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Review Article

In Search of a New Paradigm for the Treatment of Obstructive Sleep Apnea

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Abstract

Obesity is a civilization disease of the 21st century, which is associated with excessive accumulation of fat tissue due to a positive energy balance. Obesity increases the risk of diseases such as: for hypertension, diabetes, obstructive sleep apnea. The impact of obesity on respiratory disorders is multifactorial. The distribution of body fat in obese people has a greater impact on the respiratory system than body weight or body mass index (BMI). Obstructive sleep apnea is one of the few diseases in which obesity may be both a cause of the disease and its consequence.

Sleep is one of the basic physiological needs and is an important element for the proper functioning of the body. Sleep deprivation significantly affects immune disorders, the development of insulin resistance, obesity and diabetes. This review focused on the analysis of available publications regarding the current treatment of obstructive sleep apnea and the possibilities offered by tirzepatide. According to current medical knowledge, weight loss is associated with a reduction in breathing disorders during sleep. Previous recommendations for the treatment of OSA focused mainly on symptomatic treatment and weight loss. Currently, it seems justified to include drugs that may affect the cause of the problem in the standard of treatment. Current research shows that tirzepatide is one of the GLP-1 and GIP analogues that effectively reduces the mass of fat tissue that accumulates in the neck and chest in the case of obstructive sleep apnea.

Keywords: *Obesity; Obstructive Sleep Apnea; Fat Tissue; BMI; Tirzepatide*

Introduction

The World Health Organization (WHO) defines obesity as excessive accumulation of fat tissue in the body, which may lead to deterioration of health, and overweight as pre-obesity, i.e. the degree of excess fat tissue that does not yet meet the criteria for diagnosing obesity [1]. There are many different interpretations and definitions of obesity, but all of them agree that obesity is a chronic disease.Due to its pathogenesis, obesity can be divided into primary and secondary [2]. Primary obesity is a consequence of positive energy balance and accounts for a significant proportion of obesity cases. Secondary obesity accompanies various disease states, such as hypothyroidism,

obstructive sleep apnea syndrome, Cushing's syndrome, polycystic ovary syndrome, but may also be the result of damage to the central nervous system, as well as the occurrence of chromosomal defects, rare genetic syndromes or chronic use of certain medications, e.g. glucocorticosteroids, some antidepressants, neuroleptics.Data from numerous studies indicate that the consequence of obesity is an increased risk of developing many complications, including: type 2 diabetes, hypertension, coronary heart disease, congestive heart failure, lipid disorders, stroke, gallstones, osteoarthritis, sleep apnea, and some types of cancer [3].

The impact of obesity on disorders of breathing mechanics and the values of lung ventilation parameters is multifactorial. It may be caused by the accumulation of fat in the upper respiratory tract, in the chest and abdominal walls, and by systemic inflammation [4]. The distribution of fat tissue in obese people has a greater impact on the function of the respiratory system than body weight and body mass index (BMI) [5].

Spirometric tests conducted in adults suffering from obesity showed a slight decrease in the values of dynamic parameters - forced expiratory volume in 1 second (FEV1 - forced expiratory volume in 1st second) and forced vital capacity (FVC) - and an unchanged value of the FEV1/FVC index [6]. The risk factor for reduced FEV1/FVC is significantly increased abdominal obesity, regardless of BMI value [7].

The impact of obesity on disorders of breathing mechanics and the values of lung ventilation parameters is multifactorial. It may be caused by the accumulation of fat in the upper respiratory tract, in the chest and abdominal walls, and by systemic inflammation [8]. The distribution of fat tissue in obese people has a greater impact on the function of the respiratory system than body weight and body mass index (BMI) [9].

Spirometric tests conducted in adults suffering from obesity showed a slight decrease in the values of dynamic parameters - forced expiratory volume in 1 second (FEV1 - forced expiratory volume in 1st second) and forced vital capacity (FVC) - and an unchanged value of the FEV1/FVC index [10]. The risk factor for reduced FEV1/FVC is significantly increased abdominal obesity, regardless of BMI value [11].

Excessive deposition of fatty tissue in the chest and abdomen reduces chest mobility, causes atelectasis of the basal lung areas and increases peripheral airway resistance [12]. As the consequence of the ventilation of the lower parts of the lungs deteriorates, unlike the upper parts, which show normal or increased ventilation.

