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Review of Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Agonists for Treatment of Adult Obese Patients with Obstructive Sleep Apnea

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ABSTRACT

Although there are multiple risk factors for obstructive sleep apnea, obesity is a significant actionable risk factor that is increasing worldwide. Studies have shown that weight loss whether through bariatric surgery or medications is associated with improvement in obstructive sleep apnea severity. This review summarizes the underlying mechanisms of glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide receptor agonists pertaining to weight loss and then summarizes the studies which show beneficial effects on weight loss in obese adults with or without diabetes. We then review the available studies showing a reduction in obstructive sleep apnea severity in adult patients with obesity primarily through weight reduction. Potential limitations and implications of treatment with these medications for obstructive sleep apnea will be reviewed.

Introduction

Although there are multiple risk factors that contribute to obstructive sleep apnea (OSA) such as older age, hypothyroidism, genetic predisposition, airway anatomy, male gender, post-menopausal state, opioids or respiratory depressant medications, and lifestyle habits of alcohol or tobacco use, obesity is a significant actionable risk factor[1]. One-seventh of the world's population, approximately one billion people, are estimated to have OSA and obesity is the main risk factor. The World Health Organization estimates that global obesity affects two billion adults worldwide and has increased over the past 5 years[2]. Given the significant role of obesity in the pathophysiology of OSA, the American Academy of Sleep Medicine (AASM) recommends repeating a sleep study when a patient experiences a 10-20% reduction in weight[3]. In addition, the American Thoracic Society recommends early comprehensive lifestyle interventions for weight loss as routine treatment in overweight or obese patients with OSA[4].

Although body mass index (BMI) is a widely used tool to diagnose obesity, it fails to capture the numerous health consequences associated with excess weight. Complications associated with obesity include obstructive sleep apnea, increased risk of stroke, depression, gastroesophageal reflux, renal disease, osteoarthritis, type two diabetes, cancer, gallbladder disease, liver disease, and an increased risk of cardiovascular disease[5]. In terms of sleep apnea, an increase of weight by 10% was found to have an approximate 32% increase in the apnea hypopnea index (AHI) and a six-fold increase in the risk of developing moderate to severe OSA. The association between weight gain and OSA is secondary to neck circumference, excess deposition of visceral fat in the upper airway, decreased chest wall compliance, and increased total body oxygen demand. It has been shown that a change in neck circumference is positively associated with visceral fat and abdominal obesity[6,7]. Fat deposits around the neck further increases the probability of upper airway collapse in the setting of already reduced chest wall compliance, reduced lung functional residual capacity and expiratory reserve volume, and increase negative thoracic pressure in an effort to overcome abdominal pressure from truncal obesity[8,9]. The increased basal metabolic rate and oxygen consumption in obese patients leads to a constant low grade inflammation that increases the risk of cardiovascular and metabolic derangements[10].

Multiple studies have shown an improvement in OSA severity with weight loss. A systemic review and meta-analysis of bariatric surgery and OSA that evaluated 32 studies of 2,310 subjects found that bariatric surgery was associated with a significant reduction in BMI, AHI, and the respiratory disturbance index (RDI) with a 65% rate of OSA remission[11]. Another systemic review and meta-analysis comparing pharmacologic and bariatric surgical interventions to usual care, placebo, or no treatment in adults with OSA reviewed 10 trials (n = 854 adults). Four trials assessed bariatric surgeries and 6 assessed pharmacologic treatments over 13 months. The linear best estimate of the change in AHI is 0.45 events per hour for every 1% body weight lost[12]. Other studies have shown that a single 1-point decrease in BMI was shown to correspond with a decrease in the AHI by 6.2%[13]. However, a >5 % and >10% weight loss is necessary to reduce severe OSA based on the MIMOSA clinical trial[14]. Studies have shown that a 10% weight loss is associated with a 26% decrease in AHI (95% CI 18%-31%)[15,16,17]. An 18-month randomized controlled trial utilizing total body MRI after a weight loss intervention showed a direct correlation between chin and neck adipose tissue and visceral adipose tissue, further supporting that weight loss alleviates the burden of neck adipose tissue and in turn lowers the risk of upper airway collapse[18].

