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STATE OF THE ART REVIEW ON PEDIATRIC OBESITY HYPOVENTILATION SYNDROME

PAPP TASK FORCE ON SLEEP DISORDERED BREATHING 2024 - 2027

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Pediatric Obesity Hypoventilation Syndrome: Definition and Epidemiology

Obesity Hypoventilation Syndrome (OHS) is typically defined as the presence of awake hypoventilation ($PaCO_2$ >45 mm Hg) combined with obesity (BMI > 30 kg/m^2 or 95th percentile for age and sex in children) in the absence of alternative hypoventilation causes (e.g. lung parenchymal or airway disease, chest wall disorder other than mass loading from obesity, cardiac, neurologic, pharmacologic).[1] OHS has become a greater concern among children and adolescents with the increasing prevalence of severe obesity.[2]

In 2019, the Philippines has prevalence rates of overweight and obesity at 8.6% and 3.1% respectively in children , with 9.2% boys and 8.6% girls classified as overweight, and 4.3% boys and 3.1% girls categorized as obese.[3] The population prevalence of OHS among children is unknown; however, studies in adults suggest that 13–20% of patients evaluated for OSA and 31% with BMI >35 kg/m^2 have OHS.[4,5,6,7] In children, the prevalence is difficult to determine, but extrapolating from these adult data and work in children by Rosen and colleagues, the prevalence of OHS among obese children may be as high as 3–5%.[8]

[1] American Academy of Sleep Medicine. International classification of sleep disorders, text revision (ICSD-3-TR). American Academy Of Sleep Medicine. International Classification of Sleep Disorders, third edition, text revision (ICSD-3-TR). AASM. 2023.
[2] Lang JE, Bhammar D. Obesity and Lung Health in Children. InObesity and Lung Disease: A Guide to Pathophysiology, Evaluation, and Management 2024 May 28 (pp. 321-345). Cham: Springer International Publishing.
[3] World Obesity Federation. World Obesity Federation Global Obesity Observatory [Internet]. 2022.
[4] Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, Weitzenblum E. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest. 2001 Aug;120(2):369-76. doi: 10.1378/chest.120.2.369. PMID: 11502631.
[5] Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007 Jun;11(2):117-24. doi: 10.1007/s11325-006-0092-8. PMID: 17187265.
[6] Nowbar S, Burkart KM, Gonzales R, Fedorowicz A, Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004 Jan 1;116(1):1-7. doi: 10.1016/j.amjmed.2003.08.022. PMID: 14706658.
[7] Lang JE, Bhammar D. Obesity and Lung Health in Children. In Obesity and Lung Disease: A Guide to Pathophysiology, Evaluation, and Management 2024 May 28 (pp. 321-345). Cham: Springer International Publishing.
[8] Rosen CL. Clinical features of obstructive sleep apnea hypoventilation syndrome in otherwise healthy children. Pediatric pulmonology. 1999 Jun;27(6):403-9.

The classic definition of OHS based on a single *awake* $PaCO_2$ measurement has been redefined due to two overly restrictive reasons. First, pain and anxiety may trigger acute hyperventilation which can result to inaccurate lower $PaCO_2$ levels.[9] Second, hypoventilation may be predominantly nocturnal, with $PaCO_2$ normalizing shortly after waking as ventilation improves during wakefulness. [9]

Because of these two reasons, a serum bicarbonate (HCO_3^-) level >27 mmol/L has been proposed as a sensitive marker of chronic hypoventilation—analogous to "glycosylated hemoglobin" for CO_2 burden. Many patients with clinically significant nocturnal hypoventilation have normal daytime $PaCO_2$ but elevated bicarbonate. For early/low-severity disease, the ERS classification therefore incorporates bicarbonate and sleep hypoventilation rather than relying on daytime $PaCO_2$ alone. Consistent with this, the American Thoracic Society (ATS) 2019 guideline recommends including serum bicarbonate <27 mmol/L as a screening test which can aide in excluding OHS, and to undertake more extensive investigations (arterial blood gases and sleep studies) in individuals with serum bicarbonate level above 27 mmol/L.[9]

[9] Mokhlesi B, et al. Evaluation and Management of Obesity Hypoventilation Syndrome: An Official American Thoracic Society Clinical Practice Guideline. *American Journal of Respiratory and Critical Care Medicine.* 2019.