Snoring is defined as a hoarse and vibrating sound that occurs during sleep. Snoring sounds are produced by vibrations of the throat tissues due to the narrowing of the upper respiratory tract [13]. The accumulation of fatty tissue in the throat area may change the acoustic properties of breathing sounds, including the sounds of snoring. The incidence of snoring varies and ranges from 2 - 85% [14]. Anatomical risk factors for snoring associated with obesity include deposition of fatty tissue around the throat, tongue, and soft tissues of the nasopharynx [15]. Functional disorders in the group of obese patients include impaired neuromuscular reflexes of the upper respiratory tract. Habitual snoring may be an isolated symptom or occur during course of obstructive sleep apnea, the syndrome of increased resistance of the upper respiratory tract and the hypoventilation syndrome of obese people.

A positive correlation was found between more severe snoring and greater obesity expressed as neck, waist and hip circumference and the ratio of waist circumference to hip circumference [16].

Sleep is a natural process that is regulated by the circadian rhythm, nervous and hormonal systems, which is important for proper functioning and well-being [17]. Sleep deficiency can result in numerous consequences such as cognitive impairment [18], increased risk of road accidents [19], impaired immune function, reduced performance, and increased risk of disease [20]. Several years ago, research was conducted that changing lifestyles resulted in more frequent complaints about sleep problems [21]. Currently, it is believed that

insufficient sleep is a modifiable factor that has an adverse impact on the health of people around the world [22]. The relationship between the quality and duration of sleep and possible side effects appears to be complex. Sleep disorders often accompany chronic diseases [23], but they can also lead to the development of chronic diseases by negatively affecting the hormonal, metabolic and immune systems [24].

Obstructive sleep apnea is one of the few diseases in which obesity is both the cause of the problem and a complication of untreated disease. Sleep apnoea is characterised by a temporary interruption of breathing during the sleep. There are three types of sleep apnoea:

- Central sleep apnoea, which is caused by neurological problem that affects the airway and chest muscle that control breathing;
- Obstructive sleep apnoea (OSA) is the most common type of sleep apnoea. It happens when the upper airway becomes blocked many times while sleeping, reducing or completely stopping airflow [25].
- Mixed apnoea - integration of central and obstructive apnoeas.

Obstructive sleep apnea is very common, but the results of population studies indicate that it very often remains undiagnosed. This is due to low awareness of the disease in society. Care for a patient with obstructive sleep apnea varies depending on the patient's symptoms and the country. Most data indicate that significant efforts are made in well-equipped facilities to diagnose and treat people suffering from this disease, but the available data suggest that many such cases remain undiagnosed and untreated, even in developed countries. Due to its multifactorial nature, this disorder is associated with enormous economic and social costs. In 2015 the cost of diagnosing and treating OSA in the United States was USD 12.4 billion $ [26]. Based on data collected by Benjafield., *et al*. regarding the incidence of OSA among adults aged 30-69, it is estimated that the problem affects approximately 1 billion people, with approximately 425 million suffering from moderate to severe disorders for which treatment is recommended [27,28].

The basic mechanism leading to OSA is an excessive decrease in the tone of the muscles responsible for maintaining the patency of the upper respiratory tract, which leads to repeated episodes of apnea (a drop in air flow by ≥ 90% of pre-event baseline for ≥ 10 sec) or hypopnea (a drop in air flow by ≥ 30% of pre-event baseline for ≥ 10 sec and a ≥ 3% oxygen desaturation from baseline or the event is associated with an arousal), caused by a complete blockage or significant limitation of air flow [29]. These events lead to repeated episodes of hypoxia, hypercapnia, increased intrathoracic pressure fluctuations and increased activity of the sympathetic nervous system. Obstructive sleep apnea is an interdisciplinary problem, as many studies have proven the relationship between OSA and other diseases.

The phenomenon of throat constriction and closure during sleep is complex and many factors probably play an important role in the pathogenesis. Reduced ventilatory and neuromuscular activity is observed during sleep, which, combined with anatomical risk factors, plays a significant role in upper respiratory tract obstruction during sleep [30]. The cause of narrowing of the upper respiratory tract is the deposition of fat in this place [31,32] (Figure 1).

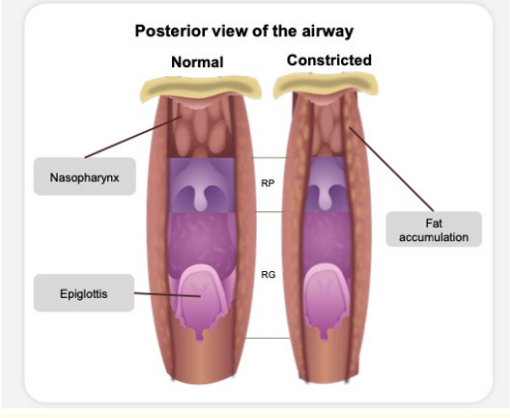

Figure 1

The most frequently mentioned causes of OSA are: deviation of the nasal septum [33], hypertrophy of the tongue [34], elongated soft palate, long uvula, facial anatomical abnormalities and significant atony of the throat muscles. From an epidemiological perspective, obesity is considered the most important risk factor for OSA [35].