Weight loss in general has a multitude of health benefits including reduction in C-reactive protein (CRP), hemoglobin A1c (HbA1C), and an improvement in lipid profile, all of which play important roles in cardiovascular risk[19]. From the Sleep AHEAD trial, which was a subset study of the

Look AHEAD trial from 2001 to 2012 studying weight loss effects on AHI, it was found that improvement of AHI was still present at year 4 despite an almost 50% weight regain. At year 10, AHI reduction had attenuated but 60.9% of subjects who underwent intensive lifestyle modification still showed improvement in OSA severity compared to baseline[20,21,22,23].

Given the benefits in OSA severity with weight loss, the purpose of this paper is to review the use of the class of medications known as the Glucagon-Like Peptide 1 (GLP1)/Glucose-Dependent Insulinotropic Polypeptide (GIP) receptor agonists for the treatment of OSA in adult patients with obesity. This review will first discuss the mechanism of weight loss using GLP1/GIP receptor agonists, summarize the available data on the weight loss benefits of these agents, their potential adverse effects, and then review the available studies utilizing these medications for the treatment of obese adults with OSA highlighting their strengths and liabilities.

Mechanism of Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Receptor Agonists for Weight Loss

Glucagon-like peptide 1 (GLP1) is an incretin hormone produced in the enteroendocrine L cells of the small intestine which binds to GLP1 receptors to stimulate glucose-dependent insulin release. Working with other hormones, such as glucose-dependent insulinotropic polypeptide (GIP), GLP1 in the postprandial setting stimulates insulin and amylin release from the pancreatic beta cells, inhibiting glucagon release from the alpha cells through somatostatin, and delaying gastric emptying while signaling satiety to the brain in concert[24]. Glucagon-like peptide 1 receptors are found in various tissues including the kidneys, lungs, heart, skin, immune cells, and hypothalamus. In the central nervous system, GLP1 has a role in regulating appetite and reward-behaviors in the medial hypothalamus and nucleus of the solitary tract. These neurons show activation following gastric distension, playing a role in satiety and insulin response. An early study showed exogenous injection of GLP-1 lead to a decrease in food intake in mice[25]. In patients who had Roux-en-Y gastric bypass or sleeve gastrectomy, GLP1 levels were increased likely due to decreased functional volume signaling release of GLP1 to delay gastric emptying[26,27].

Glucagon-like peptide 1 also promotes weight loss through adipocyte augmentation. Interleukin-6 (IL-6), a proinflammatory cytokine and an anti-inflammatory myokine found in adipocytes, has an important role in activating brown adipogenesis and thermogenesis in insulin sensitivity. Brown adipocytes act through energy expenditure through thermogenesis due to richness in mitochondria[28]. GLP1 agonists activate browning of the adipocytes in mice, and central GLP1 decreases peripheral lipid storage in white adipocytes[26,29]. The activation of invariant natural killer T (iNKT) cells, fibroblast growth factor 21 (FGF-2), and IL-6 have all been shown to contribute to adipose tissue browning. Specifically, activating iNKT cells in obese mice led to weight loss. In FGF21-null mice, mice lost less weight compared to the control group. In IL6-knockout mice, liraglutide was able to still induce some weight loss but with less thermogenic adipocyte browning[30]. Interestingly, brown and beige adipocytes are found more in cervical and supraclavicular regions compared to white adipocyte distribution in the body[30].

