Obesity Hypoventilation Syndrome

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Introduction

Obesity, an epidemic in the 21st century was introduced into the international classification of diseases half a century ago. (1) Obesity is defined as an accumulation of excess body fat, to an extent that may impair health. A crude measure of excess fat is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in metres). WHO defines overweight as a BMI of 25 or more, and obesity as a BMI of > 30 kg/m2 and extreme obesity, BMI >40 kg/m2. (2) Globally in 2005, approximately 1.6 billion adults were overweight and at least 400 million adults were obese. WHO further projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese. In the United States, a third of the adult population is obese, and from 1986 to 2000, the prevalence of BMI of 40 kg/m2 has quadrupled, and that of BMI of 50 kg/m2 has increased by fivefold. (3) Once considered a problem only in high-income countries, obesity is on the rise in low- and middle-income countries, particularly in urban settings. Changes in diet, coupled with increasingly inactive lifestyles, have led to major epidemics of obesity in several Asian countries including India. (4) The obesity epidemic is not only impacting adults, it is a global phenomenon affecting children and adolescents. (5)

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Obesity is associated with arterial hypertension, coronary artery disease, diabetes mellitus and degenerative joint disease. Recently, there has been an increased awareness pulmonary consequence of obesity as a major source of morbidity. Obese patients also have compromised respiratory function while awake and upright. Their ventilatory functions worsen in supine position and when they sleep. Obese patients demonstrate various breathing abnormalities in sleep (6) obstructive apnoeas and hypopnoea; obstructive hypoventilation due to increased upper airway resistance; and central hypoventilation. In addition to the sleep related breathing disorders, some obese patients hypoventilate while awake, exhibiting a partial pressure of carbon dioxide ($PaCO_2$) greater than 45 mm Hg accompanied by sleep disordered breathing or sleep apnoea and this is called the obesity - hypoventilation syndrome (OHS). Patients with OHS display a worse prognosis than patients with obstructive sleep apnoea (OSA) (7) and use more health-care resources (8).

The definitions of overweight and obesity is based on epidemiological studies in the developed countries. Preliminary information from developing nations suggests that lower cut-off levels for both BMI and waist circumferences are necessary for populations who are at particular risk from comparatively modest degrees of overweight. (9) The 'Asian Indian Phenotype' characterized by less of generalized obesity as measured by body mass index (BMI) but greater central body obesity as shown by greater waist circumference (WC) and waist-to-hip ratios (WHR). This leads to unique biochemical and hormonal changes including higher plasma insulin levels, greater insulin resistance, lower HDL cholesterol, higher triglyceride levels, increased small dense LDL cholesterol as well as small dense HDL cholesterol and C-reactive protein and leptin levels but

decreased adiponectin levels. Thus many Asian Indians are "metabolically obese" and may have a higher prevalence of OHS. (10)

Historical Perspective

The first historical description of OHS is by Charles Dickens in 1837, who described "Joe" a fat, somnolent coach boy in "The Posthumous Papers of the Pickwick Club". (11) After 119 years, in a case report titled "Extreme Obesity Associated With Alveolar Hypoventilation a Pickwickian Syndrome" (12), reported the case of a 51-year-old business executive, 5 feet 5 inches and weighed 118 kg. He played poker and on one occasion was dealt a hand of three aces and two kings, but "he failed to take advantage of this opportunity because he had dropped off to sleep". The term obesity - hypoventilation syndrome OHS (13) was used in 1955 by Auchincloss and colleagues in patients with obesity, daytime hypercapnoea and hypoxemia, polycythemia, hypersomnolence and right ventricular failure. This syndrome gained attention among general physicians after Bickelmann et al described it as the "Pickwickian syndrome" (14).

Definition

Thus, obesity-hypoventilation syndrome (or alveolar hypoventilation in the obese) is defined as chronic alveolar hypoventilation ($PaO_2 < 70$ mmHg, $PaCO_2 > 45$ mmHg) in obese patient with a body mass index > 30 kg/m who have no other respiratory disease explaining the gas anomalies. (15) Recently published definition of OHS (16) use the following criteria: 1) extreme obesity (body mass index (BMI) _30 kg/m2); 2) excessive daytime sleepiness; 3) chronic daytime hypercapnoea (arterial carbon dioxide tension ($PaCO_2$) _45 mmHg); and 4) severe OSA (apnea-hypopnea index (AHI) _30/h or severe oxygen desaturation).

Epidemiology

The exact prevalence of OHS in the general population is not known but one-fifth of patients with OSA also have OHS (6). The estimated prevalence of OHS among patients with OSA is reported between 10% and 20% but is likely to be higher in the subgroup of patients with extreme obesity (i.e., BMI _ 40 kg/m2). (17) There is no clear racial or ethnic predominance. Because of

cephalometric differences, OHS associated with OSA occurs at a lower BMI in Asians compared to whites. (18) The impact of "metabolic obesity" on prevalence of OHS in these populations is yet to be studied.

