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An Overview on Obesity hypoventilation syndrome

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Abstract:

Background: Obesity hypoventilation syndrome (OHS) is a serious and underdiagnosed disorder characterized by obesity, chronic daytime hypercapnia, and sleep-disordered breathing in the absence of other causes of alveolar hypoventilation. OHS is associated with significant cardiopulmonary morbidity, increased healthcare utilization, and higher mortality compared with eucapnic obese individuals and patients with obstructive sleep apnea alone. Early identification of OHS remains challenging, particularly in resource-limited settings, highlighting the need for reliable and easily accessible diagnostic indicators.

Keywords: Obesity hypoventilation syndrome; Obesity; Hypercapnia; Sleep-disordered breathing; Respiratory failure.

Introduction:

Obesity hypoventilation syndrome (OHS) is a clinical disorder characterized by the presence of obesity, chronic daytime hypercapnia, and sleep-disordered breathing in the absence of other identifiable causes of hypoventilation. The prevalence of OHS has increased in parallel with the global rise in obesity, making it a growing public health concern. Among obese patients referred for sleep evaluation, OHS is estimated to affect up to 20% of individuals with obstructive sleep apnea (OSA), yet it remains frequently underdiagnosed **(1).** Failure to recognize OHS early may result in delayed treatment and progression to chronic respiratory failure.

The pathophysiology of OHS is complex and multifactorial, involving impaired central ventilatory drive, increased mechanical load on the respiratory system, reduced lung volumes, and altered gas exchange during sleep and wakefulness. Chronic hypoventilation leads to sustained hypercapnia and hypoxemia, which contribute to the development of pulmonary hypertension, right ventricular dysfunction, and systemic cardiovascular complications. Compared with eucapnic obese individuals and patients with OSA alone, patients with OHS exhibit higher rates of hospitalization, intensive care unit admission, and mortality **(2).**

Despite its significant clinical impact, OHS is often misdiagnosed as chronic obstructive pulmonary disease or heart failure, particularly in obese patients presenting with dyspnea and hypoxemia. This diagnostic challenge underscores the need for simple, accessible, and reliable markers to facilitate early identification of OHS in routine clinical practice. Several studies have highlighted the potential role of biochemical and physiological parameters, such as serum bicarbonate levels, arterial blood gases, and sleep study indices, as practical screening tools for early diagnosis **(3).** Early recognition and appropriate management of OHS are essential to reduce morbidity, improve quality of life, and decrease mortality in this high-risk population.

In 1836, Charles Dickens published his serialized book “The Posthumous Papers of the Pickwick Club” in which he described obesity-hypoventilation syndrome, which is defined as alveolar hypoventilation in an obese individual during wakefulness that cannot be explained to other conditions that lead to hypercapnia, such as chronic obstructive lung disease (COPD) or obstructive sleep apnea (**4).**

Epidemiology

The increasing prevalence of obesity has led to a corresponding rise in the occurrence of OHS, not only among adults but also among children and adolescents. Epidemiological studies conducted on different populations have demonstrated that the prevalence of OHS in patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) and obesity ranges from 10% to 20%. This percentage can escalate to 27% in patients with a BMI greater than 40 kg/m2 and even as high as 50% in those with a BMI greater than 50 kg/m2 (**5).**

Thus, the prevalence of OHS is directly related to the prevalence of obesity within each population. For example, the prevalence of OHS in patients with OSA in Japan is only 9%. In contrast, it reaches 20% in the United States, which is unsurprising given that the United States has the highest obesity rate globally. In fact, one-third of the US population has a BMI above 30 kg/m2 (**5**).

However, the prevalence of OSAHS in the Mexican population stands at 3.3%, with men being more affected than women at a rate of 4.4% and 2.2%, respectively. However, the prevalence of OHS is presently unknown. The association between gender is not clearly defined; some research findings suggest that it is more prevalent in men, while others claim it is more common in women. Additionally, there is not a higher incidence in any race or ethnicity. However, OHS occurs at a lower BMI range in the Asian population (**6).**

Regrettably, most cases of OHS are diagnosed belatedly, typically during the fifth or sixth decade of the patient's life, when hospitalization is required because of some complication or another. This presents a significant challenge, and the multidisciplinary medical staff must remain vigilant, especially given the continuing rise in the prevalence of obesity (**5**).

Definition

Obesity hypoventilation syndrome (OHS) is defined by the presence of obesity (body mass index (BMI) ≥ 30 kg/m2), chronic alveolar hypoventilation leading to daytime hypercapnia (PaCO2 ≥ 45 mmHg) as well as sleep-disordered breathing (SDB), after excluding other causes for hypoventilation (such as neuromuscular, metabolic, lung, or chest wall diseases; **Figure 1**) **(7)**