Pediatric Obesity Hypoventilation Syndrome: Pathophysiology

Obesity hypoventilation syndrome (OHS) in children is a multifactorial disorder defined by obesity, sleep-disordered breathing—most commonly obstructive sleep apnea (OSA)—and chronic daytime hypoventilation with resultant hypercapnia. Diurnal hypercapnia is a defining feature and should prompt evaluation after excluding alternative respiratory, neuromuscular, or metabolic causes. [10] OHS has long been studied and was first described in 1955; since then, extensive research has clarified the complex pathophysiological mechanisms underlying the disease. Normal sleep physiology involves reduced upper airway muscle tone, increased upper airway resistance, decreased tidal volume and respiratory rate, and greater reliance on chemical control of breathing.[11] In healthy children, these sleep-related changes produce modest, well-tolerated hypoxemia and hypercapnia, particularly during deeper sleep and REM. When excess adiposity is present, however, the added mechanical load on the chest wall and diaphragm reduces ventilatory capacity and reserve and compounds the normal sleep-related reduction in minute ventilation, promoting maladaptive nocturnal hypoventilation. Impaired central respiratory drive further diminishes the ability to respond to rising carbon dioxide, worsening nocturnal and daytime gas exchange, while sleep-disordered breathing such as OSA intermittently obstructs the airway and amplifies nocturnal hypoxemia and hypercapnia. The core pathophysiology of pediatric OHS therefore reflects three interrelated mechanisms—excessive mechanical load, impaired central drive, and sleep-related breathing abnormalities—that act synergistically to produce progressive ventilatory impairment and eventual sustained daytime hypercapnia. Neurohormonal and genetic factors likely influence individual susceptibility and disease severity. [11,12]

[10] Li AM, Chan KCC, editors. Paediatric sleep disorders: Case-based practical guide. 1st ed. Cham: Springer; 2022.
[11] Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. Respir Care. 2010;55(10):1347–1365.
[12] Mokhlesi B, Tulaimat A. Recent advances in obesity hypoventilation syndrome. Chest. 2007;132(4):1322–1336. doi:10.1378/chest.07-0027

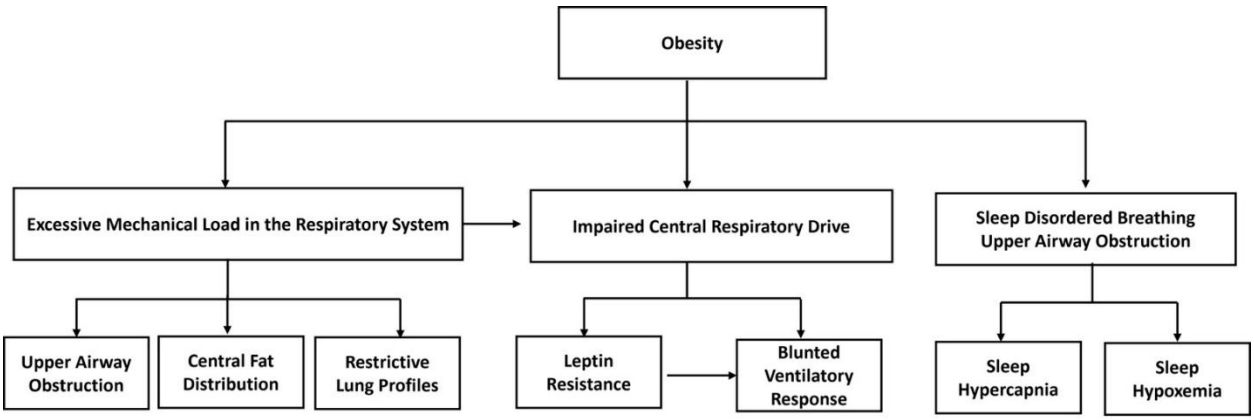

Figure 1. Pathophysiology of OHS

Excessive mechanical load on the respiratory system

Upper airway obstruction

Approximately 90% of patients with obesity hypoventilation syndrome (OHS) have coexisting obstructive sleep apnea (OSA), demonstrating upper-airway obstruction during sleep. They have been observed to exhibit higher upper-airway resistance in both upright (sitting) and supine positions compared with eucapnic individuals with OSA.[13]

Central fat distribution

Patients with OHS have a higher degree of central fat distribution which affects respiratory mechanics.[1,14] This pattern of adiposity results in a more cephalad displacement of the diaphragm leading to inefficient mechanical performance. This is further worsened in the supine position. Centrally distributed weight also reduces lung volumes to a much greater degree than weight deposited peripherally. This would contribute to greater reductions in lung volumes and more marked mechanical ventilatory constraints.