Obesity and OSA independently increase the likelihood of common complications: hypertension, coronary heart disease, cardiac arrhythmias, heart failure, and metabolic disorders. Epidemiological studies show that 70% of people diagnosed with OSA are obese.

The most important anthropometric feature of obesity that increases the risk of OSA is neck circumference and corrected neck circumference [36]. This index is calculated by adding 4 cm to the measured neck circumference if the patient suffers from hypertension; an additional 3 cm if he snores habitually and another 3 cm if he reports a feeling of suffocation and choking at night. The corrected neck circumference is an indicator of the risk of OSA when it is 48 cm in men and 46 cm in women. This mechanism involves the deposition of fatty tissue in the neck, which then narrows the throat, making it more susceptible to collapse. Other risk factors include: changes in the structure of the upper respiratory tract causing disruption of their patency, retrognathia, alcohol consumption before bedtime, use of hypnotic or myorelaxant drugs, nicotinism, postmenopausal state in women, family history of sleep apnoea, race/ethnicity [37]. In addition, excessive amounts of fatty tissue surrounding the chest and abdominal cavity may lead to a reduction in the amplitude of respiratory movements, consequently reducing the vital capacity of the lungs and ventilation. As a result, hypoxemia and hypercapnia occur during apneas and hypoventilation [38].

The research shows that OSA has a significant impact on the increase in insulin resistance [39]. Sleep deficiency and sleep deprivation have been recognized as risk factors for decreased insulin sensitivity over 15 years ago [40]. Weight gain, insulin resistance and a greater risk of type 2 diabetes are associated with sleep disorders, and in particular with obstruation, which is an independent factor in the development of insulin resistance.

OSA symptoms can be divided into night and day symptoms. Nighttime symptoms include snoring, noticed episodes of apnea, nocturnal gastroesophageal reflux, waking up with a feeling of suffocation or shortness of breath, nocturia [41], excessive sweating (mainly in the upper half of the body), interrupted sleep, and trouble falling asleep due to anxiety. However, those occurring during the day include: excessive daytime sleepiness (assessed most often using the Epworth Sleepiness Scale [ESS]), fatigue, dry mouth after waking up, morning headaches [42], concentration and memory problems, irritability, libido disorders, impotence [43]. However, the majority of patients are asymptomatic. Many patients report only fatigue during the day, which may be a rather non-specific symptom. Therefore, it is important to objectively distinguish between drowsiness and fatigue. For this purpose, the Epworth Sleepiness Scale (ESS [44]) can be used. You can get a maximum of 24 points, but above 9 points you can suspect excessive sleepiness and focus on additional diagnostics of the patient for OSA. The gold standard for diagnosing OSA remains polysomnography (PSG) under supervised conditions in a sleep laboratory.

The PSG test result is presented as the number of respiratory events per hour (h, hour). Sometimes the test result is expressed as the apnea hypopnea index (AHI) [25] or the respiratory effort-related arousals index (RDI = AHI + RERA [respiratory effort related arousals]).

The diagnosis can be made based on the PSG result if the RDI is above 15/h or above 5/h with at least one of the following symptoms: falling asleep during activity against one's will, fatigue, insomnia, waking up with a feeling of shortness of breath, choking choking, episodes of pauses in breathing, and loud snoring noticed by the environment [45]. Depending on the result, there are three degrees of severity of OSA. AHI defines the number of apnoas or hypoapnoeas per hour of sleep (Table 1). Obstructive sleep apnea is a very common condition with very adverse consequences; affects nearly 1 billion [41] people worldwide, with as many as 425 million adults aged 30 - 69 suffering from moderate or severe OSA. According to available data, among the population of people with OSA in the United States, as many as 33.2% suffer from mild OSA, while 14.5% - moderate or severe OSA. The incidence is increasing mainly in Asian countries, as well as in Black populations [46].

Mild OSA	≥5 AHI to <15 AHI per h
Moderate OSA	≥15 AHI to <30 AHI per h
Severe OSA	≥30 AHI per h

Table 1

In both developed and developing countries, awareness of the occurrence of OSA is usually low, and additionally limited diagnostic and treatment options result in a lack of widespread knowledge dissemination [47].

