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LITERATURE REVIEW

Weight loss therapy for obstructive sleep apnea – Literature review

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ABSTRACT

Obstructive sleep apnea is a chronic disease characterized by the appearance of apnea or hypopnea episodes during sleep. This condition is associated with several risk factors. Among them, the most important is obesity and it is the only potentially curable. The treatment is polimodal and it involves several therapeutic directions. The purpose of this paper is to establish the role of obesity in the etiology of sleep apnea, as well as the role of the weight loss in its management, both through intensive lifestyle interventions and surgical therapy.

KEYWORDS: apnea, sleep, obesity, bariatric, dietary.

INTRODUCTION

Obstructive sleep apnea (OSA) represents a medical condition that refers to episodes of important decrease or interruption (hypopnea or apnea) of the respiratory airflow during sleep[1].

The severity of the disease may be quantified using the apnea-hypopnea index (AHI), represented by the mean number of periods of apnea and/or hypopnea per hour of sleep. Obstructive sleep apnea is classically defined by the AHI greater than 5 episodes/hour of sleep and obstructive sleep apnea syndrome is defined by AHI greater than 5 episodes/hour of sleep, along with daytime sleepiness, according to the American Association of Sleep Medicine[2].

This medical condition appears twice more frequently in men than in women, as well as snoring. The prevalence of obstructive sleep apnea is permanently increasing in the last years, with an incidence of approximately 50% in the male population and 37% in the female population[3,4].

Obesity is considered one of the most important risk factors associated with OSA and weight loss one of the most important therapeutic strategies. This literature review tries to demonstrate the role of obesity in OSA syndrome, as well as the underlying mechanisms involved in this association.

OSA'S RISK FACTORS

The appearance and the severity of obstructive sleep apnea are related to the coexistence of multiple risk factors[5]. People with OSA are at greater risk of stroke[6], cardiac diseases (coronary artery disease, heart failure, arrhythmias)[7], hypertension[8], psychosocial morbidity, type II diabetes[9]. The obstructive sleep apnea has effects upon the quality of life of the patients involved[10], determining cognitive malfunctioning and affecting work performance[11]. Obesity has an important role in the development of obstructive sleep apnea and it has the main characteristic of being reversible[12,13].

Coexistence of obesity and obstructive sleep apnea is well known and it involves inflammatory processes, insulin resistance, dyslipidemias and hypertension, but the underlying mec hanisms remain to be established.

According to Ayyad et al., OSA estimated prevalence in obese patients is 42-48% in men and 8-38% in women[14]. Approximately 60-70% of the patients with OSA are obese[11]. OSA can also be found in normal-weight persons, especially in women. In their study, Franklin et al. showed that 39% of normal weight women had OSA, but with low odds of having severe forms of apnea (0.1%)[15].

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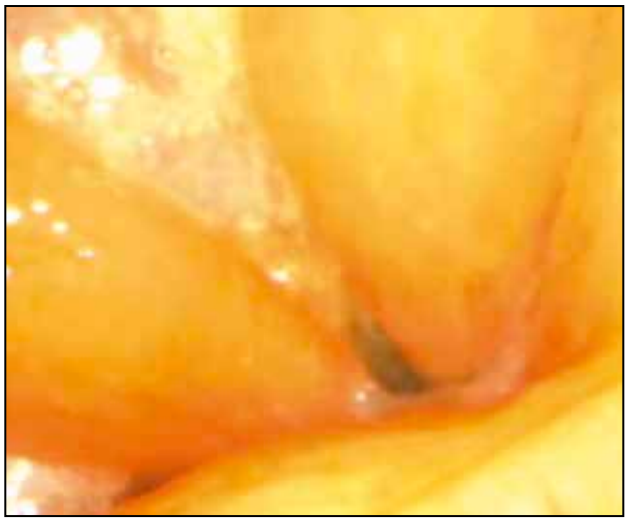

Figure 1 Hypopharynx: (a) Open airway. (b) Concentric obstruction.

In 98% of the patients with morbid obesity (BMI ≥ 40 kg/m^2), OSA was reported and the BMI was proportional to the prevalence of obstructive sleep apnea[16].

A study conducted in 2015 by the National Sleep Foundation Sleep in America reported that almost 60% of the obese persons are at risk of developing OSA, according to Berlin Questionnaire[17].