[13] Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183(3):292–298. doi:10.1164/rccm.201008-1280CI

[14] Orozco González BN, Rodriguez Plascencia N, Palma Zapata JA, Llamas Domínguez AE, Rodríguez González JS, Diaz JM, Ponce Muñoz M, Ponce-Campos SD. Obesity hypoventilation syndrome, literature review. Sleep Adv. 2024;5(1):zpae033. doi:10.1093/sleepadvances/zpae033

Restrictive lung profiles and increased work of breathing

Patients show low FVC and FEV1 and a normal FEV1/FVC ratio consistent with a restrictive ventilatory defect. These changes in lung function stem from a combination of abnormal chest wall mechanics and diminished respiratory muscle strength. Additionally, functional residual capacity (FRC), total lung capacity (TLC), and expiratory reserve volume (ERV) are also reduced.[1] A low ERV may lead to small airway closure and air trapping, contributing to expiratory flow limitation and the development of intrinsic positive end-expiratory pressure (PEEPi/auto-PEEP). These changes, again, are more marked in the supine position further increasing the work of breathing during sleep.

The characteristic breathing pattern in OHS, often shallow and rapid, further contributes to increased dead space ventilation. Decreased ventilation of the lower lobes coupled with decreased FRC may lead to ventilation-perfusion (V/Q) mismatch, aggravating oxygen desaturations and ultimately leading to hypoxemia.

Altogether, these mechanical limitations significantly increase the respiratory load during sleep, playing a key role in the development and progression of hypoventilation in OHS.

Impaired central respiratory drive

Blunted hypercapnic and hypoxic ventilatory response

The chemical control of breathing becomes the predominant driver of ventilation in sleep and alterations in oxygen and carbon dioxide can easily be tolerated by normal individuals bringing a picture of relative hypoxemia and hypercapnia.[15] OHS patients, however, have been found to have impaired central respiratory drive and have problems with normalizing PaCO2 levels via compensatory mechanisms.[5] This said increase in respiratory rate in response to hypoxia and hypercapnia is diminished.[15] This blunted chemosensitivity contributes significantly to the pathogenesis of chronic hypoventilation and hypercapnia.

Leptin resistance

Leptin is a hormone produced by adipose tissue that acts on hypothalamic receptors to regulate appetite and stimulate ventilation. Animal studies using leptin-deficient ob/ob mice show features resembling OHS, including impaired respiratory mechanics, reduced ventilatory responsiveness, and awake hypercapnia, which improve with leptin replacement.[2,4] These findings support leptin's role as a respiratory stimulant in mammals. In humans with obesity, circulating leptin levels are typically elevated rather than deficient, reflecting increased adipose mass and a

[15] Mokhlesi, B., Kryger, M. H., & Grunstein, R. R. (2008). Assessment and management of patients with obesity hypoventilation syndrome. *Proceedings of the American Thoracic Society*, *5*(2), 218-225.

compensatory response to chronic CO2 retention. Despite high serum leptin, many patients with OHS demonstrate impaired respiratory drive and a blunted ventilatory response to hypercapnia, a phenomenon best explained by central leptin resistance.[4]

When leptin signaling to the brain is intact, it reduces appetite, increases energy expenditure, and augments minute ventilation, which can protect against CO2 retention.[2] In contrast, leptin resistance permits progressive ventilatory impairment despite elevated serum leptin.[16]

Sleep-disordered breathing

The presence of sleep-disordered breathing is a key diagnostic component of OHS and may manifest as either obstructive sleep apnea and/or central hypoventilation. Obstructive events can lead to acute hypercapnia, particularly if the post-apnea compensatory hyperventilation is inadequate to blow off the accumulated CO2. Over time, these repeated episodes can lead to chronic awake hypercapnia and other proposed additional mechanism is attributed to an eventual increase in renal bicarbonate concentration.[15] As a response to CO2 retention and inability of the respiratory system to address this by increasing minute ventilation, the renal system responds by decreasing bicarbonate clearance to compensate for acidosis.[17] The resulting cycle of nocturnal hypoventilation, sustained hypercapnia, and compensated respiratory acidosis contributes to the progression of OHS.[15,17]

[16] Kalra SP. Central leptin gene therapy ameliorates diabetes type 1 and 2 through two independent hypothalamic relays; a benefit beyond weight and appetite regulation. *Peptides*. 2009;30(10):1957-1963. doi:10.1016/j.peptides.2009.07.021

[17] Orozco González BN, Rodriguez Plascencia N, Palma Zapata JA, Llamas Domínguez AE, Rodríguez González JS, Diaz JM, Ponce Muñoz M, Ponce-Campos SD. Obesity hypoventilation syndrome, literature review. Sleep Advances. 2024;5(1):zpae033.