Due to the numerous connections between OSA and other diseases, this problem should be treated interdisciplinary, and therefore this disorder is associated with a high social and economic burden.

Available publications describe a clear relationship between the occurrence of OSA and an increased risk of diseases and deaths due to cardiovascular diseases.

The relationship between OSA and hypertension has been noted in the available literature for many years. A large prospective study in a group of 1,889 patients diagnosed with OSA, initially without AH, was carried out in Spain in 1994-2000 [48]. It has been proven that patients with OSA developed AH much more often than healthy people. Additionally, in recent years, OSA has been recognized as the most common cause of resistant hypertension and one of the main causes of secondary hypertension [49].

According to various sources, the incidence of OSA in patients with resistant hypertension may range between 73 - 82%. The situation is similar in people with atrial fibrillation (76 - 85%). In the group of people who experienced a stroke, as many as 71% of them had a problem with OSA [27].

Moreover, there are many studies proving the relationship between OSA and glucose metabolism disorders. The incidence of OSA among patients with type 2 diabetes reaches 65 - 85% [27], while in patients with obesity it is 71 - 95% [27].

Patient education is the basis for the treatment of any disease. In the case of OSA, it should include a discussion of the pathophysiology, risk factors, clinical consequences of OSA, and therapeutic modalities. The patient should be informed about the beneficial effects of weight loss and the need to avoid modifiable risk factors [50]. Additionally, new research shows that educational activities - both behavioral and patient support - are associated with better compliance [51].

Due to the fact that OSA is a disease affecting various aspects of human life, the treatment itself should be multidirectional, but also focus on treating the cause, and not only the symptoms of the disease. Even mild OBS is significantly associated with an increased risk of hypertension, cardiovascular disease [52], as well as greater mortality [53] in population-based prospective studies.

The focus has been mainly on symptomatic treatment. The treatment algorithm depends on the stage of the disease. In the case of mild OSA, the use of intraoral appliances and behavioral treatment is recommended. For patients with moderate OSA, intraoral appliances and positive pressure therapy (CPAP) are recommended as the treatment of choice. Patients with severe OSA are treated with CPAP or BiPAP machines. In all patients, regardless of the stage of the disease, it is recommended to take preventive measures related to weight loss (a 10% reduction in body weight translates into a 10% reduction in AHI). Until now, the basic method of treatment was to use a continuous positive airway pressure (CPAP [27,54]).

Currently more and more attention is paid to causal treatment. Obesity is a major risk factor for OSA occurrence. The mechanismus of obesity-related-OSA are not completely understood but may be related to increased tongue fat [55]. Another important element of treatment is weight loss in overweight or obesity. Special attention should be paid to the importance of weight loss [56] in the context of patients with OSA and in improving their prognosis and reducing the severity of obstructive sleep apnea. Until now, patients have decided on bariatric surgery, but the risk and cost of surgical intervention may be too burdensome for some patients. Loss of body weight in patients with OSA can bring many benefits in various aspects, both regarding the patient and economic and social.

A study conducted by Peppered., *et al*. proved that 10% weight gain predicted ca. 32% increase in AHI and a 6-fold increase in the risk for developing moderate-to-severe sleep-disordered breathing [57]. Johannson., *et al*. in their study showed that weight reduction from a low-energy diet improved OSA in men with obesity in a 9-week study.

According to research conducted several years ago, a great attention was paid to a significant impact of weight reduction as an important factor improving the quality of life in people with obstructive sleep apnea.

The etiology of obesity is the result of many factors, including genetic, psychological, metabolic and environmental factors, including nutritional ones [58]. Obesity, despite the wide variety of causes and complex pathogenesis, is always a manifestation of positive energy balance. In the Framingham study [59], the inheritance of visceral fat was estimated at 36% and that of subcutaneous fat at 57%. The gene pool has not changed that much over the last 100 years. Therefore, gene expression depends on environmental factors, i.e. a constantly maintained positive caloric balance and/or a sedentary lifestyle. In addition to changing the lifestyle, increasing physical activity, there is currently the possibility of pharmacological treatment of obesity.

An important cause of metabolic disorders leading to the development of obesity or difficulties in reducing body weight, according to some authors, may be disorders in the release of enterohormones under the influence of food, its absorption and utilization. Hormones produced in the intestines play a key role in regulating eating behavior, energy and glucose homeostasis [60]. The human body, through gastrointestinal hormones and the intestinal-pancreatic axis, regulates the secretion of metabolic hormones: insulin, C-peptide and glucagon [61]. In 1932 Belgian [62] physiologist Jean La Barre was the first to use the word incretin to describe an intestinal hormonal factor whose action is to stimulate or contribute to the stimulation of the secretion of pancreatic hormones.

