REVIEW

J Rhinol 2023;30(1):1-5 | https://doi.org/10.18787/jr.2023.00010 pISSN 1229-1498 / eISSN 2384-4361
www.j-rhinology.org

Weight Loss for Obstructive Sleep Apnea: Pharmacological and Surgical Management

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Obstructive sleep apnea (OSA) is a relatively common sleep disorder characterized by repetitive narrowing or obstruction of the upper airway, including the nasal cavity, pharynx, and larynx, during sleep. OSA can cause a variety of symptoms and/or complications, such as excessive daytime sleepiness, reduced concentration, hypertension, type II diabetes, and stroke. Accordingly, an accurate diagnosis and appropriate treatments are required for OSA. Obesity is an important risk factor for OSA and is characterized by the abnormal accumulation of fat in the body, including the upper airway. When the body weight increases, adipose tissue accumulates in the pharynx, which can narrow the diameter of the upper airway and lead to dysfunction of the pharynx dilator muscles. These changes caused by weight gain can cause or exacerbate OSA. Various therapeutic options exist for patients with overweight or obesity, including diet, behavioral modifications, exercise, pharmacological treatments, and surgical procedures. Of these, diet, behavioral modifications, and exercise constitute the first-line management for obesity. However, their results are relatively unsatisfactory, and pharmacotherapy and bariatric surgery are generally implemented in obese patients with OSA. Therefore, the purpose of this paper is to review pharmacological and surgical management strategies for obesity that are currently commonly used in overweight or obese adult patients with OSA.

Keywords: Obstructive sleep apnea; Obesity; Weight loss; Pharmacotherapy; Bariatric surgery.

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disease caused by intermittent partial or complete collapse of the upper airway during sleep. It is estimated that about 936 million people worldwide suffer from OSA, among whom more than 425 million have moderate to severe OSA [1]. In Korea, the prevalence of OSA is reported to be 4.5% in men and 3.2% in women [2,3].

Obesity is a disease caused by the abnormal accumulation of fat in the body, and it is attracting attention as a critical risk factor for OSA [4,5]. According to a survey conducted by the Ministry of Health and Welfare, the obesity rate in Korea increased from 31.7% in 2007 to 38.3% in 2020 based on a body mass index (BMI) ≥25 kg/m^2, and this proportion is expected to continue increasing with the spread of Western lifestyles [6,7]. Increasing weight is accompanied by various pathophysiological changes in the body. The accumulation of adipose tissue in the pharynx may narrow the diameter of the upper airway and cause abnormalities in the function of the pharyngeal dilator muscles. These changes can lead to OSA. In addition, if abdominal fat, especially visceral fat, accumulates, the chest volume decreases and the functional residual capacity during breathing decreases, which can reduce the quality of sleep [5,8,9].

Many studies have shown moderate to severe OSA to be highly correlated with BMI. In the Wisconsin Sleep Cohort Study, a 10% increase in body weight was associated with a six-fold increase in the risk of developing moderate to severe OSA over 4 years and a 32% increase in the apnea-hypopnea index (AHI) [10]. As OSA becomes more common with the increasing prevalence of obesity in modern society, weight loss must be considered as a treatment for overweight or obese

Received: January 15, 2023 **Revised:** February 6, 2023
Accepted: February 8, 2023

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patients with OSA.

Successful treatment of overweight and obesity requires a number of approaches to resist maintaining the body's homeostasis. Although diet, exercise, and behavioral modification are generally the first-line management for weight loss, many patients may need more effective management, such as pharmacological or surgical treatments, to achieve clinically significant weight loss and maintain an appropriate weight. This article reviews the pharmacological treatments approved by the Food and Drug Administration (FDA) and surgical management for obese patients with OSA.

PHARMACOLOGICAL AND SURGICAL MANAGEMENT

Pharmacological management

Diet, exercise, and behavioral modification are the first-line treatment for obesity, and pharmacological management can be considered if no significant weight loss occurs even after 3 to 6 months of the first-line treatment. In Western countries, pharmacological therapy can be considered if the BMI is ≥30 kg/m^2 or ≥27 kg/m^2 with cardiovascular complications or OSA [11]. The Korean Society for the Study of Obesity recommends considering pharmacological treatment if the BMI is ≥25 kg/m^2 or ≥23 kg/m^2 with cardiovascular complications or OSA [12].