Pediatric Obesity Hypoventilation Syndrome: Signs and Symptoms

The clinical signs and symptoms of pediatric Obesity Hypoventilation Syndrome (OHS) range from respiratory, cardiovascular, metabolic and neurologic manifestations. The clinical presentation varies, with severe cases presenting as acute respiratory failure, with or without an underlying pulmonary condition.[18]

Respiratory manifestations

Children with OHS may present with the following: dyspnea on exertion, tachypnea or bradypnea, and exercise intolerance.[1], [19] Chest findings may be normal, but in severe and chronic cases, shallow respiration and signs of respiratory failure may be seen.[20]

The presence of nighttime symptoms of OSA such as chronic snoring, witnessed apnea, breathing struggles, and enuresis, accompanied by daytime hypercapnia in an obese child is highly suggestive of OHS.

Cardiovascular manifestations

Children with OHS have chronic hypoxemia and hypercapnia causing pulmonary vasoconstriction resulting in pulmonary hypertension and right cardiac dysfunction. Blood pressure elevation, jugular venous distention, rales on chest auscultation, loud P2 heart sound and edema of the lower extremities are clinical features suggestive of cor pulmonale.[3]

Neurocognitive symptoms

Impaired focus, memory impairment, and erratic moods are common in OHS patients with OSA due to intermittent hypoxia and nocturnal hypoventilation causing sleep disruption. These may lead to poor academic performance and cause long-term neurodevelopmental deficits.[2,21]

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[18] Witmans M, MacLusky I, Zielinski D, Amin R. Section 10: Obesity hypoventilation in children. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2018 Aug 16;2(sup1):75-7.
[19] Cataletto, M. Sharma, G. et al. Pediatric Hypoventilation Syndrome. 2021. Medscape [Internet]
[20] Fadl AA, Shahatah MA, Asiri AY, Ogran MY, Alyami AT, Alasmari AM, Albishri AM, Alnasser AN, Jadkarim AM, Alrehaili RA, Aljazzar SA. Overview on Pediatric Obesity Hypoventilation Syndrome. Saudi Medical Horizons Journal. 2023 Oct 29;3(3):110-7.
[21] Al-Shamrani A, Alharbi AS. Diagnosis and management of childhood sleep-disordered breathing: Clinical approach. Saudi Medical Journal. 2020;41(9):916.

Metabolic dysfunction

Obesity entails significant metabolic abnormalities such as insulin resistance, dyslipidemia, and hepatic steatosis. Thus, children with OHS have a higher likelihood of having type 2 diabetes, nonalcoholic fatty liver disease, and metabolic syndrome.[22,23]

[22] Kostas K, Alexandra S, Kyriaki K. Childhood obesity and its associations with morbidity and mortality in adult life. Diabetes Compl. 2018;2(4):1-2.
[23] di Palmo E, Filice E, Cavallo A, Caffarelli C, Maltoni G, Miniaci A, Ricci G, Pession A. Childhood obesity and respiratory diseases: which link?. Children. 2021 Feb 25;8(3):177.

Pediatric Obesity Hypoventilation Syndrome: Diagnostic Approach

The diagnosis of pediatric OHS requires a precise, multi-faceted approach that integrates objective physiologic data with targeted ancillary tests to confirm the characteristic triad of: (1) obesity (typically BMI ≥95th percentile for age/sex), (2) awake alveolar hypoventilation with daytime hypercapnia ($PaCO_2$ >45 mmHg), and (3) sleep-disordered breathing. Early and accurate diagnosis is crucial for timely intervention and improved long-term outcomes.[24,25]

The detailed approach below emphasizes the importance of objective physiological data and a systematic investigation to ensure correct and timely diagnosis of pediatric OHS. The focus on specific criteria and the multidisciplinary approach is crucial for effective management and improved patient outcomes.[1,26]

International Classification of Sleep Disorders (ICSD) diagnostic criteria for pediatric OHS[27] (all A–C must be met)

A. Awake hypoventilation

- $PaCO_2$ >45 mmHg while awake, measured by arterial PCO_2, end-tidal PCO_2, or transcutaneous PCO_2.

B. Obesity

- BMI >95th percentile for age and sex in children *(adult threshold: BMI >30 kg/m²)*.