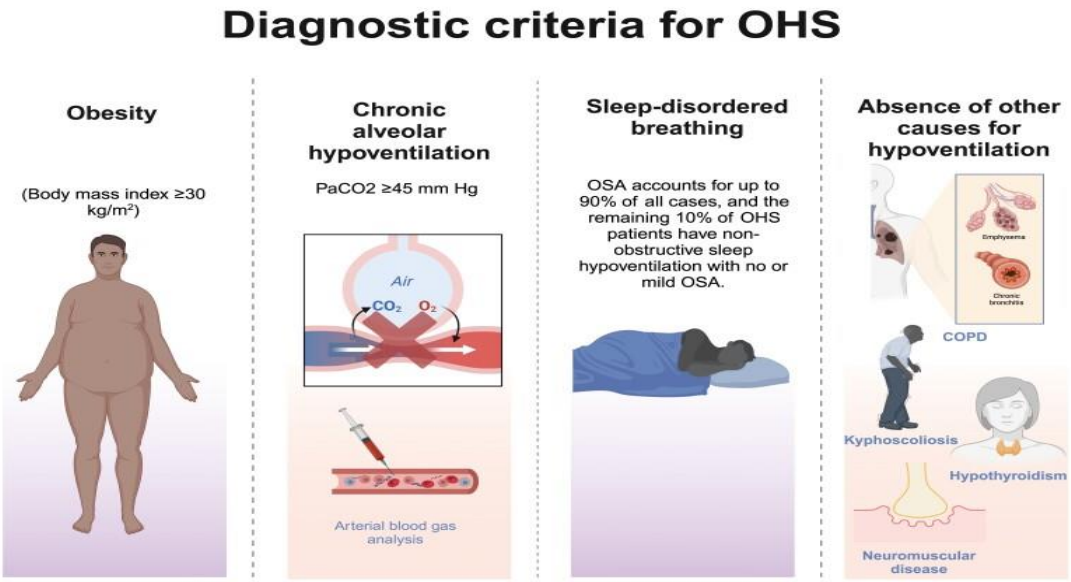

Figure 1. Diagnosis of obesity hypoventilation syndrome. The diagnosis is made by the combination of obesity, sleep-disordered breathing, and daytime hypercapnia in the absence of a neuromuscular, mechanical, or metabolic cause of hypoventilation (some of these conditions include chronic obstructive pulmonary disease, restrictive lung disease, kyphoscoliosis, hypothyroidism, neuromuscular diseases, and central hypoventilation). COPD, chronic

obstructive pulmonary disease; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PaCO2, arterial carbon dioxide tension; PaO2, partial pressure of oxygen (**5**).

The existence of a sleep disorder is one of the characteristics that patients with OHS present. Within these, obstructive sleep apnea (OSA) is the most prevalent respiratory disorder occurring during sleep and accounts for up to 90% of all cases. The remaining 10% of OHS patients have non-obstructive sleep hypoventilation with no or mild OSA (**7**).

OSA is a sleep disorder characterized by the repeated collapse of the upper airways, leading to partial or complete airway blockage. This can result in decreased oxygen levels and interrupted sleep, causing fatigue, sleepiness, and other symptoms affecting quality of life. The diagnosis of OSA is determined by the presence of related symptoms, such as sleepiness, habitual snoring, gasping, breath-holding, or choking during sleep, as well as the identification of more than five predominantly obstructive respiratory events/hour (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals) measured by polysomnography or out of center sleep testing (apnea–hypopnea index (AHI) of ≥ 5 events/h). Alternatively, a diagnostic criterion of an obstructive respiratory event rate of 15 events/h can be used, even without symptoms or associated comorbidities. An AHI ≥ 30 events/h is primarily classified as severe (**8).**

According to the American Academy of Sleep Medicine, this sleep-related hypoventilation is defined as the presence of PaCO2 of greater than 55 mmHg for over 10 minutes or an increase in PaCO2 by greater than 10 mmHg during sleep, in comparison to a PaCO2 more significant than 50 mmHg for more than 10 minutes in the awake supine value (**9).**

Pathophysiology

OHS is a medical condition that results from changes in the respiratory system due to excess adipose tissue. Pathophysiological mechanisms responsible for this syndrome have recently been proposed. The increase in chest wall thickness reduces lung volume, leading to a decrease in the functional residual capacity (FRC) (**10**). This can impede the muscular function of the diaphragm, decreasing pulmonary adherence and increasing the resistance of the lower airway. The characteristic breathing pattern that arises because of alveoli closing prematurely during expiration includes low tidal volume and increased respiratory rate. This heightened respiratory rate further contributes to increased dead space ventilation. Additionally, the decreased ventilation of the lower lobes and the FRC reduction may lead to changes in ventilation-perfusion (V/Q), ultimately resulting in hypoxemia (**9**).

Another explanation is alterations in the respiratory drive; obese patients tend to increase their respiratory capacity to maintain normal CO2 levels in their bodies. However, alterations in their respiratory drive can lead to hypoventilation, especially during rapid eye movement sleep. During this stage of sleep, there is a general relaxation of the muscles, and the diaphragm and central impulses control ventilation. If this pattern continues, it can lead to a secondary depression of the respiratory centers, resulting in hypercapnia during the day. This could explain the high prevalence of central hypoventilation in the OHS **(11).**

Eucapnic patients can normalize the PaCO2 levels via compensatory augmentation of alveolar ventilation, which increases CO2 clearance; but in OHS patients, the compensatory mechanism is disrupted, causing the retention of CO2. In response to CO2 accumulated beyond the ventilatory capacity to be cleared, the renal system decreases bicarbonate clearance to compensate for the hypercapnic pH drop. This built-up in bicarbonate eventually blunts the ventilatory response to CO2, thus causing the development of nocturnal hypoventilation. This chronic accumulation of CO2 leads to chronic hypercapnia and compensated respiratory acidosis (**5**).