Pathophysiology

Obese sleepy patients fall into 2 categories

a) Those with the sleep-related breathing disorders or sleep apnoea syndromes most common OSA and

b) Those with sleep-related breathing disorders with awake hypoventilation

Sleep-related breathing disorders in OHS

Since most patients with OHS display repeated upper airway obstruction during sleep, OHS has been considered as the most severe type of OSA, hence the term *hypercapoeic OSA* has also been used to describe OHS. However, a small number of patients with OHS do not experience sleep apnea (19) but demonstrate *sleep hypoventilation*, defined as an increase in $PaCO_2$ during sleep by 10 mm Hg above wakefulness or a significant oxygen desaturation that is not explained by obstructive apneas or hypopneas. This syndrome is termed the *sleep hypoventilation syndrome (SHVS)*.

Awake hypoventilation in OHS

It is unclear why some morbidly obese individuals have waking alveolar hypoventilation while others with similar obesity do not. Obesity may not be related with development of daytime hypercapnoea alone, as BMI shows no significant correlation with $PaCO_2$ in OHS. Body weight per se does not correlate with chronic daytime hypercapnoea, though weight loss in OHS patients can reverse daytime hypercapnoea. (20) There are three principal causes explaining alveolar hypoventilation in obese subjects: high cost of the work of respiration, dysfunction of the respiratory centers, repeated episodes of nocturnal obstructive apnea. (21)

Martin and Sanders (22) suggest that the alveolar hypoventilation in OHS is a mixed disorder of "can't breathe" (chest wall and respiratory muscle disorder) and "won't breathe" (decreased ventilatory drive disorder). Obesity results in an increase in the work of breathing

that reduces alveolar ventilation resulting in an elevated arterial PaCO2. This resets the set-point of the central nervous system chemoreceptors to a higher PaCO2, with consequent depression of ventilatory drive. Some evidence suggests that patients with OHS may have a measurable premorbid impairment of ventilatory chemoresponsiveness. This impairment is unlikely to be congenital as studies have shown no evidence of impaired ventilatory chemoresponsiveness in first degree relatives of patients with OHS. (23) The impairment of ventilatory chemoresponsiveness in OHS, therefore, is likely to be an acquired and reversible consequence of severe OSA.

In obese patients with chronic hypercapnoea, nocturnal polysomnography (NPSG) shows overlap of associated pulmonary disease with a ventilatory sleep disturbance in some cases. (24) Chronic airway obstruction has been demonstrated to play a major role in the development of daytime hypercapnoea in cases of OSA even in the absence of obesity (25). This condition is called "overlap syndrome" (26). However, subjects with OHS generally do not have airway obstruction. OHS should be distinguished from airway obstruction and other conditions that are commonly associated with hypercapnoea.

The discovery of the anti-obesity hormone leptin (the name is derived from the Greek "leptos" meaning "thin"), the product of the *ob* gene, has fuelled a recent surge of interest in the mechanisms regulating mammalian fat stores. (27) Leptin is a modulator of respiratory drive in patients with OHS. (28) Leptin is a protein produced by adipose tissue that circulates to the brain and interacts with receptors in the hypothalamus to inhibit eating. Leptin circulates in the plasma in the free and protein bound forms. The hormone elicits appetite suppression and weight loss. Leptin-deficient mouse (ob/ob) develops OHS. (29) In obese humans, however, serum leptin is up to four times higher than in lean subjects, indicating that human obesity is associated with a central resistance to the weight-lowering effects of leptin. In patients with OHS, serum leptin is a better predictor of awake hypercapnoea in obesity than the BMI. Thus, adverse respiratory mechanics, diminished ventilatory response to a respiratory load, (30) and decreased leptin levels or leptin receptor density, may all attenuate hypercapnoeic ventilatory responsiveness, (31) and interact to promote the development of OHS.

Diagnosis of OHS

In general, OHS is seen in middle-aged men. However, some recent studies show female preponderance. (32) Most abnormalities in OHS are related to obesity such as higher hematocrit, higher total cholesterol, systemic hypertension, diabetes mellitus and more impaired pulmonary functions. OHS is associated with severe symptoms of sleep-related breathing disorders i.e. loud habitual snoring, nocturnal choking episodes, morning headaches and excessive daytime sleepiness (EDS). EDS due to sleep fragmentation caused by obstructive sleep apnea results in intellectual deterioration, personality and behaviour changes, depression and psychosis, deficits in thinking, perception, memory and ability to learn and more serious automobile and industrial accidents. (33) Another important feature of OHS is daytime hypercapnoea (chronic hypoventilation). Summary of clinical features of OHS are shown in table 3. In contrast to patients with simple OSA, dyspnoea, lower extremity edema, and low oxygen saturation during wakefulness, pulmonary hypertension and cor pulmonale are common. (34)