In his study on the population-based Wisconsin Sleep Cohort Study, Young *et al.* showed that obesity has an impact on 41% of the patients with mild sleep apnea (AHI≥ 5) and on 58% of patients with moderate to severe forms of OSA (BMI ≥25 kg/m^2)[11]. These findings highlight the necessity of implementing long-term programs in order to prevent the appearance of OSA and other metabolic effects of obesity.

The severity of OSA in overweight or obese patient is correlated with the distribution of adipose tissue. Fat accumulation in the central part, android type (apple shaped) and in the upper body is linked to the metabolic syndrome, atherosclerosis and OSA. From the weight measurements, waist circumference is more important than body mass index (BMI), weight and total fat quantity. An increased waist circumference may predict the appearance of OSA even in non-obese patients[18].

The mechanisms of obesity determining OSA are being constantly investigated and there are several hypothesis involved[19].

Obesity determines anatomic modifications inducing upper airway narrowing, collapse and reduction of the airflow during sleep (Figure 1)[20] . Obese individuals have extrinsic narrowing of the peri-pharyngeal area[21]. The collapsibility of the upper airway is more important in obese persons, compared to non-obese individuals[22], and does not seem to decrease significantly when the oropharynx is enlarged by mandibular advancement[23]. The upper airways collapse determines hypoxia and hypercapnia, frequent arousals and increase in the respiratory effort, with subsequent sympathetic system activation and systemic inflammation.

The mechanical effect of obesity consists in increased peri-pharyngeal fat tissue, with effects on maintaining the airway patency by the dilator muscles, with increase in collapsibility during sleep[21]. Also, the central adiposity may decrease the neuromuscular activity of the upper airways[20].

Obesity and central adiposity, in particular, determine decreased lung volumes and increased pharyngeal collapsibility, due to the negative intrapulmonary pressure. Secondary, patients need higher levels of air pressure from CPAP[20].

The distribution and the metabolic activity of fatty tissue are coordinated by various molecular signalling pathways, which are responsible for neural control of the upper airway collapsibility. Adipose tissue has the capacity of secreting pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-∝, IL-6, profibrogenic adipokine leptin, with an inhibiting action on the neuromuscular control of the upper airways[23,24].

Leptin plays the role of an appetite suppressant, which is associated with satiety sensation, weight intake and distribution of the adipose tissue, in central obesity. Sleep deprivation is associated with low levels of leptin, which stimulates the hunger mechanisms[25].

Leptin has an effect upon the hypothalamus, to decrease food intake and to increase the metabolic rate[26]. Obesity determines a state of metabolic resistance to leptin effects. Intermittent hypoxia stimulates leptin expression and its release from the adipose tissue. Its effect may be inhibited by other inflammatory factors, such as leptin receptor and C-reactive protein[25], which have the ability of binding circulating leptin and decreasing its central nervous system action[26]. The levels of leptin receptor and C-reactive protein are high in obstructive sleep apnea, compared to normal individuals[27] and their levels decrease by weight loss.

Ghrelin has the role of stimulating the appetite and is proven to have elevated serum concentrations in patients with obstructive sleep apnea. Treatment of OSA, especially weight loss, is able to reduce ghrelin levels, leading to decreased appetite[28].

TREATMENT

The role of obstructive sleep apnea therapy is to improve the clinical symptoms – the quality of sleep, in terms of apnea-hypopnea index and oxyhemoglobin saturation levels, and to decrease the potential associated morbidity. Patients should be aware that OSA

is a chronic disease, which requires long-term therapeutic approach.

The therapeutic main directions are postulated by several guidelines, including the American Academy of Sleep Medicine, the American Thoracic Society (ATS), the American College of Physicians and the International Geriatric Sleep Medicine Force[29].

The therapeutic management includes medical, behavioural and surgical methods for the treatment of obstructive sleep apnea. Adjunctive methods are recommended either to supplement the main direction, either in case of therapeutic failure, depending on the sleep apnea severity and the patients' anatomy, medical history and personal preferences[1].

Patients should be assessed before and after the initialisation of the treatment, in terms of subjective outcomes (resolution of daytime sleepiness - Epworth Sleepiness Scale; quality of life specific measures, patients and family satisfaction) and objective measures (evolution of AHI, multiple sleep latency and test for maintenance of wakefulness).

