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Research Article

Obesity and Breathing Related Sleep Disorders: Concise Clinical Review

Ines Maria Grazia Piroddi[1], Sofia Karamichali[2], Cornelius Barlascini[3] and Antonello Nicolini[1]*

[1]*Respiratory Diseases Unit ASL4 Chiavarese, Italy*
[2]*Department of Allergy and Respiratory Diseases, IRCSS AOU San Martino-IST, Italy*
[3]*Hygiene and Health Medicine Unit ASL4 Chiavarese, Italy*

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***Corresponding author**

Antonello Nicolini, Respiratory Diseases Unit, Italy, Tel: +39 0185329145; Fax +390185329121; Email: antonellonicolini@gmail.com

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Abstract

The increasing prevalence of obesity has lead to an increase in the prevalence of sleep disordered breathing in the general population. Obesity is a serious disorder resulting in significant health impairment. Obese adults are at increased risk of morbidity and mortality from acute and chronic medical conditions. Obesity is associated with anatomic alterations that predispose to upper airway obstruction during sleep. Obesity and sleep related breathing disorders occur to a particular subgroup that includes obese patients with hypoventilation correlated with Hypercapnic-OSA (obstructive sleep apnea), Hypercapnic-OSA with OHS (hypoventilation syndrome) and OHS without OSA.

OHS is a disease entity distinct from simple obesity and OSA. OSA is a common disorder. Obesity and particularly central adiposity are potent risk factors for OSA. They can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and through central nervous system–acting signaling proteins (adipokines) that may affect airway neuromuscular control. Specific molecular signaling pathways encode differences in the distribution and metabolic activity of adipose tissue.

The OHS is characterized by the combination of obesity (BMI>30 kg/m^2), daytime awake hypercapnia and hypoxemia , in the presence of sleep-disordered breathing without other known causes of hypoventilation, such as severe obstructive or restrictive parenchymal lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome. It is estimated that 90% of patients with OHS also have OSA. Patients with OSA typically have normal control of breathing and obesity is not a necessary condition; patients with OHS are morbidly obese, have hypoventilation during wakefulness with increased arterial PCO_2 and decreased arterial PO_2, as well as nocturnal hypoventilation. The gold standard for the diagnosis is monitored polysomnography during sleep. In stable hypercapnic patients therapeutic choice will depend on two factors: underlying diagnosis (presence or absence of OSA) and severity of hypercapnia.

Introduction

The increasing prevalence of obesity mostly in the developed world has lead to an increase in the occurrence of breathing disordered during sleep. As the obese people, due to consumption of too many calories, suffer from hypertension, dyslipidemia, coronary heart disease, peripheral vascular disease (both, venous and arterial), diabetes mellitus, osteoarthritis and gout, they carry an increased risk of morbidity and mortality from these acute and chronic medical conditions. Here we are concerned with the consequence of obesity on respiratory diseases such as obstructive sleep apnea and hypopnea syndrome characterized by repeated airway collapse during sleep [1,2]. Sleep-Related Breathing Disorder (SBD) is a term used to describe a spectrum of respiratory disturbances that occur during sleep and comprises OSA, Central Sleep Apnea (CSA), and Obesity Hypoventilation Syndrome (OHS) [1]. OSA remains an important medical condition because of its high prevalence and its association with numerous cardiovascular and non cardiovascular consequences if left untreated. Alveolar hypoventilation in obesity results from complex interactions between obesity, ventilatory mechanics, central ventilatory control, sleep apnea and degree of Forced Expiratory Volume /1 second (FEV_1) abnormality [3]. OSA and OHS and CSA are often the frequent basic cause in the pathogenesis of hypoventilation in the obese subject [4]. They may be generated as a consequence of hyperventilation response that follows obstructive apnea. Moreover, there is a subset of patients in which obesity is associated with hypoventilation correlated with hypercapnic-OSA, hypercapnic-OSA & OHS and OHS without OSA (Figure 1).