Glucose-dependent insulinotropic polypeptide is secreted by the enteroendocrine K cells in the small intestine after food introduction and glucose sensing through the sodium-glucose cotransporter -1 (SGLT-1). It has a role in anabolic metabolism that increases insulin levels, glycogen storage, and adipose tissue fat accumulation. GIP increases lipoprotein lipase expression that breaks down triglycerides in chylomicrons[31,32,33]. Previous studies had shown that co-administration of GLP1 and GIP have synergistic effects in pancreatic cells[34]. Using mouse genetic models, a dual GIP/GLP1 agonist showed an increased adipocyte glucose uptake, insulin signaling, adipocyte functions, central anorexic

effect, and lipid clearance. In the absence of insulin, it also increases lipolysis[35]. It is hypothesized that the GIP/GLP1 synergism acts on the central nervous system (CNS) to reduce food intake[36].

Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Receptor Agonists for Weight Loss in Obese Adults with and without Diabetes

The current GLP1s analogs on the market include semaglutide (Wegovy®, Ozempic®, Rybelsus®), liraglutide (Sexanda®, Victoza®), dulaglutide (Trulicity®), exenatide (Byetta®), and tirzepatide (Mounjaro®, Zepound®) (GLP1/GIP). The current FDA approved GLP1 for obesity alone are Saxenda®, Wegovy®, and Zepbound®. Oral GLP1s such as orforglipron and danuglipron are currently undergoing phase 3 clinical trials.

A systematic review and meta-analysis of GLP1 agonists showed significant weight loss and cardiovascular risk reduction in non-diabetic obese groups. Medications studied included semaglutide 2.4mg, liraglutide 3mg, tirzepatide 15mg, orforglipron 24mg, exenatide 10 and 20mg. Fourteen studies showed an 8.77kg significant difference in weight loss compared to placebo. Tirzepatide exhibited the most weight loss at 17%, semaglutide 12%, orforglipron 10%, and exenatide 3.3%. However, in BMI reduction, semaglutide had the greatest reduction with a mean weight loss of 4.41 kg/m^2 [37].

In a review of 14 studies of GLP-1 receptor agonists for patients with or without diabetes, liraglutide 3mg and semaglutide 2.4mg added to lifestyle intervention resulted in weight loss. Semaglutide compared to liraglutide resulted in greater weight loss. The mean weight loss difference between GLP1 receptor agonists and placebo as add-on to lifestyle intervention in patients with diabetes was 4% to 6.2% compared to 6.1 to 17.4% in people without diabetes[38]. Semaglutide compared to liraglutide resulted in greater weight loss. In another study, liraglutide showed a dose-dependent weight loss curve. The most significant weight loss of 5-10% was shown in the liraglutide 3mg group[5]. If patients who were not able to tolerate escalation to a maximum dose of 3mg, a Swiss retrospective study found that there was still clinically meaningful weight loss with use of liraglutide at a lower dose[39].

In the STEP trial, semaglutide 2.4mg used on obese patients without T2DM showed a 10.3% - 17.4% reduction in mean weight, averaging 14.9% in reduction, and 86.4% of the patients lost > 5% mean weight compared to 31.5% in the placebo group[5,38]. Sixty-nine percent of subjects of the semaglutide group had at least 10% weight loss compared to 12% subjects in control, and 50.5% had 15% weight loss compared to 4.9% in control[40]. In a meta-analysis of 23 randomized controlled trials (RCT), it appeared that liraglutide 3mg was less effective than semaglutide 2.4mg for weight loss. Semaglutide 2.4mg had up to 12.47kg of weight loss compared to liraglutide 3mg losing up to 5.24kg. However, there were more adverse side effects in the semaglutide group[41].

Tirzepatide is a dual GLP1/GIP agonist that has equal affinity to native GIP receptors but weaker affinity to native GLP1 receptors[42]. Despite the realization that the detailed mechanism of action is not fully known, animal studies of a combined GLP1+GIP agonist showed remarkable weight loss. In the SURMOUNT trial, obese patients without diabetes were divided into weekly tirzepatide 5mg, 10mg, 15mg vs placebo for 72 weeks. At the end of the study, the 5mg group lost about 15% body weight, 10mg group 19.5%, 15mg group 20.9%, and the placebo group with just 3.1%. Overall, the study showed 85-91% of patients having more than 5% weight loss compared to 35% in the placebo group. The study found that 36.2% of patients in the 15mg tirzepatide group had at least 25% weight reduction, which was comparable to patients who receive bariatric surgery with 25-30% weight reduction[43].