Some studies have demonstrated the role of leptin as a respiratory stimulant, and how leptin resistance related to obesity can contribute to a decline in respiratory control. Furthermore, insulin-like growth factor has been identified as a possible factor in developing this condition (**7).**

Another explanation is the alteration of respiratory functions during sleep, respiratory alterations can occur due to the physiological changes in obesity amplified during supine sleep. The excessive fat surrounding the upper airway and the reduction in lung volume can cause the pharynx to collapse. Patients with OHS have been observed to experience obstructive apneas and hypopneas of longer duration compared to patients with OSA alone, indicating a poorly compensated ventilatory response. (**Figure 2**). Patients with obesity may also present with diastolic ventricular dysfunction, which increases their risk of developing post-capillary pulmonary hypertension (**12).**

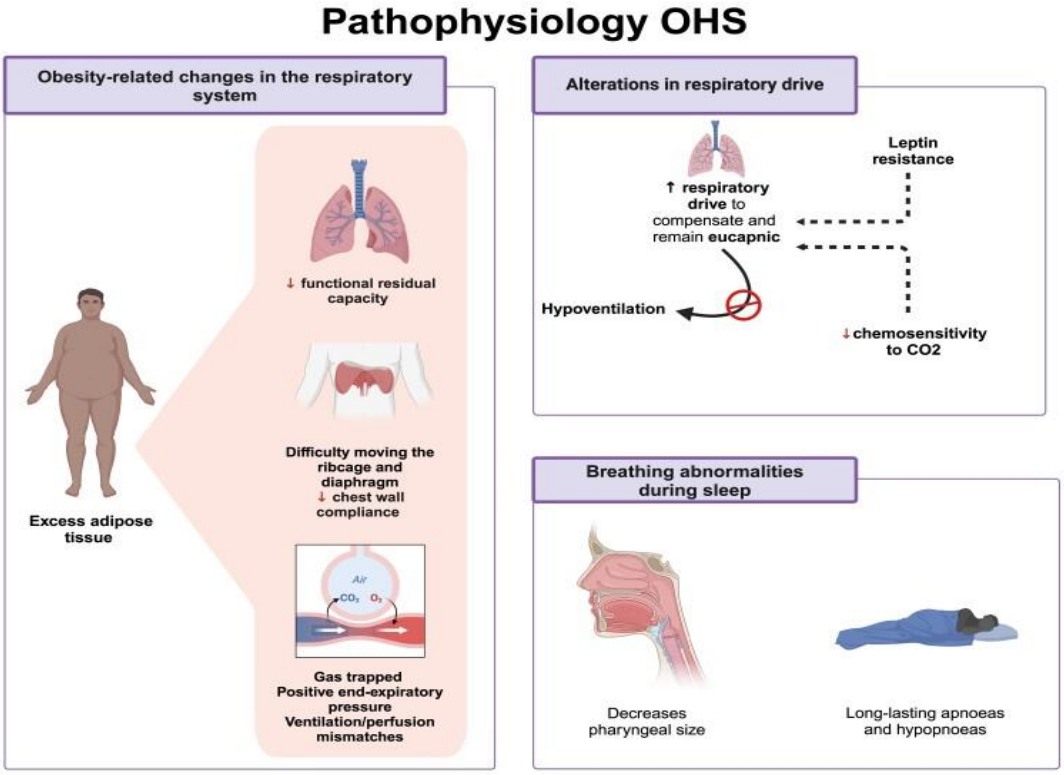

Figure 2. Main pathophysiological mechanisms of OHS. OHS is a medical condition caused by excess body fat, which changes the respiratory system, reducing lung volume and causing air trapping. Alterations in respiratory drive and leptin resistance are factors that contribute to the development of this condition. Patients with OHS experience obstructive apneas and hypopneas during supine sleep (**5**).

It is noteworthy that a significant proportion of these patients display hypoxemia, which has been linked to hypercapnia during the day. Such sustained hypoxia may delay sleep activation in response, as observed in clinical studies (**5**).

Blood Gas Changes in OHS

In Obesity Hypoventilation Syndrome (OHS)**,** arterial blood gas (ABG) analysis typically reveals characteristic abnormalities reflecting chronic hypoventilation**,** impaired gas exchange**,** and compensatory changes (**13).**

Table (1): Blood Gas Changes in OHS (13).

Parameter	**Typical Change**	**Explanation**
$PaCO_2$ (arterial CO_2)	**↑ Elevated (> 45 mmHg)**	Due to chronic hypoventilation and CO_2 retention

PaO_2 (arterial O_2)	**↓ Decreased (< 70 mmHg)**	Reflects alveolar hypoventilation and V/Q mismatch
pH	**Normal or slightly ↓ (e.g., 7.35–7.37)**	Mild acidemia may be present; usually compensated over time
HCO_3^- (bicarbonate)	**↑ Elevated (> 28 mmol/L)**	Renal compensation for chronic respiratory acidosis
O_2 saturation (SpO_2)	**↓ Often < 90% during sleep or wakefulness**	Worsens during REM sleep or supine position

Prognosis (Morbidity and Mortality)

As is well established, patients diagnosed with OSAHS are at an increased risk of developing chronic degenerative diseases, such as metabolic, cerebrovascular, and coronary diseases. This can lead to higher mortality rates (**5**).