To date, four medications have been approved by the FDA as long-term obesity treatments: a lipase inhibitor (orlistat), the phentermine-topiramate complex, a glucagon-like peptide 1 (GLP1) receptor agonist (liraglutide), and the naltrexone-bupropion complex. A serotonin 2 receptor agonist (lorcaserin) was excluded from the FDA's list of medications for obesity management in 2020. In order to achieve effective weight loss and minimize side effects from drugs, it is necessary to properly adjust the dose of the drug and to confirm the patient's medical history and target weight.

Orlistat, which was approved by the FDA in 1999, induces weight loss by reducing fat absorption through the inhibition of the action of pancreatic lipase. Orlistat is known to have little systemic effect because most of it cannot be absorbed into the body and is excreted in the feces. A double-blind study showed an average weight loss of 9.6% in the group that took orlistat (120 mg three times a day) for 1 year, compared to 5.6% in the placebo group. Therefore, orlistat showed a weight loss effect of approximately 3% compared to the placebo group [13]. Orlistat may cause steatorrhea, stool urgency, and fecal incontinence due to decreased lipid absorption, and it may lead to abdominal discomfort. In addition, orlistat should not be used in pregnant women or patients with malabsorption syndrome, in whom nutrient absorption is important. Because orlistat can interfere with the absorption of vitamin K and affect the pharmacological action of warfarin, an appropriate medical history should be taken before use [14].

The phentermine-topiramate complex, which was approved by the FDA in 2012, acts on the central nervous system to inhibit appetite and induce weight loss. Phentermine is known to play a role in suppressing appetite by promoting the secretion of norepinephrine [15,16]. Although the exact mechanism of topiramate's weight loss effect has not yet been identified, animal experiments have suggested that it may be due to increased energy consumption resulting from the increased activity of lipoprotein lipase in brown fat and skeletal muscles [16]. According to a related study, the group taking the phentermine-topiramate complex (15/92 mg) for 56 weeks showed an average weight loss of 9.8 kg, and the group taking a dose of 7.5/46 mg showed an average weight loss of 7.8 kg. These results showed a higher weight loss effect than the weight loss of 1.2 kg that occurred in the group that did not take the drug [14,15]. The phentermine-topiramate complex can cause side effects such as increased heart rate, dry mouth, headache, insomnia, and increased intraocular pressure. It is contraindicated in pregnant women and in patients with cardiovascular disease, hyperthyroidism, glaucoma, and hypersensitivity to sympathomimetic amines, and mentally unstable patients. Therefore, in patients with OSA who have cardiovascular disease or are suspected of having contraindications, caution is required before using the drug [17,18].

A GLP1 receptor agonist (liraglutide) was approved by the FDA in 2014 as a treatment for obesity. It delays gastric emptying, so that food passes more slowly from the stomach to the small intestine, and acts on the central nervous system to suppress appetite and induce weight loss [19]. In a related study, the group taking 3.0 mg of liraglutide daily showed an average weight loss of 8.0%, while the group taking 1.8 mg showed an average weight loss of 4.7%. Both groups showed a higher weight loss effect than the 2.6% weight loss observed in the group that did not take the drug [20]. The adverse effects of liraglutide mainly include gastrointestinal side effects such as nausea, vomiting, diarrhea, constipation, and abdominal pain. Headache, dizziness, and rare side effects such as gallstones, cholecystitis, pancreatitis, acute renal failure, and medullary thyroid carcinoma have also been reported. As gastrointestinal side effects are common, caution is needed for use in patients with inflammatory bowel disease or gastroparesis. Liraglutide is contraindicated in pregnant women and patients with a history or family history of medullary thyroid cancer [20].