In a phase 2 double blinded randomized trial, obese patients with at least one comorbidity but without T2DM were divided into 5 groups

(orforglipron 12mg, 24mg, 36mg, 45mg, vs placebo) for 36 weeks. It was shown that at the end of the study, patients who took orforglipron lost 9.5% to 14.7% weight vs 2.3% in placebo[44]. Oral orforglipron and danuglipron are currently in the process of FDA approval for weight loss reduction. Retatrutide is a triple agonist of GLP1, GIP, and glucagon receptors (GCG). In its phase 2 double blind randomized controlled trial, in obese patients treated with 1mg vs 4mg vs 8mg vs 12mg vs placebo for 48 weeks. There was a dose-dependent weight loss. Specifically, in the 12mg group, 100% of subjects lost more than 5% weight, 93% lost more than 10%, and 83% lost more than 15%. Overall, retatrutide showed a mean weight reduction of 24.2% after 48 weeks. It is hypothesized that the GLP-GIP effect may be further synergistically enhanced in the setting of GCG activation[45].

Adverse Effects of Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Receptor Agonists

The most common side effects that patients experience when initiating GLP1 receptor agonists are gastrointestinal symptoms, including nausea, vomiting, diarrhea, which are attributable to the effect of delayed gastric emptying. These mostly self-limiting symptoms were observed especially during faster escalation of dose or at higher doses[46,47]. As the mechanism of GLP1 results in delaying gastric emptying, patients who attempt to continue eating the same portion size may experience nausea and diarrhea due to overdistention of stomach. However, some patients experienced symptoms of nausea during the fasting state as well, suggesting that there may be more than one mechanism at play. Diarrhea was thought to be related to alterations in motility and absorption. Nonetheless, symptoms usually are tolerable and can be treated with supportive measures. A relative contraindication is patients who have gastroparesis. Although GLP1 receptor agonists appear to have renal protective effects, it is important to closely monitor patients with severe nausea, vomiting, and diarrhea due to increased risk of acute kidney injury. The FLOW trial assessing GLP1 receptor agonists in chronic kidney disease was stopped early due to evidence of renal protection with semaglutide[48].

In addition, some patients had a higher incidence of pancreatitis and biliary disease, such as cholelithiasis and cholecystitis[46]. In the liraglutide SCALE trial, a higher dose was associated with an increased risk of a gallbladder event at 2.5% vs 1% in the placebo group. Similarly, in the PIONEER study, cholelithiasis was observed to be increased in the semaglutide group. A meta-analysis showed a 28% increased risk of cholelithiasis with GLP1 treatment. The detailed underlying mechanism is still unclear, but a proposed theory is the increased risk of sludge formation in setting of decreased gallbladder motility and reduced cholecystokinin that promotes gallbladder emptying[47]. Studies showed that there was an asymptomatic increase in plasma lipase and amylase within hours of administration of semaglutide. In the tirzepatide study, there were four cases of pancreatitis evenly distributed across treatment groups including the placebo group[47]. Given the concern of increased risk of pancreatitis, it is currently recommended to avoid GLP1 receptor agonists in patients with a history of pancreatitis or discontinue the medication in patients who develop pancreatitis[49].

Glucagon-Like Peptide 1 and Glucose-Dependent Insulinotropic Polypeptide Receptor Agonists for Adult Patients with Obesity and Obstructive Sleep Apnea