In contrast, patients diagnosed with OHS, despite having the same degree of obesity as those with OSAHS, usually experience more significant morbidity and mortality rates if left undiagnosed and untreated promptly. Additionally, the quality of life of such patients is often worse, both compared to obese patients without hypercapnia and those with hypercapnia due to other causes, mainly due to excessive sleepiness (**12**).

Morbidity

Patients with obesity and concomitant hypercapnia have a higher risk of morbidity compared to those without hypercapnia. Patients with OHS exhibit a higher frequency of medical consultations, emergency services usage, more extended hospital stays, intensive care unit (ICU) admissions, invasive mechanical ventilation requirements, and perioperative complications (**7**).

In comparison to obese individuals without hypoventilation, patients with OHS are at a higher risk of heart failure (OR 9, 95% CI: 2.3 to 35), angina pectoris (OR 9, 95% CI: 1.4 to 57.1), and cor pulmonale (OR 9, 95% CI: 1.4 to 57.1) (**9**).

OHS patients also exhibit a greater prevalence of pulmonary hypertension, reportedly up to 88%, compared to those with only OSAHS, which is 15%. Most OHS patients belong to group III, associated with chronic hypoxemia, while a minority is within group II, associated with left heart failure or obese cardiomyopathy. Moreover, this patient group has a higher prevalence of systemic arterial hypertension (55%–88%), diabetes mellitus, and osteoarthritis **(14).**

Appropriate diagnosis and treatment of OHS can significantly reduce hospital stay from 7.9 to 2.5 days per year (**7**).

Mortality

The primary causes of mortality in OHS patients include hypercapnic respiratory failure, exacerbated cor pulmonale, or pulmonary thromboembolism. Studies indicate that patients with OHS who decline continuous positive airway pressure (PAP; CPAP) management have an alarmingly high mortality rate of up to 46% within 50 months of follow-up (**12**). Furthermore, hospitalized patients who do not receive treatment have a mortality rate of 23% at 18 months, compared to only 6% in obese patients without hypercapnia. However, when treated with noninvasive ventilation (NIV), the mortality rate at 18 months is reduced to only 3%, with rates of 8% and 30% at 2 and 5 years, respectively. Early identification and treatment can prevent hospital admissions, ICU stays, the use of mechanical ventilation, and death **(5).**

Diagnosis and clinical manifestations

OHS is typically diagnosed either when an afflicted patient reaches a high state of acuity, in the form of acute-on-chronic hypercapnic respiratory failure, or alternatively, when ambulatory care is escalated to include evaluation by pulmonary or sleep specialists (figure 3) **(7).**

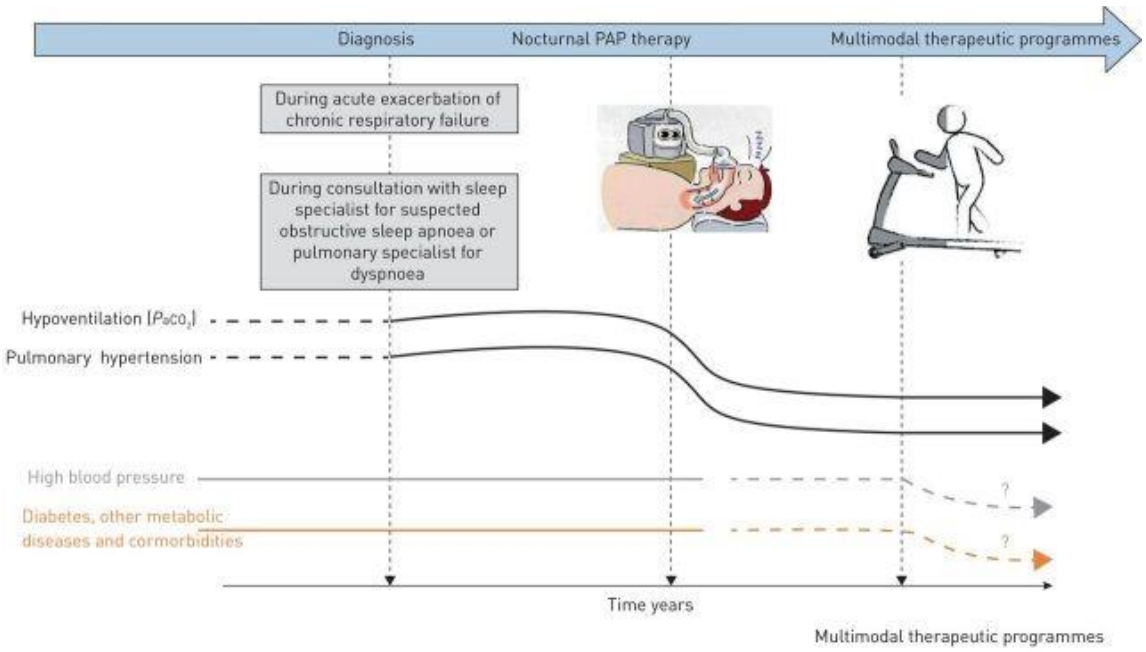

Figure 3. Management of patients with obesity hypoventilation syndrome (OHS) from diagnosis to integrated care to modify health trajectories. After being diagnosed with OHS, these patients are typically initiated on positive airway pressure (PAP) therapy (continuous positive airway pressure or noninvasive ventilation). Although respiratory insufficiency improves quite consistently in patients adherent to PAP therapy, pulmonary hypertension may also improve in some patients with OHS.. **(7).**

