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Commentary

The Application of GLP-1 Receptor Agonists and SGLT2 Inhibitors in Obstructive Sleep Apnea: Breakthrough or Overhyped?

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In June 2024, *The New England Journal of Medicin*e (NEJM) published an article titled "Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity", reporting the results of a Phase III clinical trial on the use of tirzepatide in patients with moderate to severe obstructive sleep apnea (OSA) and obesity.[1] The study demonstrated that tirzepatide significantly reduced the apnea-hypopnea index (AHI), a key indicator for assessing the severity of OSA. Over the course of the 52-week study, patients who did not receive continuous positive airway pressure (PAP) therapy experienced an average reduction in AHI of 25.3 events per hour, while those using PAP therapy saw a reduction of 29.3 events per hour. Additionally, tirzepatide significantly reduced patients' body weight and the nocturnal hypoxia burden associated with OSA. These findings suggest that tirzepatide not only effectively reduces body weight but also markedly improves OSA symptoms, potentially reducing the dependence on PAP therapy. Further research indicates that this drug may also reduce cardiovascular disease risk, offering new hope for personalized treatment approaches in the future.

For patients with OSA combined with metabolic syndrome, continuous positive airway pressure therapy and lifestyle-based metabolic interventions (such as dietary adjustments and weight loss) have been shown to significantly improve health outcomes. These interventions not only help alleviate OSA symptoms but also improve cardiometabolic health and reduce the risk of cardiovascular diseases. Treating OSA-related obesity, even with modest weight loss, can lead to significant cardiometabolic improvements, such as lowering blood pressure, improving insulin sensitivity, and reducing inflammatory markers.[2] However, despite the effectiveness of these interventions, long-term adherence remains a challenge. Many patients struggle with maintaining lifestyle changes and consistent use of PAP, leading to lower compliance. Therefore, current research is actively exploring new treatment methods to address the metabolic disturbances associated with OSA. Pharmacological therapies, such as glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, have shown potential in improving OSA and related metabolic issues.[3,4] These treatments may not only directly affect metabolic pathways but also reduce body weight, lower systemic inflammation, and enhance cardiovascular health, providing new treatment options for patients who find it difficult to adhere to traditional therapies.

The emergence of GLP-1 receptor agonists (GLP-1RAs) marks a shift in the approach to treating metabolic diseases, particularly in managing type 2 diabetes and obesity. A substantial body of evidence suggests that these drugs play a critical role in the long-term control of these conditions, sparking widespread interest in their potential application in obesity-related conditions like OSA. GLP-1RAs function through various mechanisms, including the activation of GLP-1 receptors on pancreatic β-cells, enhancing glucose-dependent insulin synthesis and secretion, thereby reducing the risk of hypoglycemia.[5] Additionally, GLP-1RAs delay gastric emptying, increase satiety, reduce food intake, and support weight management. Furthermore, these drugs act on the hypothalamus, inhibiting orexigenic pathways that control appetite, thereby further supporting weight management.

Existing research indicates that GLP-1RAs have a positive impact on OSA treatment, particularly in significantly reducing AHI.[6,7] The improvements in daytime sleepiness scores and AHI resulting from GLP-1RA intervention are closely related to reductions in body weight, body mass index, and waist circumference.[8,9] Moreover, GLP-1RAs may improve respiratory control through mechanisms independent of weight management.[10] The hypothalamus contains GLP-1 receptors, which play a role in regulating the sleep-wake cycle and respiratory drive. GLP-1RAs can modulate neurotransmitter release when interacting with these receptors, which may enhance respiratory stability and reduce apnea episodes, independent of weight changes. GLP-1RAs have been shown to affect the sensitivity of chemoreceptors, particularly in the carotid bodies, which detect changes in blood oxygen and carbon dioxide levels. By altering chemoreceptor responsiveness, GLP-1RAs can improve respiratory drive, contributing to more stable breathing patterns during sleep. GLP-1RAs also possess anti-inflammatory properties that reduce systemic inflammation, which is often elevated in OSA patients. This reduction can im-