Effects of Obesity on Sleep

Obesity is associated with anatomic alterations that predispose to upper airway obstruction during sleep. These alterations may include excessive adiposity around the pharynx and chest. In the former, increases in neck circumference and fat deposited around the upper airway may narrow down the airway. It is known that the upper airway is more easily compressed and is higher in obese people compared with non-obese individuals. In these people the pharynx is not expanded by extending mandible. As for the chest, obesity and especially central obesity have been associated with

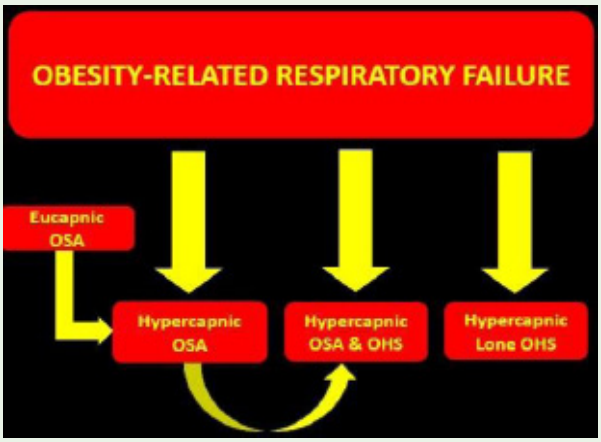

Figure 1: Obesity related respiratory failure disorders.

reductions in lung volume, which leads to a loss of caudal traction on the upper airway, and an increased risk in pharyngeal collapse; thus obesity in the neck and thorax increases continuous positive airway pressure requirements and produce a greater severity of sleep apnea. Thus, obesity imposes mechanical loads on both the upper airway and respiratory system that predispose to upper airway narrowing, collapse, and airflow obstruction during sleep [5,6]. Obesity also is associated with structural defects that compromise the airway, but the correlation is not linear. Greater obesity does not correlate with degree of apnea and it is difficult to measure local adiposity [2,3]. There may be anatomical deformities in the nose, uvula, or tonsil which become critical when obesity is involved. The mechanisms causing these elevations in upper airway mechanical loads in obesity are not well understood. It needs to be said that more is known about therapy than pathophysiology in this kind of disorders [3-5]. The pattern of obesity plays an important role in the ventilatory consequences. FEV_1 is sometimes moderately reduced in patients with severe or massive obesity, but the Forced Expiratory Volume/1 sec / vital capacity (FEV_1/VC) ratio is normal in the absence of associated bronchial disease [3-6]. These effects may be mediated by circulating adipokines, which influence body fat distribution and CNS activity. As patients with sleep apnea lose weight, improvements in upper airway function and disease severity are likely to reduce according to the weight loss as well relative changes in protective and pathogenic adipokines, as shown below [5,6].

Obesity also induces an inflammatory state directly, because adipose tissues are abundant source of pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), IL-6, as well as the pro-fibrogenic adipokine leptin [7]. In addition, adipose tissue elaborates humoral factors that may act centrally on the regulation of upper airway neuromuscular control. Leptin has been demonstrated to stimulate CO_2 ventilatory responses in mice [8,9]. Its action is antagonized by other adipose-related factors, namely the Soluble Leptin Receptor (sOB-R) and C - reactive protein (CRP), which bind circulating leptin and can decrease its Central Nervous System (CNS) uptake and action. Levels of sOB-R and CRP are elevated in sleep apnea compared with matched control patients and decline with weight loss and the loss of visceral compared with central adiposity [7]. There is also evidence that neuro-hormonal changes such as leptin resistance may have a fundamental role in ventilatory control of obese patients with hypercapania [7,10]. It has previously been observed that serum leptin was a better predictor for the presence of OHS in obesity than BMI or calculated body fat mass [10]. Central leptin resistance (indicated by increased circulating leptin levels) may not just reflect a resistance to the satiety effects of leptin but also a resistance to the respiratory stimulatory effects. Alternatively, the increased leptin levels in OHS relative to eucapneic OSA with obesity may reflect a compensatory rise to counter hypoventilation [10]. Current evidence indicates that sleep apnea is associated with fundamental disturbances in upper airway mechanical and neuromuscular control and suggests that a combined defect is required to produce sleep apnea [11].