Unfortunately, a delay in diagnosis is common; the diagnosis typically occurs during the 5th and 6th decades of life, and during this delay OHS patients utilise more healthcare resources than comparably obese eucapnic patients. In one study, 8% of all admissions to a general intensive care unit met diagnostic criteria for obesity-associated hypoventilation (BMI >40 $kg \cdot m^{-2}$, P_{aCO2} >45 mmHg and no evidence of musculoskeletal disease, intrinsic lung disease or smoking history). All of these patients presented with acute-on-chronic hypercapnic respiratory failure. Of these patients, nearly 75% were misdiagnosed and treated for obstructive lung disease (most commonly chronic obstructive pulmonary disease) in spite of having no evidence of obstructive physiology on pulmonary function testing **(15).**

Patients with OHS tend to be severely obese (BMI ≥40 $kg \cdot m^{-2}$), have severe OSA (≥30 $events \cdot h^{-1}$) and are typically hypersomnolent. Compared with patients with eucapnic OSA and similar BMI, patients with OHS are more likely to report dyspnoea and manifest cor pulmonale (**15**).

The definitive test for diagnosing alveolar hypoventilation is room air arterial blood gas. However, simple tests to screen for OHS may aid clinicians and patients who may be reluctant to undergo an arterial puncture or in clinical scenarios when arterial blood gas analysis is not readily available. The tests evaluated by many investigators to identify patients likely to have OHS are natural consequences of hypoventilation, namely an elevated serum bicarbonate levels and hypoxaemia. Although serum bicarbonate <27 $mEq \cdot L^{-1}$ has a 97% negative predictive value for excluding a diagnosis of OHS, a serum bicarbonate level ≥27 $mEq \cdot L^{-1}$ should lead the clinicians to perform a confirmatory arterial blood gas analysis (**7**).

Apart from hypercapnia, increased bicarbonate level may also reflect multimorbidity and polypharmacy, which should be taken into account when used to screen for OHS. Hypoxaemia assessed by pulse oximetry is

simple and makes it an attractive tool for identifying obese patients that are likely to be hypercapnic. However, clinicians must recognise that there are a variety of reasons for which severely obese patients may be hypoxaemic but not hypercapnic (*e.g.* microatelectasis and increased right to left shunt) (**16).**

Ultimately, a rise in carbon dioxide levels (≥45 mmHg) during wakefulness is necessary to define hypoventilation. There are a variety of techniques to measure carbon dioxide such as daytime arterial blood gases, arterialised capillary blood gases, venous blood gases, end-tidal carbon dioxide and transcutaneous carbon dioxide monitoring. Each of these techniques has advantages and disadvantages (**17**). The reliable and practical method for identifying sleep hypoventilation is to measure carbon dioxide levels continuously during sleep by end-tidal or transcutaneous monitoring. Improving technologies should greatly expand our ability to identify and quantify nocturnal hypoventilation in sleep laboratories, or even at home (**18).**

Cabrera Lacalzada and Díaz-Lobato (19) suggested categorising OHS into mild, moderate or severe based upon daytime P_{aCO2}, daytime arterial oxygen tension (P_{aO2}), BMI or apnoea/hypopnoea index (table 2).

Table 2. Proposed classification system for obesity hypoventilation syndrome (**18).**

	Mild	**Moderate**	**Severe**
$\boldsymbol{P_{aCO2}}$ **(mmHg)**	46–60	60–80	>80
$\boldsymbol{P_{aO2}}$ **(mmHg)**	>70	60–70	<60
BMI (kg·m^{-2})	30–40	40–50	>50
Apnoea/hypopnoea index (events·h^{-1})	<5	5–15	>15
Comorbidities	No	No	Yes

- ✓ **Hypercapnia:** A sensitive screening test for chronic hypercapnia is an elevated serum bicarbonate level (>27 mEq/L). However, this is not a specific test, and elevation can occur in several other diagnoses, including vomiting, dehydration, medications, etc. Arterial blood gas (ABG) is a more definitive test for alveolar hypoventilation and defines hypercapnia as the partial pressure of arterial CO_2 ($PaCO_2$) greater than 45 mm Hg. PaC02 is the preferred measurement over $Sp0_2$ or HCO_3 levels (**20).**
- ✓ **Hypoxemia:** Hypoxemia during wakefulness is uncommon in OSA alone and requires confirmation by an ABG showing PaO less than 70 mm Hg. Hypoxia can be measured noninvasively through pulse oximetry. Another tool used in evaluating OSA and OHS is the polysomnogram.
- ✓ **Complete blood count:** Polycythemia due to chronic hypoventilation and hypoxia may be present. Blood tests can rule out secondary causes of erythrocytosis and other mimicking diagnoses like hypothyroidism.
- ✓ **Pulmonary function testing (PFT) and imaging:** If hypercapnia is confirmed, other causes should be ruled out with PFTs, chest X-ray, or computed tomography (CT) scan as clinically indicated. The PFT results in OHS can reveal a moderate restrictive defect without evidence of airway obstruction, but it may also be normal.
- ✓ **Sleep study:** Polysomnography with continuous nocturnal lCO_2 monitoring is the gold standard for evaluating OHS. In addition, the oxygen nadir and percent time spent below O_2 saturation (SpO_2) of 90% suggests OHS.
- ✓ **Cardiac studies:** Electrocardiogram (ECG) and echocardiogram help assess right heart enlargement and failure secondary to pulmonary hypertension that develops late in OHS.