The common mainstay of all the guidelines is that all patients should be offered continuous positive air pressure at the time of the diagnosis, because this therapy remains the gold standard due to its effects on improving the quality of life, daytime sleepiness and cognitive functioning, in all forms of OSA.

In case of the patients with mild/moderate forms OSA, who refuse CPAP therapy or its therapeutic effect is not optimistic, oral appliances should represent an alternative therapy, because they improve the quality of sleep and they have better tolerance in some of the patients[17]. Surgical techniques for upper airways permeabilisation, maxillofacial approaches for jaw advancement and bariatric surgery are recommended in selected patients.

Behavioural strategies options include weight loss, for a BMI less than 25 kg/m^2, exercise, positional therapies and avoidance of alcohol intake before sleep. However, in case of severely obese patients, none of these options treats the accompanying obesity. The weight excess is the only factor that may be reverted, in order to cure or to decrease the severity of OSA. Other factors related to OSA that may be modified include smoking, alcohol intake and nasal obstruction[11].

Weight loss. Between obesity and obstructive sleep apnea there are complex and bidirectional relationships. Randomized clinical studies reported that even small reductions of weight determine positive effects on sleep apnea outcomes (10-15% weight decrease determines 50% reduction in sleep apnea severity in moderately-obese male patients). A moderate 5% weight loss is able to prevent OSA from worsening and is able to control the sleep apnea symptoms in the long term[30].

Weight decrease determines reduction in the insulin resistance and the levels of serum triglyceride, when it is combined with CPAP, as well as a reduction of blood pressure.

Clinical studies upon patients with sleep apnea reported a decrease in the upper airways collapsibility during sleep, associated with weight loss, which may be determined by reduction of the mechanical loads and pharyngeal neuromuscular improvement. Humoral factors, such as leptin, adiponectin and ghrelin, may modulate the weight changes. The increase in ghrelin levels is proportional to weight loss, while leptin and adiponectin modulate the weight loss from the subcutaneous or visceral adipose tissue.

The American Academy of Sleep Medicine establishes the main recommendations for the weight loss, through a lifestyle modification (dietary and exercise), as well as surgical options, for decreasing the severity of obese OSA patients[1]. After substantial weight loss (≥10% of total body weight), patients should be reassessed using a polysomnography, to re-establish the need or the adjustments of CPAP therapy[29].

Diet. Dietary weight loss should be proposed in case of all overweight or obese patients[31]. According to the clinical studies performed in the past years, dietary-driven weight loss may improve obstructive sleep apnea, due to its effect of reducing the collapsibility of the upper airways, by modifying the anatomy and the functions[32].

Weight loss determines also an increase in the vital lung capacity, total lung volume, functional residual capacity and in the forced expiratory volume[33,34]; this increase in lung volumes and function may increase tracheal traction upon the pharynx. In case of persistence of sleep apnea or lack of symptomatic reduction, patients should be investigated for other concomitant ENT pathologies.

The dietary effect on obstructive sleep apnea is related to a significantly decreased nocturnal oxygen desaturation index after weight loss.

As expected, patients who benefit most of dietary weight loss usually have severe forms of sleep apnea (AHI>30) and higher weight (BMI) – in these patients, the first step is losing visceral fat, instead of subcutaneous adipose tissue, with metabolic improvement. Even minimal weight loss can be beneficial, because of the preferential loss of visceral fat first instead of subcutaneous fat, which has metabolic advantages[32,35].

There are several diets recommended for weight loss in sleep apnea. Caloric restriction diets which request a smaller amount of intake calories, compared to expenditure, tend to be over-rated, due to the compensatory mechanisms which trigger hunger with subsequent increased food attempt, in order to restore the adipose tissue, to a homeostatic point[36].

Instead of this diet, there were proposed a series of

dietary factors for decreasing the anabolism, like low intake of refined sugar, increased amounts of mono-unsaturated fatty acids with decreased amounts of trans-fatty acid intake, elevated omega-3 aliments with adequate protein quantities.

Low-carbohydrate diets have multiple forms, according to the carbohydrate intake and they may vary from moderate (26–45%) to very low-carbohydrate intake (20–50 g/day or <10% from a 2000 kcal/day diet). Low-carbohydrate diet is more efficient than low-calorie intake diet, in moderately obese patients, who presented a significantly loss in the abdominal circumference and a decrease of total body weight[37].