Obstructive Sleep Apnoea

Obstructive sleep apnea is characterized by temporary but intermittent episodes of upper airway obstruction resulting in cessation of breathing or reduction in tidal volume in sleep. Apnea termination requires arousal and the resulting frequent awakenings lead to daytime symptoms such as daytime sleepiness, and impaired concentration [12], snoring, hypoventilation, hypoxemia, leading to sleep fragmentation, poor sleep, mood problems, and poor quality of life. Several risk factors, including obesity, gender differences; age, familial factors, enlarged tonsils and adenoids, and craniofacial abnormalities (retrognathia and micrognathia) have been associated with an increased prevalence of obstructive sleep apnea in the general population. Among these, obesity is one of the strongest sleep apnea risk factors. It has been shown that OSA is present in more than 50 percent of a population of adult obese patients with a mean Body Mass Index (BMI) higher than 40 [13]. Nocturnal hypoventilation seems to be present in more than 29 percent of severe obese population. There is a relationship between body weight change and Apnea-Hypopnea Index (AHI): a 10% weight gain has been shown to predict an approximate 32% increase in the AHI; a 10% weight loss predicted a 26% decrease in the AHI, and a 10% increase in weight predicted a six fold increase in the odds of developing moderate to severe SBD [11,14]. OSA is common, under-diagnosed and treatable syndrome. In developed countries, it is reported to affect between 3-7% of middle-aged men and 2-5% of women. Furthermore, it has been reported that OSA is present in about 6% of population between the ages of 50-70 years [15]. OSA is more common in men than in women. This has been attributed to differences in anatomical and functional properties of the upper airway, differences in craniofacial morphology and fat deposition, and different ventilatory responses to arousal from sleep. Central obesity accounts for the strong male predominance of this disorder, whereas peripheral adiposity may protect women from developing sleep apnea [5].

In addition to fat distribution pattern in the upper airway, upper airway anatomy and function may also contribute to gender differences in OSA. Upper airway collapsibility is greater in males than in females. Some reports support that upper airway resistance during sleep is higher in males than in females [16,17]. Hormonal status may also have impact on sleep apnea susceptibility, particularly in women. Postmenopausal women demonstrate increase in sleep apnea prevalence and severity compared with pre-menopausal women [18,19].

Obesity Hypoventilation Syndrome

Clinically OHS is considered to be a severe form of obstructive sleep-related breathing disorder in obese patients. Obesity

Hypoventilation Syndrome (OHS), formerly described as "Pickwickian syndrome" is characterized by the combination of obesity (BMI >30 kg/m^2) , daytime awake hypercapnia (partial pressure of arterial carbon dioxide ($PaCO_2$) > 45 mm Hg at sea level) and hypoxemia (partial pressure of arterial oxygen (PaO_2) > 70 mm Hg at sea level) in the presence of sleep-disordered breathing without other known causes of hypoventilation, such as severe obstructive or restrictive parenchymal lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease, and congenital central hypoventilation syndrome [20].