Treatment

Currently, no established protocol for managing OHS exists, and treatment is typically centered on correcting SDB, reducing weight, and managing comorbidities (Figure 4). In clinical practice, the management of

patients may vary according to the acuity of the condition (Figure 5). Specifically, the approach to managing a patient with stable OHS differs from that of a patient exacerbated in an emergency room; in this case, it is crucial to systematically rule out potential complications, including pulmonary thromboembolism, pneumonia, or acute respiratory acidosis (**21**). These conditions should be treated immediately to prevent any further complications.

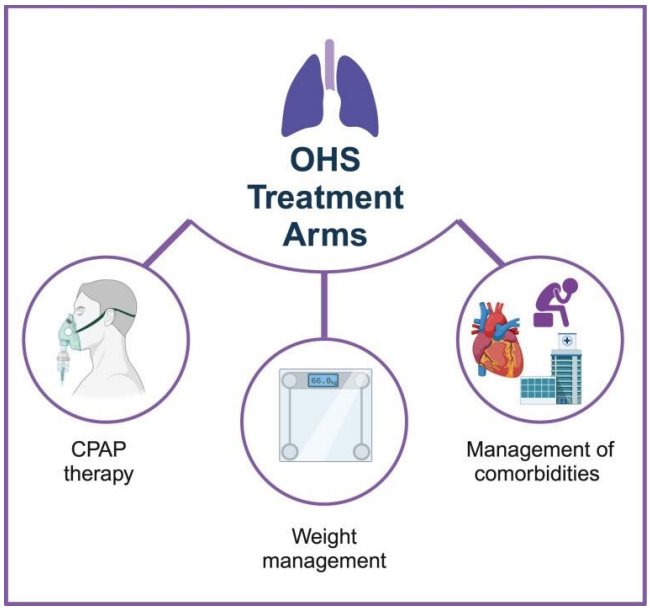

Figure 4. The mainstays of OHS treatment. The treatment approach involves correcting sleep disordered breathing, reducing weight, and managing comorbidities (**5).**

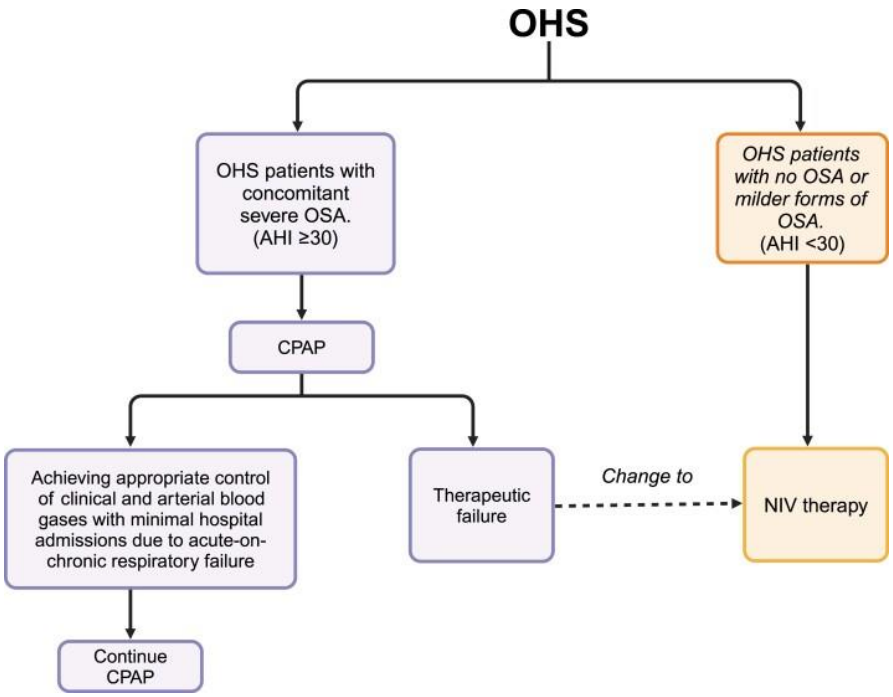

Figure 5. General management of OHS. Continuous positive airway pressure (CPAP) is the first-line treatment for OHS patients with severe obstructive sleep apnea (OSA). For OHS patients with no OSA or milder forms of OSA, noninvasive ventilation (NIV) should be considered the primary therapy. If patients initially treated with CPAP do not respond positively to therapy despite objectively documented high levels of adherence to CPAP, they should be switched to NIV therapy. AHI, apnea–hypopnea index (**5).**