Orally administered glucose causes less fluctuation in glucose concentration than that administered intravenously, but a lower glucose value causes a greater increase in insulin levels. This difference was referred to as the incretin effect. This process suggests that it is caused by the secretion of intestinal peptides triggered by nutrients, which then act on the pancreas to stimulate insulin secretion. In 1987 the first incretin [63] was discovered - glucagon-like peptide 1 (GLP-1), produced in L cells of the intestine, which has its GLP-1R receptors, among others, in the pancreas. Additionally, GLP-1 is also produced in the brain, and its receptors are located in key areas related to food intake and glucose control. Another gastrointestinal hormone is glucose-dependent insulinotropic polypeptide (GIP). GIP receptors are found in pancreatic islet cells, the hypothalamus and adipose tissue. GIP inhibits gastric secretion activity, stimulates insulin secretion, and has insulin-like action on adipose tissue inhibiting lipolysis and promoting lipogenesis [64].

The GLP-1 analogues have been the rescued preparations so far.

Blackmann., *et al*. [65] as one of the first, they published a study on the benefits of liraglutide in patients with OBS. In both liraglutide and placebo groups, greater weight reduction was associated with greater reduction in AHI.

In patients with overweight or obesity suffering from OSA, body weight reduction is beneficial for many reasons. First of all, the loss of excessive body weight affects the reduction of fat surrounding the upper respiratory tract (in particular tongue). In addition, the reduction

of excessive body weight improves the cardiometabolic profile, i.e. reduction of blood pressure, tissue sensitivity to insulin increases. Moreover, patients report less fatigue, drowsiness, the quality of life and general well-being increases.

In this review manuscripts, we analyze research findings on tirzepatide and discuss its future guideline use as a treatment for obstructive sleep apnea.

So far, analogues of glucagon-like peptide 1 (GLP-1 analogue) were used in the treatment of diabetes mellitus and obesity, but over time tirzepatide was developed. It is a new molecule that is able to control blood sugar levels by combining double agonism of glucose-dependent insulinotropic polypeptide (GIP) and the already mentioned GLP-1 receptors. These are incretin hormones released in the intestines in response to food intake.

Currently, SURMONT-OSA [66] is in the third phase of the study, which is conducting research on the treatment of patients with OSA and obesity with tirzepatide. The subject of the study is to assess the severity of OSA (assessment according to AHI) and improvement after treatment. The main factors qualifying patients for the study were obesity (BMI ≥ 30 kg/mc), moderate to severe OSA (AHI ≥ 15 events/h in polysomnography), age ≥ 18 years and at least 1 attempt at weight loss. This study aims to demonstrate the effectiveness of tirzepatide at the maximum tolerated dose over 52 weeks of treatment compared to placebo in patients with obesity and OSA (moderate to severe). Analysis of secondary outcomes of SURMOUNT-OSA1 analysis suggested use of tirzepatide was associated with greater reductions in mean AHI (55.0% vs 5.0%) and mean body weight (18.1% vs 1.3%) than placebo therapy from baseline to 52 weeks.

Secondary outcomes of SURMOUNT-OSA2 analysis suggested use of tirzepatide was associated with greater reductions in mean AHI (62.8% vs 6.4%) and mean body weight (20.3% vs 2.3%) than placebo therapy from baseline to 52 weeks [64].

According to the study results, it can be concluded that losing body weight reduces the volume of fat in the tongue and, consequently, reduces AHI in patients with OSA [67].

Previous treatments for OSA have been significantly limited and have been based on relieving symptoms rather than treating the cause of the disease. And although in many patients CPAP treatment allows to reduce the severity of the symptoms of the disease, many patients are still unable to accept this form of treatment. Moreover, there is no data in the available literature that could confirm a beneficial effect on cardiovascular events [68,69].

Conclusion

It seems reasonable to include detailed guidelines based on pharmacotherapy using GLP-1 and GIP analogues in the standards and guidelines for the treatment of OSA, in addition to recommendations for weight loss. As already mentioned, OSA is caused by excessive accumulation of fat tissue in the neck area. With preparations that act directly on adipose tissue at our disposal, it can be assumed that during the treatment there will also be a reduction of adipose tissue, and it will also be a direct causal treatment of the disease. Moreover, by treating OSA and obesity, we reduce the risk of numerous complications associated with the disease.

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