It is estimated that 90% of patients with OHS also have OSA [21] because approximately 1.5% of the United States population has severe obesity and OSA, and 10-20% of the severely obese patients with OSA have OHS. The prevalence of OHS among the general adult population in the United States is estimated to be 0.15-0.3% [22]. The prevalence of OHS is 11% in patients with known OSA and 8% in bariatric surgical patients [23]. OHS is a disease entity distinct from simple obesity and OSA. Patients in whom OHS is diagnosed consume greater levels of healthcare resources than eucapnic patients with OSA [24]. In order to confirm the diagnosis of OHS, other pulmonary, thoracic, metabolic or neuromuscular diseases accounting for the gas anomalies should be excluded [25]. Daytime hypercapnia is the distinguishing feature of OHS that separates it from simple obesity and OSA. OHS is usually associated with OSA and pulmonary hypertension. Major clinical features are hyper somnolence, dyspnea and headache in combination with polycythemia, cyanosis and right heart failure [11,25]. Compared to similarly obese individuals without daytime hypercapnia, patients with OHS have significantly impaired respiratory system mechanics with a restrictive ventilatory pattern [26]. In addition to alveolar hypoventilation, also ventilation–perfusion mismatching secondary to pulmonary atelectasis contributes to hypoxemia in OHS [27].

There are three leading hypotheses for the pathogenesis of chronic daytime hypoventilation in OHS: i) impaired respiratory mechanics because of obesity, ii) leptin resistance leading to central hypoventilation, and iii) impaired compensatory response to acute hypercapnia in OSA.

Compared with obese patients with eucapnia, patients with OHS demonstrate four main clinical features: i) more severe upper airway obstruction, ii) impaired respiratory mechanics, iii) blunted central respiratory drive, and iv) increased incidence of pulmonary hypertension [23].

The Relationship between OSA and OHS

There are many similarities between OHS and OSA and the clinical presentation is similar: excessive daytime sleepiness, fatigue and/or morning headaches. Furthermore, 11-15% of obese OSA patients present with hypercapnia, and a majority of the hypercapnic obese manifest OSA. Hypercapnia is more frequent in obese than in non-obese OSA subjects [28].

Patients with OSAS typically have normal control of breathing (without daytime hypoventilation) and for them obesity is not a necessary condition. Patients with OHS are morbidly obese, have hypoventilation during awakeness with increased arterial PCO_2 and decreased arterial PO_2, as well as nocturnal hypoventilation [12] (Figure 2).

The mechanisms by which OSA may induce hypercapnia are not well understood. It may be that hypercapnia in OSA develops as a consequence of a reduced inspiratory effort against an obstructed airway. Therefore, ventilatory load compensation (the normal response to maintain alveolar ventilation in the face of mechanical impediments) is impaired in OSA. This impairment may be the result either of an inability of fatigued muscles to recover between apneic episodes or of diaphragmatic dysfunction as a consequence of periodic hyperventilation episodes following apneas [29]. Also, there may be depressed ventilatory response to chemical stimuli (bicarbonate, carbon dioxide, oxygen, pH etc.) producing a reduction in compensatory ventilation. The maintenance of eucapnia during sleep requires a balance between CO_2 loading during apnea and CO_2 clearance in the intervening period. Thus hypercapnia occurs when, after an apnea, the amount of ventilation is insufficient to eliminate the CO_2 loading that occurred during apnea. Whether this type of blunted response is a consequence of increased load or represents a protective adaptation to chronic hypoxia, hypercapnia and sleep fragmentation is unknown. The hypothesis that OSA is a part of OHS has not been yet accepted. While OSA can exist with or without hypercapnia, hypercapnia in obesity patients is a defining feature of OHS. Furthermore, in these patients hypercapnia persists after eliminating apneas and hypo apneas after Continuous Positive Airway Pressure (CPAP) ventilation. In fact some authors proposed calling the condition Obesity Hypoventilation Syndrome 'OHS without OSA. For them, this entity may be diagnosed in two situations: hypercapnia in obese patients without OSA or COPD (OHS