Treatment of OHS should consider comorbid conditions, and it is important to recommend goals to be achieved and addressed, one of which is cardiorespiratory rehabilitation as well as targeted weight loss. “The addition of the rehabilitation program produced significant improvements in both functional performance and exercise capacity as well as increases in muscle size and strength, again supporting the enhanced effect of rehabilitation in addition to NIV” **(22).**

A. CPAP:

CPAP is the primary mode of treatment for OHS cases with concomitant severe OSA. However, in cases where CPAP is ineffective, Bi-level PAP may be necessary, particularly at the onset of treatment due to hypercapnia during acute exacerbation or hospitalization with decompensation. It is important to emphasize that NIV should be considered as first-line therapy for patients with no OSA or milder forms of OSA. If patients initially treated with CPAP have no favorable response to therapy despite objectively documented high levels of adherence to CPAP, they should be changed to NIV therapy (**5**).

On the other hand, according to a study by Masa et al., patients with OHS adopting NIV or CPAP can significantly alleviate hypercapnia symptoms during wakefulness. Interestingly, studies have shown that both long-term NIV therapy and CPAP treatment are equally effective, regardless of the severity of baseline hypercapnia. As such, clinicians can confidently prescribe CPAP treatment to this patient group, regardless of their initial PaCO2 levels; however, they must be reassessed to ensure the hypercapnia is resolved (**7).**

A prospective study was conducted on patients with stable OHS and undergoing positive pressure treatment to evaluate the efficacy of CPAP and Bi-level PAP. The study demonstrated that CPAP effectively eliminated respiratory events in 57% of patients, while the remaining patients required Bi-level PAP due to persistent hypoxemia or a high residual AHI. Notably, patients who did not respond to CPAP had a significantly higher BMI of 61.6 ± 17 kg/m2 compared to those who responded 56.5 ± 1.2 kg/m2 (**5**).

In 2008, Piper et al. reported no significant differences in treating patients with either CPAP or Bi-level PAP if adherence was equal and improvements in excessive daytime sleepiness, hypoxemia, and hypercapnia were observed. Additionally, the study showed that up to 80% of patients responded adequately to CPAP, indicating that it is an effective treatment option for most patients with OHS (**7**).

Therefore, it is strongly suggested that CPAP be titrated at the outset of treatment, given the higher costs associated with Bi-level PAP and the evidence presented in the literature. However, the evaluation of each patient’s unique clinical scenario is imperative. The use of Bi-level PAP should be considered when a patient is unable to tolerate high pressures, when hypoxemia and/or hypoventilation persist despite eliminating obstructive events, and when the patient continues with hypercapnia following three months of CPAP treatment (**23**).

In positive pressure therapy, the administration of oxygen becomes necessary when the patient, despite overcoming various respiratory events, maintains a saturation below 88% at sea level. Oxygen supplementation is required if T90 exceeds 10% at sea level. Recent studies have shown that sleep-related hypoxemia, which measures T90, is correlated with cardiovascular events. T90 is classified into four categories: light (T90 ≤ 5%), mild (T90 5%–10%), moderate (T90 10%–25%), and severe (T90 > 25%). This classification helped stratify the risk of hypertension in OSA patients. In the case of Mexico City, located at an altitude of 2400 meters above sea level, the threshold for oxygen supplementation is set at a maximum T90 of 30% (**23**).

Patients who adhere well to positive pressure therapy have improved their quality of life after six months of CPAP treatment (**5**).

Moreover, CPAP or Bi-level PAP treatment has been shown to be effective in improving arterial blood gases in patients experiencing respiratory disorders. The efficacy of other positive pressure treatments in such patients has yet to be well established. As stated earlier, in cases where CPAP is ineffective, Bi-level PAP may be necessary, particularly at the onset of treatment due to the presence of hypercapnia. Bi-level PAP may also be better tolerated by patients, particularly when the CPAP pressures required to eliminate respiratory events are unmanageably high (**7**).

However, in cases where the patient does not respond adequately to CPAP or Bi-level PAP, alternative therapies such as average volume-assured pressure support (AVAPS) can be considered. AVAPS integrates the characteristics of both volume and pressure-controlled noninvasive ventilation. In Bi-level PAP mode, volume is the dependent variable, whereas in AVAPS mode, pressure is the dependent variable (**24**).

B. Bi-level PAP

Bi-level PAP substantially improves clinical parameters such as oxygenation, sleep quality, and health-related quality of life in patients with OHS. The addition of AVAPS to BPV-S/T provides additional physiologic improvements and benefits on ventilation quality, thus resulting in a more efficient decrease of transcutaneous PCO2 compared to BPV-S/T therapy alone. This, however, did not provide further clinical benefits regarding sleep quality and health-related quality of life in the present group of highly selected patients (**24**).