The naltrexone-bupropion complex was approved by the FDA in 2014 as an obesity treatment. Although the mechanism through which it induces weight loss has not been accu-

rately identified, it is thought to act on the hypothalamus and mesolimbic dopamine circuits to cause satiety and increase energy consumption [21]. A related study showed that the group taking the naltrexone-bupropion complex (32/360 mg daily for 56 weeks) showed an average weight loss of 6.1%, and the group taking a dose of 16/360 mg showed an average weight loss of 5.0%. The weight loss effect in both groups was higher than that (1.3%) observed in the group that did not take the drug [21,22]. Common side effects of the naltrexone-bupropion complex include nausea, constipation, headache, vomiting, dizziness, insomnia, and dry mouth. Its use is contraindicated in pregnant women and patients with uncontrolled hypertension, and because naltrexone is an opioid antagonist, it cannot be used in patients taking opioids. Substantial caution is required before use because patients with OSA often have high blood pressure [21,22].

Multiple studies have investigated whether pharmacological treatment, such as the phentermine-topiramate complex and GLP1 receptor agonist (liraglutide), can improve OSA through weight loss. According to a study conducted by Winslow et al. [15], the AHI decreased from an average of 44 to 14 events/h after 28 weeks in 22 patients taking 15/92 mg of the phentermine-topiramate complex, whereas the AHI decreased from an average of 45 to 27 events/h in 23 patients in the placebo group. Compared to the placebo group, OSA improved to a greater extent in the phentermine-topiramate complex group. In addition, in the patients who took the phentermine-topiramate complex, body weight decreased by an average of 10.3% over 28 weeks, whereas the placebo group showed an average body weight reduction of 6.1% over 28 weeks, indicating that weight loss was also more effective in the phentermine-topiramate complex group than the placebo group. A significant positive correlation between weight loss and AHI reduction was confirmed [15]. According to a study conducted by Blackman et al. [23], the AHI of 134 subjects who took 3.0 mg of liraglutide for 32 weeks decreased by an average of 12.2 events/h (from 49.0 to 36.8), whereas the AHI of 142 subjects in the placebo group decreased by an average of 6.1 events/h (from 49.3 to 43.2). OSA improved more in the liraglutide group than in the placebo group. In addition, body weight decreased by an average of 5.7% and 1.6% over 32 weeks in the liraglutide group and placebo group, respectively. These findings indicated that weight loss was also more effective in the liraglutide group than in the placebo group [23].

Surgical management

Bariatric surgery can be considered if no significant weight loss occurs with non-surgical treatment such as diet, exercise, behavioral therapy, or pharmacological management. In Western countries, bariatric surgery is indicated for patients with a BMI of ≥40 kg/m^2 or those with a BMI of 35–40 kg/m^2 with serious comorbidities such as cardiovascular disease, diabetes, and OSA [12,24]. According to the International Federation for the Surgery of Obesity and Metabolic Disorders-Asian Pacific Chapter consensus statement, it is recommended that Asian people consider surgical treatment if the BMI is ≥35 kg/m^2 with type 2 diabetes, or ≥30 kg/m^2 with uncontrolled type 2 diabetes or metabolic syndrome [12,24].

Bariatric surgery is generally classified into three methods: 1) intake restriction surgery, which reduces the volume of the stomach so that people can easily feel full with less food; 2) absorption inhibition surgery, which restricts digestion and absorption; and 3) combined surgery, which involves both of the above methods. Sleeve gastrectomy and adjustable gastric banding are intake restriction procedures, and biliopancreatic diversion and duodenal switch inhibit absorption [12,25]. Roux-en-Y gastric bypass is a representative example of combined surgery [12,25]. General contraindications to bariatric surgery include psychiatric disorders, obesity due to endocrine disorders, and conditions placing patients at high risk for general anesthesia. Bariatric surgery is not recommended for adolescents whose bone growth has not been completed or secondary sexual characteristics have not been expressed [24].

Sleeve gastrectomy is an irreversible surgical procedure that reduces gastric volume by resecting approximately 70%–80% vertically along the great curvature of the stomach, preserving the pyloric sphincter. It has fewer side effects of nutritional deficiency than other intake restriction methods. Weight loss after sleeve gastrectomy has been reported to be 60% at 2 years and 50%–55% at 10 years [11,25]. However, there is a possibility of complications, including leakage along the ablation edge, stenosis, and the development or exacerbation of gastroesophageal reflux disease. Furthermore, the frequency of subsequent weight gain due to gastric volume expansion is relatively high during long-term follow-up [11,25].

