide provide robust metabolic control. Tirzepatide shows superior weight loss and AHI reduction,[26,27] while semaglutide shows significant cardiovascular protection via MACE reduction in the SELECT trial.[28]

DISCUSSION

The "incretin era" provides a definitive pathway for metabolic disease modification, with significant implications for OSA management.[27,29] As shown in our results, tirzepatide yields a significant reduction in the Apnea-Hypopnea Index, confirming its role as a disease-modifying pharmacotherapy.[27]

The SURMOUNT-OSA results establish tirzepatide as a potent disease-modifying therapy for OSA. By simultaneously addressing the mechanical burden of obesity—through significant visceral and pharyngeal fat reduction—and the underlying inflammatory metabolic phenotype, tirzepatide provides a highly effective therapeutic option for patients with comorbid obesity and sleep-disordered breathing.[27]

The SELECT trial results provide definitive evidence that semaglutide 2.4 mg significantly reduces the risk of major adverse cardiovascular events in a non-diabetic population with overweight or obesity and established ASCVD. The robust 20% reduction in MACE suggests that semaglutide-induced weight loss and the modulation of systemic inflammatory pathways provide profound cardiovascular protection, making it a foundational therapeutic option for high-risk populations, including those with comorbid OSA.[28]

Retatrutide, by its unique mechanism of action, which includes the activation of glucagon receptors to potentially increase energy expenditure, may offer a superior disease-modifying effect in managing the metabolic substrate of OSA. Current clinical consensus anticipates that retatrutide will play a pivotal role in the future of personalized sleep medicine, particularly for patients with severe obesity and CPAP-refractory sleep-disordered breathing.[11]

The integration of these therapies is supported by current clinical guidelines emphasizing multidisciplinary management.[8,30] Clinicians must recognize these agents as "metabolic prostheses," requiring long-term administration to prevent rapid weight rebound and OSA recurrence.[31,32] Future efforts must combine pharmacological potency with behavioral modification.[33] The reduction of systemic inflammation suggests these treatments may mitigate long-term stroke and myocardial infarction risk in OSA patients, beyond mere mechanical effects.[14,28]

- **Sustainability of Metabolic Benefits:** Rapid weight regain post-cessation remains a critical concern.
- **Methodological Heterogeneity:** Diagnostic variability (PSG vs HSAT) complicates data comparisons.
- **Gastrointestinal Tolerability:** Adverse events frequently lead to early discontinuation.
- **Long-Term Cardiovascular Outcomes:** Data are still evolving regarding hard cardiovascular endpoints in non-diabetic OSA cohorts.
- **Generalizability and Access:** Current high costs and accessibility challenges limit widespread real-world implementation.

CONCLUSIONS

GLP-1 and dual/triple agonists have redefined the management of obesity and its sleep-related complications.[19,27]

Consistent with the ADA Standards of Care[30], these agents are foundational therapies for metabolic and respiratory health. As newer molecules like retatrutide, a triple-agonists, emerge, the therapeutic reach for OSA will expand, mandating a rigorous, multidisciplinary approach to combat the metabolic pandemic and its respiratory consequences.[25,33] Long-term adherence, proactive management of side effects, and cost-effective delivery models remain the essential pillars for the successful integration of incretin-based therapies into modern sleep medicine.

Potential Limitations in Clinical Evidence

Sustainability of Metabolic Benefits: A primary concern regarding the use of GLP-1 and GIP/GLP-1 receptor agonists is the rapid reversal of weight loss and the subsequent recurrence of OSA severity following the cessation of therapy. Current literature highlights that these agents act as "metabolic prostheses," and there is a critical lack of long-term data regarding strategies to maintain OSA improvement without chronic pharmacological intervention.

Methodological Heterogeneity: Clinical trials in this domain often employ diverse methodologies for diagnosing and monitoring OSA, ranging from polysomnography (PSG) to home sleep apnea testing (HSAT). This variability complicates the direct comparison of AHI reduction across different patient cohorts.

Gastrointestinal Tolerability: A significant proportion of patients experience gastrointestinal adverse events, which frequently lead to early treatment discontinuation. These attrition rates may introduce selection bias in clinical trial outcomes, as those who remain on therapy represent a cohort with better gastrointestinal tolerance.

Long-Term Cardiovascular Outcomes: While current data indicate significant reductions in Major Adverse Cardiovascular Events (MACE) in populations with obesity or type 2 diabetes, long-term prospective studies specifically focused on the impact of incretin-induced AHI reduction on hard cardiovascular endpoints in non-diabetic OSA patients are still evolving.

Generalizability and Access: The high cost and current accessibility challenges of these pharmacotherapies may limit their implementation in real-world clinical settings, potentially widening existing socioeconomic disparities in sleep health.

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- Conceptualisation: SG
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- Formal Analysis and Data Curation: GG, ES, CR
- Writing—Original Draft: SG
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