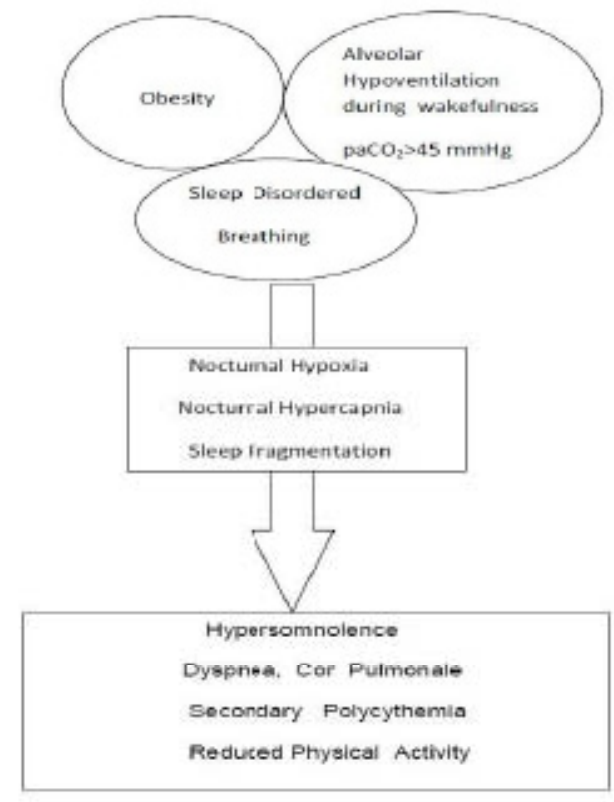

Figure 2: Pathophysiology of obesity related sleep disorders.

without OSA); and persistence of hypercapnia in OSA patients who are receiving CPAP, OHS with OSA) [30,31]. Multivariate analysis showed that hypercapnia was associated independently with HCO_3 levels and daytime oxygen saturation, and these parameters had high sensitivity and specificity in predicting OHS [32]. Evidence suggests that elevated bicarbonate levels and decreased oxygen saturation in obese OSA patients should prompt clinicians to exclude OHS [33]. Moreover, routine measurement of serum bicarbonate in obese patients can be a useful screening tool for early diagnosis of OHS and/or sleep disordered breathing [22,23]. Further studies have shown considerable similarities between obese subjects with only elevated base excess or raised bicarbonate and no daytime hypercapnia and those obese patients with hypercapnic chronic respiratory failure. This supports supporting the concept that obesity-related hypoventilation is a clinical spectrum. Metabolic compensation in the presence of eucapnia probably identifies subjects with early OHS at the milder end of the spectrum. Thus an obese patient with an isolated increased base level or raised bicarbonate should not be dismissed as normal. Whether early detection of obesity-related hypoventilation makes a difference in the long term needs to be tested in appropriate randomized controlled trials [34,35].

Morbidity and Mortality

Obesity and OSA are associated with a spectrum of co-morbidities such as coronary artery disease, heart failure, stroke and metabolic syndrome, which result in increased morbidity and mortality. Furthermore, patients with OSA are at increased risk of developing postoperative complications including arrhythmias and hypoxemia. Several studies showed that patients with OHS may experience higher morbidity and mortality than patients who are similarly obese and have OSA. The mortality rate in patients with untreated OHS is high [23,36].

Diagnosis

An essential requirement for correct diagnosis of OSA is a correct anamnesis, recording the family history (history of OSAS) and personal antecedents such as tonsillectomy/adenoidectomy in childhood, alcohol intake, the use of muscle relaxant drugs, obesity, etc. It is also important to establish the profession of the patient, since in some professions OSAS constitutes a medical emergency. A proper physical examination is also required including height, weight, BMI, cardiovascular evaluation and exploration of the upper airway (nasal passages, oropharynx and hypo pharynx, and larynx). The clinical examination should be complemented by radiological study in the form of either conventional lateral X-rays or a multidimensional X-ray study, which will reveal the craniofacial anatomical alterations predisposing to OSAS [2]. The diagnosis of OSA is established by Polysomnography (PSG) which monitors the sleeping state, respiration, electrocardiogram, movements of the legs, oximetry and snoring. In addition, PSG records the distribution of the stages of sleep, the number of awakenings, the number of apneas or hypo-apneas, the starting time of sleep, and the hours of efficient sleep (hours asleep/hours in bed) [37]. The gold standard is monitoring by polysomnography in a sleep laboratory. This modality uses multiple biometric recording devices to accurately quantify the number of apnea (a 90% reduction in tidal volume lasting 10 seconds) and hypo-apnea (a reduction in tidal volume of 50-90%, lasting 10 seconds accompanied by 3% decrease in oxyhemoglobin saturation) episodes occurring during the experimental night's sleep. PSG also provides the Apnea / Hypo-Apnea Index (AHI); in this context apnea is very serious and can only be treated surgically when AHI >30, while AHI 15-30 defines moderate apnea, and an AHI score of < 15 indicates mild apnea [37-39]. The Epworth Sleepiness Scale (ESS), arousal index (per hour frequency of arousals from sleep), minimum oxygen saturation (during sleep), the multiple sleep latency test (measurement of how quickly a subject will fall asleep during the day), the quality of life measure Functional Outcomes Sleep Questionnaire and compliance (measured as time per night using the device) are required to complete the diagnosis.