Given the available data on GLP1/GIP and significant weight loss in obese patients with and without diabetes, recent studies have shown promising results in the treatment of obese patients with OSA. The SURMOUNT-OSA trials

were two phase 3, double blind randomized controlled trials involving obese, adult non-diabetic patients with moderate to severe OSA not on PAP therapy in one group and on PAP therapy in another group. In the study groups, participants were given either tirzepatide 10mg or 15mg vs placebo for 52 weeks. The baseline mean AHI was 51.5 in the without-PAP group and 49.5 in the PAP group with a mean BMI of 39.1 and 38.7. Patients were started with the 2.5mg dose then escalated to the maximum tolerated dose of 10mg or 15mg by week 20. In Trial 1, the mean change in AHI at week 52 was -25.3 events per hour with tirzepatide without PAP and -5.3 in the placebo group. In Trial 2 (on PAP), the tirzepatide group had an AHI reduction of -29.3 vs -5.5 in the placebo group. Overall, this study showed a significant decrease in AHI up to 29.3 (58.7% from baseline). Secondary endpoints included systolic blood pressure, inflammatory marker CRP, and PROMIS - questionnaire of SRI (sleep related impairment) and SD (sleep disturbance), which all had significant reduction in the pooled participants receiving tirzepatide compared to placebo[50].

In the SCALE Sleep Apnea Trial, liraglutide 3mg was compared to placebo to determine whether weight loss reduced OSA severity. In this randomized, double-blind trial, non-diabetic participants with obesity and moderate to severe OSA not using PAP were randomized for 32 weeks to liraglutide 3mg (n=180) or placebo (n-179). In the liraglutide 3mg group, patients had a reduction of 5.7% in body weight vs only 1.6% in the controlled group. Furthermore, there was a significant reduction in AHI of -12.2 in the liraglutide group compared to -6.1 in the placebo group, showing a significant association between weight loss and improvement in AHI[51,52]. Jiang et al.[53] conducted a two-center prospective randomized controlled study. They randomized patients with type 2 diabetes mellitus (T2DM) with severe OSA to CPAP and treatment with liraglutide (n=45) vs. CPAP without liraglutide (n=45). After 3 months, the BMI, AHI and mean systolic blood pressure in the liraglutide treatment group were significantly lower than those in the control group. The minimum oxygen saturation was significantly higher in the liraglutide group compared with that in the control group after 3 months of follow-up. There was no difference between the two groups in terms of side effects ($P > 0.05$). There was only one patient in the liraglutide group that dropped out of the study at day 8 due to gastrointestinal symptoms.

One study suggested that the reduction in OSA severity may not be related to weight loss. Amin et al.[54] studied the treatment of OSA with a GLP-1 receptor agonists. They recruited 27 adults with moderate to severe OSA. There were 18 subjects in the treatment arm that received increasing doses of a GLP-1 receptor agonist (liraglutide) from 0.6mg to 1.8mg. There were 9 adults in the control arm. All participants received a polysomnogram at the start and completion of the 4-week study. The overall AHI for the treated group decreased from 50±32 to 38±30 ($P= 0.002$). Seventy percent of the subjects in the treatment arm showed a decline in AHI by 44% or 20±12 events per hour while 30% showed no response to treatment with AHI 52±41 at baseline vs 55±39 at follow-up. There was no significant change in AHI in subjects in the control group. There was no significant change in BMI for responders at baseline and follow-up and no change in BMI for the control group. Unfortunately, the study had several major limitations. Subjects were not randomized; the study size was small and of short duration, and there was insufficient time for adequate weight loss with the use of liraglutide.

To determine whether GLP-1 analogs have additive effects with CPAP and effects on cardiovascular disease risk, O'Donnell et al.[55] conducted a randomized study comparing CPAP, a GLP-1-mediated weight loss regimen (liraglutide) and combination treatment in patients with moderate to severe OSA and a BMI of 30-40 kg/m^2 with no history of diabetes. CPAP alone and in combination with liraglutide resulted in greater reduction in AHI than liraglutide alone (mean difference, -45 and -43 events/h, respectively, vs. -12 events/h). Both

liraglutide and combination treatment led to significant weight loss, but only CPAP alone resulted in significant decrease in vascular inflammation. They recommended large randomized controlled studies to assess the benefit of CPAP therapy in modifying early CV disease.