The "Mediterranean diet" consists in consuming elements (50% carbohydrates) found in the Mediterranean region, in olive-growing areas, and is equally effective to a low-carbohydrate diet (40% carbohydrate) in moderately obese patients[38].

Pharmacological methods for weight loss. Sibutramine is considered a serotonin and noradrenaline inhibitor, which stimulates weight loss by inducing satiety and thermogenesis, with consecutive increased expenditure of the energy[39]. The results of sibutramine administration in OSA are still uncertain. In a randomised study conducted on overweight patients with OSA, sibutramine has proven no efficacy in decreasing AHI or body weight, while its positive effects on weight loss, AHI decrease, insulin sensitivity and lipid profile were observed in obese patients[40].

In January 2010, Sibutramine was redrawn from the market by the Medicines and Healthcare products Regulatory Agency, due to possible cardiovascular risks (non-lethal myocardial infarction and stroke), greater than the benefits[41].

Orlistat is a drug used to treat obesity, by inhibiting gastrointestinal lipase, with reduced fat absorption and caloric intake and represents another therapeutic option for the management of weight loss[42]. The official recommendations from the producers are that the drug should be accompanied by a low-calorie diet, for proper results.

Exercise. Among the methods of losing weight, exercise seems to be the most cost-efficient and easy-to-use treatment option, with important effects on OSA severity and its consequences (cardiovascular disorders, glucose intolerance, fatigue). Even though, initially, the benefits of exercise were attributed to weight loss, there are other mechanisms through which it realizes the positive outcomes[43,44].

At the time of exercising, respiratory muscles, along with the diaphragm, present an increased metabolic rate and respiratory recruitment, which improve fatigue resistance and increase the upper airways diameter, with a consecutive reduction in the airways resistance, and opposed pharyngeal collapse in sleep[43].

In individuals with a sedentary lifestyle, it is frequent to have inferior limbs fluid retention, which, during sleep, changes position and accumulates in the neck, with an increased laryngeal compression. Through this mechanism, the severity of OSA may be accentuated, in terms of excessive daytime sleepiness. This effect is more evident in patients that have hypervolemia (renal or heart failure, hypertension)[45].

Increased slow-wave sleep - during exercise, body temperature increases and facilitates sleep onset, by activation of heat-dissipating mechanisms and sleep-inducing processes by the hypothalamus.

Studies have shown that regular exercising proves an anti-inflammatory effect, by inhibiting C-reactive protein, TNF and IL-6, especially in obese patients, usually associated with sleepiness, fatigue, cardiovascular and metabolic complications[44].

Obesity may appear as a consequence of obstructive sleep apnea, due to sleep deprivation, which induces reduced physical activity, exercise performance and energy metabolism.

The results of several studies show that physically active individuals have lower risk of OSA, compared to sedentary persons. A 10-year follow-up from the Wisconsin Sleep Cohort study reported a reduced incidence of mild and moderate OSA in active persons, while a decrease in exercise duration was associated with worsening symptoms of OSA. Experimental studies also indicate significantly improvements in the severity of sleep apnea, only with exercise[46].

The symptomatic improvement in OSA, after dietary weight loss, could be temporary, because the condition tends to relapse, whether the patient has regained weight or not[47,48].

The results of a meta-analysis indicate that dietary approach and exercise have the same effect on weight loss – when comparing a 15-week diet, diet and exercise and exercise alone, it was proven that adding exercise to diet could provide extra 20% weight loss[46].

Surgery. Bariatric surgery represents a therapeutic alternative method for achieving major weight loss in a short time. It is indicated in adults with a body mass index higher than 40 kg/m^2, and in those with a BMI between 35 and 39.9 kg/m^2, in association with severe comorbidities, in whom dietary approach was ineffective (according to the National Institute for Health and Clinical Excellence Guidelines)[49]. Patients proposed for bariatric surgery should have undergone all other means of weight loss in the last 6 months, without effect. Before surgery, patients are managed by a specialist in obesity, evaluated for comorbidities that may interfere with the surgery and anaesthesia[50]. Bariatric surgery is recommended in adjunction to CPAP therapy of OSA in obese patients.

In the current practice, there are multiple surgical procedures that may be performed for the manage-

ment of OSA, such as laparoscopic adjustable gastric band (LAGB) or Roux-en-Y gastric bypass (RYGB), laparoscopically performed sleeve gastrectomy (LSG) and laparoscopic bilio-pancreatic diversion. Among these techniques, the LAGB and RYGB are most commonly used[49].