Chest radiograph and high resolution computed tomography (HRCT) is essential to exclude other causes of hypercapnoea. Pulmonary function testing commonly shows a restrictive defect due to obesity, may identify an obstructive abnormality due to associated airway disease and the flow volume loop may show upper airway obstruction (35) (Figure). Laboratory testing includes complete blood count for secondary erythrocytosis, thyroid function tests to exclude hypothyroidism and serum cortisol levels if Cushing's disease is suspected. An electrocardiogram (ECG) and 2-dimensional echocardiography (2 D ECHO) is useful to assess pulmonary hypertension and right ventricular and right atrial enlargement.

Pulse oximetry demonstrates hypoxemia during wakefulness. Patients with OHS have an elevated serum bicarbonate level due to the metabolic compensation for the chronic respiratory acidosis. Therefore, serum bicarbonate level may be a reasonable test to screen for hypercapnoea. It was recently shown (36) that the serum bicarbonate level combined with the severity of OSA can be used as clinical predictors of OHS in patients with morbid obesity and OSA.

Definitive diagnosis of OHS includes in-laboratory polysomnography (PSG) to demonstrate sleep related

breathing disorders and arterial blood gas (ABG) analysis necessary to confirm the presence and severity of daytime hypercapnoea. (37)This involves recording of multiple variables during sleep, including the neurological variables like electroencephalogram (EEG), electro-oclugram (EOG) and electromyogram (EMG) and cardio-respiratory variable like airflow, O2 saturation, snoring and heart rate. Limited sleep studies that measure relevant respiratory variables in the home may be useful if in-laboratory PSG is not possible. PSG showing apnoea hypopnoea index (AHI) > 5 apnoeas per hour is considered positive for presence of sleep apnea (Figure). In addition, oxygen desaturation, changes in heart rate and rhythm, EEG arousals and periodic limb movements may also be seen.
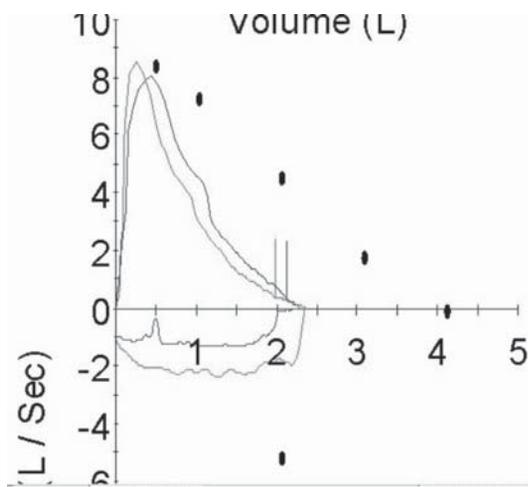

Fig 1: Flow volume loop in a case of obesity hypoventilation syndrome showing flattening of the inspiratory loop suggestive of variable extrathoracic upper airway obstruction.

Treatment of OHS

Treatment of OHS is consists of i) treatment of associated sleep apneas, ii) treatment of hypoventilation and iii) treatment of obesity. Treatment of sleep apnoea and nocturnal hypoventilation is by positive airway pressure (PAP) therapy. While autoadjusting PAP can be used in patients with simple OSA, laboratory based titration is preferred in patients with OHS to monitor associated hypoventilation. Nocturnal PAP therapy (CPAP or bi-level PAP) results in improvement in chronic daytime hypercapnoea and hypoxia as well. Nocturnal non invasive ventilation in the form of bi-level PAP may be required for most patients to take care of sleep apnoea and hypoventilation.
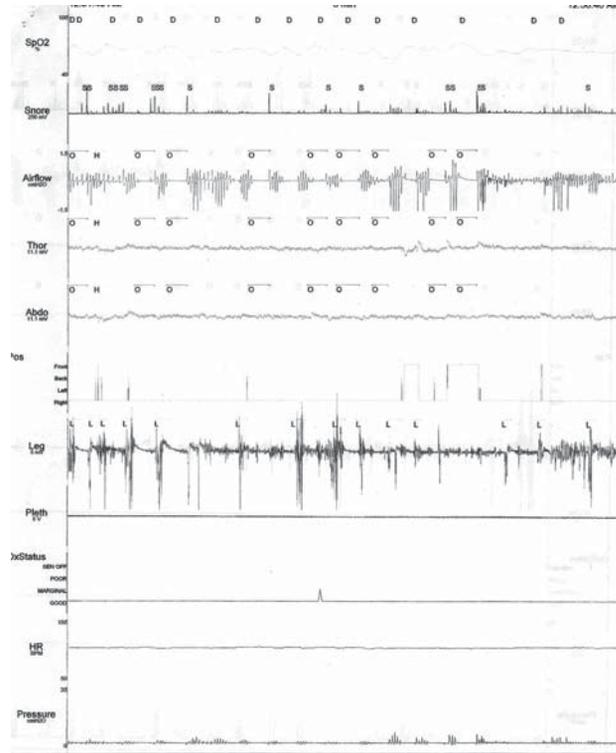
Fig 2: Nocturnal polysomnography with cardio-respiratory variables showing obstructive apnoeas and hypopnoeas, oxygen desaturation and periodic limb movements.