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prove upper airway muscle function, lower airway resistance, and enhance respiratory control without being solely dependent on weight loss. There is evidence suggesting that GLP-1RAs have neuroprotective effects that may enhance brainstem function, which is critical in regulating breathing. This mechanism can stabilize respiratory patterns during sleep, independent of weight loss effects. GLP-1RAs may also reduce sympathetic nervous system activity while enhancing parasympathetic activity, helping to regulate airway tone and respiratory muscles. This effect can improve overall breathing control in OSA patients, even without changes in body weight. The hypothalamus, as the primary regulator of the sleep-wake cycle, contains GLP-1 receptors, allowing GLP-1RAs to directly modulate this process. By acting on these receptors in the hypothalamus, GLP-1RAs regulate neurotransmitter release, influencing sleep quality and wakefulness.[11] This mechanism may explain the potential of GLP-1RAs to improve OSA-related symptoms of excessive daytime sleepiness.

The bioactivity of GLP-1RAs primarily depends on their interaction with GLP-1 receptors. However, due to individual differences in GLP-1 receptor gene polymorphisms and receptor expression levels, patient responses to GLP-1RAs can vary significantly.[12] Specifically, some patients may experience altered expression or function of GLP-1 receptors due to genetic polymorphisms, which could weaken or completely block the metabolic effects of GLP-1RAs. For these patients, continuing the use of GLP-1RAs, despite a lack of efficacy, may not only fail to achieve treatment goals but also increase the risk of drug-related adverse effects, including common gastrointestinal issues and more severe side effects such as pancreatitis or gallbladder disease. Therefore, promptly identifying the ineffectiveness of GLP-1RAs in certain patients and discontinuing their use can offer multiple benefits. First, it can reduce patient exposure to potential unnecessary side effects, improving the overall risk-benefit ratio of the treatment. Second, avoiding ineffective treatment can significantly reduce unnecessary healthcare costs, making it more economically sustainable. There is growing evidence that genetic polymorphisms in GLP-1 receptor genes can significantly impact an individual's response to GLP-1RAs. These genetic variations may lead to differences in receptor expression levels or functional activity, affecting the drug's efficacy in treating both obesity and OSA. For example, some patients with certain GLP-1 receptor gene polymorphisms might exhibit reduced receptor expression or altered receptor signaling, resulting in a diminished response to GLP-1RAs. Personalized medicine approaches can help identify patients who are more likely to benefit from GLP-1RA therapy by evaluating their genetic profiles. By conducting genetic testing before treatment initiation, clinicians can tailor therapy to those with the highest likelihood of responding, thereby improving treatment outcomes and minimizing unnecessary exposure to medication for non-responders. This approach not only enhances treatment efficacy but also reduces the risk of adverse effects, such as gastrointestinal discomfort or more severe complications like pancreatitis or gallbladder disease. Furthermore, personalized medicine can optimize dosing regimens, as patients with certain genetic variants might require higher or lower doses to achieve the desired therapeutic effect. It can also help monitor potential resistance to GLP-1RAs over time, allowing for therapy adjustments as needed. Personalized adjustments based on patient genetic information and drug response are key to ensuring optimal resource utilization and maximizing patient benefit. Additionally, many patients may experience weight regain after discontinuing GLP-1RAs, sometimes returning to pre-treatment levels. Evidence suggests that this weight rebound after stopping GLP-1RA treatment may reverse its cardiometabolic benefits,[13] a problem that warrants further investigation in future research.

SGLT2 inhibitors have recently demonstrated significant efficacy in treating cardiovascular diseases, diabetes, and related metabolic disorders. Although research on their use in patients with OSA is still in its early stages, SGLT2 inhibitors have shown potential benefits. In the VERTIS CV study, ertugliflozin reduced the incidence of OSA by 48% compared to placebo.[14] Additionally, a meta-analysis of data from nine large randomized controlled trials evaluated the potential association between SGLT2 inhibitors and several respiratory diseases.[15] The results showed that SGLT2 inhibitors reduced the incidence of OSA by 65% compared to placebo.