The laparoscopic adjustable gastric banding procedure involves the placement of a band around the proximal region of the stomach, which forms a pouch, with a narrow outlet distal to the gastro-esophageal junction. The restriction degree may be modified by inflating or deflating the balloon inside the band, with saline solution through a subcutaneous port[49]. During the Roux-en-Y gastric bypass technique, the proximal part of the stomach is being excised, determining a small gastric pouch, which is joined to the roux limb of the jejunum, with results that the more distal stomach, the complete duodenum and proximal jejunum are bypassed[50].

The main directions of bariatric surgery effects on weight loss can be stated as the BRAVE effects:

- **B**ile flow alteration,
- **R**estriction of the gastric size,
- **A**natomical rearrangement of the gut and an altered flow of nutrients,
- **V**agal manipulation,
- **E**nteric gut hormone modulation[49].

These surgical procedures involve gastric resection or intestinal bypass, in order to induce a state of early satiety and a nutrient malabsorption, which determine almost 60% weight loss in the first 12-18 months postoperatively.

In a meta-analysis of bariatric studies on 22,094 patients, Buchwald et al. reported an important improvement in the majority of the patients, with AHI reduction of 33.9 and resolution of obstructive sleep apnea in almost 90% of the patients[51].

In the literature, there are few studies to compare the efficacy of dietary-induced weight loss and bariatric surgery. Recent clinical trials evaluated the superiority of gastric banding surgery on behavioural weight loss in OSA, but surgical weight loss is as effective as dietary-induced weight loss. Performing more aggressive surgeries, like gastric bypass and laparoscopic sleeve gastrectomy, is more effective at losing weight than gastric banding, and more effective in treating OSA[52-55].

A study conducted by Hutan Ashraf et al. indicated that RYGB was more effective than intensive lifestyle intervention in reducing the prevalence and the severity of obstructive sleep apnea in morbidly obese patients[56].

A meta-analysis of 12 surgical studies realized on 342 patients with OSA reported that bariatric surgery does not cure OSA and some patients will keep using CPAP therapy[57].

After bariatric procedures, positive outcomes were reported also regarding the sanguine gases – reduced oxygen desaturation and increase in minimum oxygen index. Daytime sleepiness, snoring, with hypoxemia and hypercapnia, were also improved[58]. Researchers reported an improvement in sleep efficiency and architecture, both subjectively and objectively, with a decrease in the CPAP therapy pressures[58].

Time-related effect two years postoperatively is approximately 40%, raising the need for the necessity of on-going therapy and follow-up. Although the reports results are encouraging, surgical weight loss involves risks and it does not seem to be investigated in terms of long-term effects[59].

Bariatric surgery is not a cure for the obstructive sleep apnea and the patients will continue treatment, in order to minimize the complications of the disease, because, even postoperatively, most of the patients present a residual AHI usually greater than 15 events/hour[49].

CONCLUSIONS

Obstructive sleep apnea is a medical condition, with great impact upon morbidity and mortality. Obstructive sleep apnea and obesity are interrelated and the severity of OSA increases with total body weight, especially in abdominal deposition. Obesity produces increased adipose tissue, narrowing the upper airway, and abdominal fat tissue, decreasing tracheal tension, with a final effect of upper airway collapsibility.

The therapeutic approach is complex and consists of different methods, related to the patients' comorbidities. Weight loss is a viable option in overweight and obese people, taking into consideration the bidirectional interrelationships between OSA severity and obesity.

Weight loss, using diet and exercise, should be proposed in all patients, but bariatric surgery should be reserved for the failure of medical and dietary methods, in obese patients, taking into consideration its potential risks. According to the studies, the greatest weight loss is obtained after bariatric surgeries, but their effects on BMI and AHI reduction are similar, with a difference on the onset.

Either approach should be maintained in the long term, in order to prevent relapses or disease worsening and all patients should be informed about the natural evolution of this condition and the risks it may involve. Patients whose obstructive sleep apnea is improved or resolved after weight loss should be warned not to regain weight, because it is associated with the relapses or worsening of OSA.

Weight loss reduces OSA severity, but the exact effects and efficacy of dietary modifications versus bari-

atric surgery, related to AHI reduction, remain to be established.

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