Adjustable gastric banding is a reversible surgical technique that reduces gastric volume by placing an inflatable adjustable gastric band on the fundus of the stomach. Although it is less invasive than other types of bariatric surgery, a disadvantage is that long-term complications occur relatively frequently due to foreign substances in the body [25,26]. The most common side effects are nausea, vomiting, obstruction, erosion, decreased esophageal movement, and reflux esophagitis. Due to the relatively high frequency of long-term complications, band removal or corrective surgery is required in 30%–40% of patients within 10 years, and the frequency of this procedure has rapidly decreased in recent years [25,26].

Roux-en-Y gastric bypass is a partially reversible surgical procedure that bypasses the remaining part of the stomach, the duodenum, and part of the jejunum by making a small bag

of about 30 mL in the proximal part of the stomach and connecting it to the jejunum. It both restricts intake and inhibits absorption [25,25]. Although this procedure has a favorable effect on weight loss, at 70% in 2 years and 60% in 10 years, sleeve gastrectomy is performed more often in Korea, where the incidence of gastric cancer is high, because gastric endoscopy is difficult after Roux-en-Y gastric bypass. In addition, there is a risk of dumping syndrome and nutrient deficiency, necessitating regular evaluations and nutrient supplementation [25,26].

Biliopancreatic diversion and duodenal switch are surgical techniques that restrict intake and inhibit absorption by bypassing the jejunum and ileum after sleeve gastrectomy. The weight loss effect is reported to be very good, at 70%–80% in 2 years and 70% in 10 years. However, nutrient supplementation is necessary, as protein and nutrient deficiencies may occur [9,25,26].

According to a meta-analysis conducted by Buchwald et al. [27] in 2004, OSA improved in 85.7% of 1,195 patients after bariatric surgery, such as adjustable gastric banding and Roux-en-Y gastric bypass. According to a 2009 meta-analysis that evaluated the effectiveness of bariatric surgery by Greenburg et al. [28], the AHI significantly decreased from an average of 54.7 to 15.8 events/h in 342 patients. However, the AHI remained above 15 events/h in about 62% of patients. According to a 2021 study conducted on 4,015 OSA patients who underwent bariatric surgery based on data from the National Bariatric Surgery Registry in the UK, 2,482 (61.8%) patients were treated with Roux-en-Y gastric bypass, 1,196 (29.8%) patients received sleeve gastrectomy, and 337 patients (8.4%) underwent adjustable gastric banding [29]. After bariatric surgery, an average weight loss of 44.5 kg was observed, and the highest rate of weight loss was seen in the patients who underwent Roux-en-Y gastric bypass. In addition, OSA improved in 2,377 (59.2%) patients, and the highest improvement rate was 64.5% in the patients who underwent Roux-en-Y gastric bypass, followed by 56.1% in the sleeve gastrectomy group and 31.2% in the adjustable gastric band group [29].

SUMMARY

The treatment of OSA patients with overweight or obesity must involve weight control. For overweight or obese patients with OSA, diet, exercise, or behavioral modifications for weight loss should be performed first. However, if there is no significant weight loss despite these treatments, pharmacological or surgical management can be very helpful for weight loss and the improvement of OSA. Medical and family history, the presence of comorbidities, physical findings, polysomnography results, and patients' opinions should be carefully considered because obese patients with OSA usually experience complications or have serious diseases. Effective personalized therapeutic options for weight loss in overweight or obese patients with OSA should be designed and applied according to the patient's individual circumstances.

Ethics Statement

Ethical approval and informed consents does not apply to this article.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article.

Conflicts of Interest

Ji Ho Choi who is on the editorial board of the *Journal of Rhinology* was not involved in the editorial evaluation or decision to publish this article. The remaining author has declared no conflicts of interest.

Author Contributions

Conceptualization: Ji Ho Choi. **Writing—original draft:** Beomsoo Kim. **Writing—review & editing:** Ji Ho Choi, Beomsoo Kim.

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Funding Statement

This study was supported by the Soonchunhyang University Research Fund.

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