Treatment approaches based on OHS phenotype

The selection of an appropriate treatment strategy for patients with OHS can be a challenging task. Treatment choice largely depends on the phenotype, which encompasses various types of breathing abnormalities during sleep. When hypoventilation predominates over obstructive events during sleep, NIV modalities such as Bi-level PAP are considered an appropriate treatment strategy. Conversely, for patients with a higher frequency of obstructive events during sleep, CPAP is a recommended first-line treatment. Patients on CPAP should be closely monitored for 2–3 months, and in case of treatment failure (when CO_2 levels do not normalize), NIV modalities such as Bi-level PAP should be considered (**20).**

Other treatments

It is imperative to educate patients with OHS about the importance of weight control and encourage them to make necessary lifestyle modifications and implement rehabilitation strategies. Although the long-term efficacy of these measures remains yet to be established, it is crucial to keep the patients informed and motivated. Bariatric surgery can be considered a viable alternative for patients who meet the criteria. However, it is essential to exercise caution while recommending this option and consider the potential risks involved. Sugerman et al. studied 61 patients with OHS who underwent bariatric surgery. After one year, 31 patients improved PaO2 (from 53 to 73 mmHg) and PaCO2 (from 53 to 44 mmHg). However, at the 5-year follow-up, only 12 patients underwent arterial blood gas analysis, which showed a significant decline in their PaO2 levels (mean PaO2 = 68 mmHg) and an increase in PaCO2 levels (mean PaCO2 = 47 mmHg). Additionally, their BMI had increased from 38 to 40 kg/m2 since the first year after surgery. The success of bariatric surgery, including weight loss and physiological parameters, depends on patient-specific variables and surgical techniques. When considering weight loss surgery, it's important to carefully weigh the potential risks of the procedure against the maximum level of anticipated weight loss. It is worth noting that even after weight reduction surgery, OSA may persist despite the resolution of OHS (**25).**

There is an increasing amount of research being conducted on the use of incretins for managing obesity. These studies aim to determine the effectiveness of incretin therapy in reducing cardiovascular risks and other complications associated with excess body fat. Despite recent studies showing significant weight loss, there are still many unanswered questions about the use of incretin therapy as a treatment for OHS. Current evidence suggests that discontinuing incretin treatment may result in weight regain and the eventual reversal of cardio-metabolic improvements **(26).**

The use of respiratory stimulants, such as medroxyprogesterone and acetazolamide, has generated considerable debate. Medroxyprogesterone acetate acts as a respiratory stimulant in the hypothalamus. Progestins have been found to improve hypercapnia and hypoxemia in patients with OHS, but not completely eliminate it. On the other hand, acetazolamide prevents the conversion of carbon dioxide to bicarbonate, which lowers pH in the brain and increases central ventilatory drive and minute ventilation. It has been shown to improve AHI, increase PaO2, and reduce PaCO2 in patients with OSA (**5**).

However, stimulants can increase negative intrathoracic pressure and promote upper airway collapse. Therefore, it is prudent to approach the use of these stimulants with due diligence and weigh the potential benefits against the possible risks involved. It is important to note that the use of medroxyprogesterone can increase the risk of venous thromboembolism. Due to this, it is not recommended to administer the medication to patients with OHS who have limited mobility. Similarly, when prescribing Acetazolamide to patients with ventilatory limitations, caution should be exercised as the drug can exacerbate acidosis and worsen dyspnea. It is important to avoid using supplemental oxygen in isolation and instead adopt a comprehensive and integrated approach for treating patients with OHS (**20).**

Treatment of the exacerbated patient

The administration of NIV represents a viable approach to reducing the need for emergency hospitalizations in patients exhibiting exacerbation. In cases where the patient is already hospitalized, prompt identification of the syndrome is essential, and treatment with NIV should be initiated without delay. Empirical recommendations favor using the Bi-level PAP based on arterial blood gases. Polysomnography is performed following hospital discharge to titrate CPAP or Bi-level PAP. Whilst NIV is important in managing exacerbation; it is imperative to establish the causes of exacerbation (such as acute coronary syndrome, pulmonary embolism, and pneumonia) and identify any possible complications in all hospitalized patients (**5**).

During an acute event, NIV should be adjusted to manage upper airway obstruction. Expiratory PAP should be titrated for this purpose. Meanwhile, inspiratory PAP should be titrated to maintain adequate tidal volumes and lower PaCO2. Phlebotomy should only be considered in patients exhibiting hematocrit levels exceeding 65% and symptomatic hyperviscosity (**7).**

Weight Management in OHS:

1. Lifestyle Modifications (27):

- Caloric restriction and exercise are first-line interventions.
- Even modest weight loss (~5–10%) can improve $PaCO_2$, PaO_2, and quality of life in OHS.
- Behavioral support and nutritional counseling enhance long-term success.

Clinical Outcomes of Weight Loss in OHS (28):

- ↓ Daytime hypercapnia ($PaCO_2$)
- ↑ Oxygenation (PaO_2)
- ↓ AHI (Apnea-Hypopnea Index)
- ↓ Blood pressure and cardiovascular risk
- ↑ Survival and reduced hospitalizations

2. Pharmacologic Therapy (29):

- Weight-loss medications (e.g., GLP-1 receptor agonists like liraglutide or semaglutide) may benefit selected patients with OHS.
- Must be used alongside dietary and behavioral modifications.
- Limited data specific to OHS, but effective in obesity and OSA**.**

3. Bariatric Surgery (30, 31):

- Most effective long-term weight loss strategy for severe obesity and OHS.
- Leads to significant improvements in:
    - $PaCO_2$ and PaO_2

- Sleep-disordered breathing indices
- Need for long-term positive airway pressure therapy

- Surgery types: Roux-en-Y gastric bypass**,** sleeve gastrectomy.

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