The potential benefits of SGLT2 inhibitors for OSA patients can be explained through several mechanisms[16]: (1) SGLT2 inhibitors promote urinary glucose excretion, leading to weight loss. Since obesity is a major risk factor for OSA, weight loss can reduce upper airway resistance, thereby decreasing the frequency and severity of apneas; (2) During supine sleep, bodily fluids may shift from the lower limbs to the thoracic and neck regions, increasing upper airway resistance and exacerbating OSA symptoms. SGLT2 inhibitors reduce overall fluid load, lowering the occurrence of this fluid shift, thus helping to improve respiratory function during sleep; (3) Nocturia can disrupt sleep, interrupting the rapid eye movement (REM) cycle and shortening REM periods, which may reduce the incidence of REM-related OSA events.

In terms of long-term management, GLP-1RAs, such as liraglutide and semaglutide, have shown significant improvements in reducing the AHI, weight, and cardiometabolic risk factors in OSA patients. The benefits of GLP-1RAs appear to be twofold: they not only support weight loss, which is critical for reducing OSA severity, but they also have independent mechanisms that may improve sleep quality by acting on hypothalamic GLP-1 receptors that regulate sleep-wake cycles. These effects suggest that GLP-1RAs could provide sustainable management of OSA, especially in patients with concurrent obesity or metabolic syndrome. For SGLT2 inhibitors, studies have shown a notable reduction in the incidence of OSA, with mechanisms involving weight loss and fluid management during sleep. By reducing bodily fluid retention and promoting weight loss, these medications help decrease upper airway resistance, a key factor in OSA pathophysiology.

Despite these positive outcomes, concerns remain regarding the potential for rebound effects after discontinuing GLP-1RAs. Evidence suggests that many patients tend to regain weight once treatment is stopped, often returning to pre-treatment levels. This weight rebound could potentially reverse the improvements in OSA symptoms, as obesity is a major contributor to OSA severity. The rebound effect also implies a possible return of cardiometabolic risks, such as increased blood pressure, insulin resistance, and inflammation, which were initially mitigated during treatment. Therefore, discontinuing GLP-1RAs may necessitate alternative strategies to maintain weight loss and prevent OSA relapse. As for SGLT2 inhibitors, although data is less conclusive, discontinuation might similarly lead to a gradual return of weight and fluid retention, potentially diminishing the positive effects on OSA. Given that the mechanism of action for SGLT2 inhibitors involves maintaining fluid balance and reducing body weight, discontinuing treatment could lead to a recurrence of fluid shifts during sleep, exacerbating OSA symptoms.

Given these considerations, both GLP-1RAs and SGLT2 inhibitors may require long-term, if not lifelong, administration to maintain their benefits in OSA management. This approach aligns with the chronic nature of both obesity and OSA, where long-term treatment is often necessary to manage these conditions effectively. However, the need for ongoing treatment raises important ques-

tions about patient adherence, potential side effects, and economic sustainability, all of which should be carefully weighed in clinical decision-making.

Currently, the dual gastric inhibitory polypeptide (GIP)/GLP-1 receptor agonist tirzepatide has been shown to significantly reduce AHI in OSA patients.[4] Additionally, dual GLP-1/glucagon receptor agonists and triple GLP-1/GIP/glucagon receptor agonists are being explored for their potential effects in overweight or obese patients with OSA. Future studies need to be longer-term and more rigorously designed randomized controlled trials to thoroughly assess the safety and efficacy of GLP-1 and SGLT2 inhibitors in various patient populations and to better determine their effectiveness in reducing OSA severity and improving cardiovascular health. It is particularly important to clarify whether these treatments require long-term or intermittent use and to understand their long-term effects on OSA. Robust data on the risk-benefit ratio of these drugs will be crucial for clinical decision-making. In the future, physicians in the field of sleep medicine should enhance their skills by integrating obesity management with GLP-1 therapy as a treatment option for patients, which will require a deeper understanding of the potential side effects and challenges that patients might face, such as resistance to injection therapies.

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