In summary, the current data suggests a favorable outcome of reduction in AHI with GLP1/GIP treatment, but more studies are need. More rigorous RCTs with sufficient length of follow-up are required before incorporating these medications into OSA treatment guidelines[56]. Sprung et al.[57] are conducting the ongoing 2020 ROMANCE trial using liraglutide in the United Kingdom. The study is a randomized controlled multicenter study of 26 weeks of subcutaneous liraglutide with or without CPAP in patients with T2DM and OSA.

Limitations of Glucagon-Like Peptide 1/Glucose-Dependent Insulinotropic Polypeptide Receptor Agonists for Treating Adults with Obstructive Sleep Apnea and Obesity

There are several limitations associated with the GLP1/GIP agonists. One limitation is that patients may not have continued weight loss with cessation of the GLP1/GIP medication. In the liraglutide SCALE trial, an extension of study was conducted, named the SCALE Maintenance Trial. Subjects who lost 5% of body weight were entered into the randomized controlled trial to either continue liraglutide vs placebo. It was found that continuation of liraglutide had significant and continued weight loss of 6.2% compared to placebo of 0.2%[92]. In the semaglutide STEP4 Withdrawal Trial, patients were taken from the previous STEP trials after 20 weeks of semaglutide 2.4mg (with mean weight loss of 10.6%), and they were split into two groups, to continue additional 48 weeks of semaglutide vs placebo. There was a significant difference in mean weight changes of -7.9% in semaglutide continuation vs +6.9% in the discontinuation group[44,58]. Thus, without the medication, patients may regain weight.

In addition to the STEP4 Withdrawal Trial, the extension of STEP1 trial looked at discontinuing semaglutide 2.4mg after week 68. From week 0-68 during treatment, the mean weight loss was 17.3% (SD 9.3%) with semaglutide and 2% (SD 6.1%) in placebo. After completely stopping treatment at 68 weeks and onward, it was noted that at week 120, the semaglutide group regained 11.6% (SD 7.7%) and the controlled group regained 1.9% (SD 4.8%), leading to a net loss of 5.6% (SD 8.9%) in semaglutide group and net loss of 0.1% (SD 5.8%) in controlled group. Blood pressure returned to baseline after withdrawal as well, while CRP, lipid panel, A1c, remained to have some relative improvements compared to prior treatment[59]. In the tirzepatide SURMONT-4 trial, a mean weight reduction of 20.9% after 36 weeks of tirzepatide 10mg or 15mg treatment was found to have 14% weight regain after 52 weeks when switched to placebo. Those who continued tirzepatide showed an additional 5.5% weight reduction[60].

The mechanism of weight regain is thought to be associated with leptin and peptide YY (PYY) in the circulation. Both hormones are responsible for satiety signaling after ingestion of food, inhibiting the sense of hunger[61]. Studies showed that the use of Liraglutide led to higher PYY and leptin[62]. This supports the notion that GLP1 agonists utilize CNS appetite suppression as a vital driver in weight loss. With this evidence, it appears that continuation of GLP1 agonists is required to maintain the benefits observed. Although it is uncertain what the subjects of these studies experience during the discontinuation phase or if discontinuing GLP1 led to a rebound effect, this phenomenon of weight regain lends credence that a component of weight loss is also behavioral and psychological if active lifestyle or healthy dietary habits are not well monitored.

A small study looked at acute (4.5 hr.) vs intermittent (4.5hrs x 2) vs prolonged (24hr) infusion of GLP1 analogs in 10 male subjects in the

setting of eating radiolabeled food. It was shown that the delayed gastric emptying was attenuated in magnitude in the prolonged infusion group[63]. Although this is a small study with a different method of administering GLP1 and may not be grossly generalized, this finding shed light on possible underlying mechanism in weight plateau for continuous administration. In the SURMONT-4 trial, tirzepatide seemed to reach a plateau of weight loss approximately at around 70 weeks, similar to that of semaglutide in the STEP5 trial[64]. Despite the possible plateau, in the semaglutide SELECT trial, it was shown to have continued and significant weight reduction and maintenance at year 4 (208 weeks)[65]. The preserved effect in weight loss was seen in all the current approved GLP1 analogs (semaglutide, liraglutide, tirzepatide)[66].