Screening, such as the validated Stop-Bang questionnaire, can identify patients at high risk of OSA. The screening tool can further be complemented by the presence of low SpO2, increased $PaCO_2$, and serum HCO_3 level to identify patients at high risk of OHS. Before major elective surgery, these patients should be referred to sleep medicine for polysomnography and C-PAP titration. An echocardiogram should be done to assess right ventricular function and pulmonary hypertension [23].

Treatment Options

The management of the treatment must include attempts to improve lifestyle of the patient and decrease obesity. The goals should be to treat respiratory sleep disturbances, diurnal hypercapnia as well as hypoxemia that may persist after correcting alveolar hypoventilation. NIV may be planned as first-line treatment to manage acute or sub-acute respiratory failure in these patients. In stable hypercapnic patients therapeutic choice will depend on two factors: underlying diagnosis (presence or absence of OSA) and severity of hypercapnia.

The recommended CPAP treatment to maintain upper airway patency eliminates apnea and hypo-apneas and restores daytime eucapnia [41]. If hypercapnia persists, despite adequate CPAP treatment, patients require augmentation of ventilation during sleep rather than simple stabilization of the upper airway, so it is recommended to use NIV [41,42]. Some published series identified greater BMI and more severe hypoventilation as predictors of lack of response to CPAP [42].

In patients with $PaCO_2$ >50 mm Hg, the initial therapeutic choice may be NIV [43]. If, after some time under NIV, the patient becomes eucapnic, and sleep studies confirm OSA, it is advisable to switch off to CPAP (after performing a full-night titration to identify optimal pressure level). If the patient remains eucapnic, long-term CPAP may be carried out [39,40]. Otherwise the patient may be switched back to NIV. In cases in which sleep studies do not show significant OSA, NIV will be the therapeutic choice. In this case, hypercapnia may be considered as obesity-related only, but additional causes such as COPD need to be sought.

Therefore the proposed management of obese patients with sleep-related breathing disorders should be:

- In eucapnic OSA patients use C-PAP in addition of oxygen therapy if hypoxemia coexists;
- In hypercapnic OSA patients try CPAP and if this corrects the hypercapnia, continue this therapy, if not, switch to NIV;

- In case of pure OHS without OSA start NIV in addition an oxygen therapy if hypoxemia coexists;
- In case of OSA and unknown OHS, try to start NIV and switch to CPAP if a normalization of parameters is obtained by CPAP; (in this case if the patient remains eucapnic we have a hypercapnic OSA patient.) If after the switch the patient has hypercapnia again is very likely to have OSA+OHS, so return to NIV [41-43].

Conclusion

Obesity sleep related breathing disorders are largely under-diagnosed and the health-related costs are higher than those related to obese patients only. Although nocturnal positive airway pressure therapies represent first-line treatment and are effective in improving patient outcomes, there is a need to offer combined treatment strategies and to assess the effect of multimodal therapeutic strategies on morbidity and mortality.

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