Table 1: Proposed WHO Classification of Overweight

BMI* (kg m2)	WHO classification	Description
<18.5	Underweight	Thin
18.5–24.9	—	Normal
25.0–29.9	Grade 1 overweight	Overweight
30.0–39.9	Grade 2 overweight	Obesity
e"40.0	Grade 3 overweight	Morbid obesity

*BMI is the weight in kilograms divided by the square of the height in metres.

Table 2: Diagnostic criteria for obesity hypoventilation syndrome

• Body mass index > 30 kg/kg2
• Daytime PaCO2 > 45 mm Hg
• Associated sleep-related breathing disorder
• (obstructive sleep apnea–hypopnea syndrome or sleep hypoventilation or both)
• Absence of other known causes of hypoventilation

Table 3: Clinical features of Obesity Hypoventilation Syndrome

Symptoms
• Loud snoring
• Disrupted sleep
• Nocturnal gasping and choking
• Witnessed apnea
• Daytime sleepiness and fatigue
• Neuropsychiatric features
• PAH/ Cor Pulmonale
Physical findings
• Obesity (BMI Wt in Kg/ Ht in mt² > 30)
• Features of associated problems like hypothyroidism, Cushing's syndrome
• Increase neck circumference >16 inches
• Systemic hypertension
• Crowded posterior airway
• Short, thick neck
• May have associated small, receding jaw
• Upper airway obstruction (UAO) on flow volume loop
• Polycythemia, hematocrit greater than 50%
• Reduced PaO2 and elevated PaCO2 during sleep
• Elevated PaCO2 during awake hours
• Pulmonary Hypertension/ Cor Pulmonale

Table 4: Treatment of OHS

• **Behavioral modifications**   Diet modification   Excercise
• **Positive Airway Pressure (PAP) therapy**   Nasal continuous airway pressure (n-CPAP)   Bilevel positive airway pressure (Bi-PAP)
• **Pharmacotherapy**   Medroxyprogesterone, carbonic anhydrase inhibitor
• **Surgical therapy**   Bariatric Surgery   Tracheostomy

If PAP therapy alone fails to achieve the desired results, oxygen supplementation for persisting hypoxemia and pharmacotherapy for respiratory stimulation must be considered. Medroxyprogesterone in a dose of 60 mg /day is useful for treatment of hypoventilation in patients with OHS. It increases the ventilatory response to hypercapnoea and also reduces the AHI. (38,39) Favourable response to medroxyprogesterone can be predicted by the ability to drop the PaCO2 by at least 5 mm Hg with voluntary hyperventilation. (40) Medroxyprogesterone however can increase the risk of venous thromboembolism. (41) Alternately acetazolamide in a dose of 250 mg/ day may be used to reduce the serum bicarbonate level and the resulting metabolic acidosis increases the minute ventilation and reduces the PaCO2. (42)

Weight loss is the only cure for OHS. It is associated with improvements in blood gases, sleep-related breathing disorders and pulmonary hypertension. (43) Unfortunately, weight loss is often difficult to achieve by means of diet and exercise. Bariatric surgery to treat obesity may be necessary and should be offered to patients who are appropriate surgical candidates. The National Institutes of Health, US consensus guidelines recommend surgical treatment for patients with a BMI greater than 35 kg/m² and an obesity-related co morbid condition (including OHS) or patients with a body mass index greater than 40 kg/m². (44) The surgical options (45) available can be grouped into 2 categories based on their weight loss mechanism. Gastric restrictive procedures include vertical banded gastroplasty (VBG), adjustable gastric banding (AGB), and Roux-en-Y gastric bypass (RYGB). The procedures causing malabsorption include biliopancreatic diversion (BPD) and biliopancreatic diversion with duodenal switch (BPD-DS). All of the procedures have been successful in improving the co morbidities associated with obesity. The most commonly performed procedure is RYGB is generally performed laparoscopically and has the best safety, efficacy, and durability, and it has been shown to be superior to AGB. All the procedures must be performed by experienced surgeons and require long-term dietary compliance and careful nutritional follow-up. (45) Finally, tracheostomy is an option to treat ppatients with the obstructive form of OHS. (46) However, improvement after several nights sleep with a nasopharyngeal tube in place should be demonstrated before such invasive form of therapy is attempted. (47,48)

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