Another limitation is the cost and high demand for GLP1/GIP medications. The current GLP1 medications range from $900 to $1400 before insurance and other discounts[67]. In another analysis based on Medicare Part D spending data, the total gross spending on semaglutide and tirzepatide had increased from $57 million in 2018 to $5.7 billion in 2022[68]. Importantly, Medicare Part D currently does not cover GLP1 medications for weight-loss only, unless patients are receiving GLP1 for other indications such as diabetes. In contrast, depending on the type of PAP machine prescribed, a CPAP device averages to about $800[69]. Although most CPAP machines can last upwards of 5 years, other costs must be accounted for such as CPAP supplies such as masks, machine filters, tubing, headgear, and humidifier water tanks every few months to ensure optimal functioning[70,71]. Depending on the required replacements, each part may range upwards of $200-$300[89].

Other factors to consider are the number of doctor visits to monitor the initiation and maintenance of GLP1/GIP drug treatment versus follow-up for use of CPAP. Furthermore, based on the available data thus far, despite significant reduction in AHI severity, patients may still have mild to moderate OSA and require continued treatment with CPAP. As such, patients may still need to be financially responsible for both GLP/GIP and CPAP machines.

Conclusion

Based on the available data, it is evident that GLP1 receptor agonists and GLP1/GIP dual receptor agonists have multiple mechanisms that regulate appetite and satiety. Studies have shown that use of these medications result in significant weight loss in patients with obesity. Studies have demonstrated significant benefits in obese patients with OSA by weight reduction leading to an improvement in AHI. From the available studies, the greatest AHI reduction was 29.3. The mechanism of utilizing GLP1/GIP for obese patients with OSA treatment is mainly through weight loss by mediating delayed gastric emptying, appetite suppression, and thermogenesis of brown adipocytes. However, other concomitant mechanisms such as inflammatory cascades and circadian rhythm may be at play as well. Nonetheless, limitations such as potential medication side effects, medication cost, and difficulty maintain weight loss must be factored into the use of these medications for OSA.

Obese patients with OSA benefit from GLP1/GIP receptor agonists by lowering the AHI severity through weight loss potentially allowing patients to better tolerate CPAP therapy with lower pressure settings or allowing them to opt for other alternative treatments such as oral mandibular advancement. Furthermore, it is important to recognize the different phenotypes of OSA, since GLP1/GIP receptor agonists are not likely to benefit the 20-25% of OSA patients that are not obese[72,73,74,75].

The long-term benefits and potential risks of GLP1/GIP receptor agonists in the setting of obese patients with OSA are not completely understood. Since one of their main driving mechanisms for weight loss is through delayed gastric emptying, providers must be cautious in patients who are at risk for underlying gastroparesis or in those who are at risk of aspiration particularly with the use of CPAP. Providers prescribing GLP1/GIP receptor

agonists in patients with OSA and obesity on CPAP should consider behavioral and dietary treatments to minimize gastroesophageal reflux and aspiration.

Currently, CPAP remains the gold standard treatment for OSA per the AASM guidelines; however, OSA will continue to require a multi-modal approach. Weight loss through surgery or medication for patients with OSA has benefits. Given the likelihood of GLP1/GIP-associated weight plateau and weight regain with medication cessation, patients will have greater success with weight loss by also having an active lifestyle and maintaining a healthy diet. As the understanding of GLP1 pharmacology advances, there may be a paradigm shift in the management of OSA. Working with primary care physicians, sleep medicine providers may utilize GLP1/GIP medications in appropriate obese candidates with OSA. Indeed, Sultana et al.[76] in their article proposed early consideration of GLP1/GIP treatment in managing obese patients who have multiple comorbidities along with OSA[77]. Given the role of GLP1 and GLP1/GIP agonists in the management of obesity and diabetes, they may one day be used for obese patients with OSA.

Conflict of Interest Statement:

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