C. Exclusion of other primary causes of hypoventilation

- Hypoventilation is not primarily due to: lung parenchymal/airway disease, pulmonary vascular disease, chest wall disorder *(other than obesity mass loading)*, medications, neurologic disorder, muscle weakness, or known congenital/idiopathic central hypoventilation syndromes.

Notes

1. Polysomnography (PSG) typically shows worsening hypoventilation during sleep when CO_2 is measured.
2. OSA is often present; if present, diagnose both OSA and OHS.
3. Oxygen desaturation is common, but not required for diagnosis.

[24] Verhulst SL, Kheirandish-Gozal L. Pediatric obesity-related respiratory disorders: An updated review. Pediatr Pulmonol. 2024;59(1):10–20.
[25] Javaheri S, et al. Obesity Hypoventilation Syndrome: Pathophysiology and diagnosis in pediatrics. Chest. 2024;165(3):734–742.
[26] Kaditis AG, et al. Pediatric OSA and OHS: Clinical presentation and diagnostic pathways. Eur Respir J. 2024;63(1):2201790.
[27] Sateia MJ. International classification of sleep disorders. Chest. 2014 Nov 1;146(5):1387-94.

4. Based on the recent ERS and ATS recommendation, serum bicarbonate has been recommended as a screening test for OHS. It should be noted that serum bicarbonate levels above 27 mmol/L is suggestive of a diagnosis of OHS.

Predisposing and precipitating factors

- Obesity is the main driver of hypoventilation and hypoxemia; greater obesity often correlates with more severe sleep-related hypoventilation, though severity varies between individuals.
- CNS depressants (e.g., alcohol, anxiolytics, hypnotics) can worsen respiratory impairment.
- Children who are hypercapnic/hypoxemic while awake typically worsen during sleep—especially REM—but awake values do not reliably predict the degree of nocturnal desaturation in an individual patient.

Differential Diagnosis [27]

The differential diagnosis of pediatric OHS includes any condition that can cause awake and/or sleep-related hypoventilation, particularly:

1) Pulmonary and vascular causes

Disorders of the airways, lung tissue, or pulmonary circulation can reduce effective gas exchange or increase ventilatory load, leading to CO_2 retention and hypoventilation—sometimes mimicking OHS.

2) Neuromuscular and chest wall causes

Conditions that weaken the respiratory muscles (e.g., diaphragm weakness) or mechanically restrict chest expansion (e.g., scoliosis/chest wall deformity) can cause chronic hypoventilation independent of obesity.

3) Endocrine/metabolic causes

Severe untreated hypothyroidism can blunt ventilatory drive and weaken respiratory muscles, producing hypoventilation and hypercapnia that may improve with thyroid replacement.

4) Medication/substance-related causes

Respiratory depressants (sedatives, opioids, alcohol, hypnotics) reduce central respiratory drive and can worsen nocturnal hypoventilation or trigger hypercapnia, especially in obese patients.

5) Central hypoventilation syndromes

These are disorders of impaired central ventilatory control (congenital or idiopathic) where breathing drive is inadequate, particularly during sleep, causing sustained hypercapnia even without airway obstruction.

6) Obesity-related syndromic causes to consider

Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD and Prader–Willi syndrome can present with severe pediatric obesity and abnormal ventilatory control/sleep-disordered breathing; identifying them matters because management and prognosis extend beyond typical OHS care.

Pediatric Obesity Hypoventilation Syndrome: Treatment Approach

The multidisciplinary approach to treatment of OHS mainly focuses on addressing the underlying mechanisms which are obesity, and sleep breathing disorder. Weight reduction, lifestyle modifications and management of OSA and non-obstructive hypoventilation with medical measures such as positive airway pressure (PAP) therapy, surgical interventions, and pharmacotherapy are the different modalities which can mitigate OHS. If left untreated, cardiovascular risks increase, leading to further complications.

The treatment goals for OHS include: achieving normocapnia during sleep and awake states; prevention of oxyhemoglobin desaturation; reversal of complications namely erythrocytosis and cor pulmonale; and relief of excessive daytime sleepiness.[28] Up to this date, only limited research studies are available in the management of OHS amongst children, unlike in the adult literature. There is insufficient evidence on the outcomes, costs, and benefits with the use of PAP therapies on the pediatric population diagnosed with OHS. Currently, conclusions and recommendations created on the potential benefits of these treatments are based on adult studies or consensus views of experts in the field.[29]

Positive Airway Pressure (PAP) Therapy

Positive airway pressure therapies are considered the first-line treatment for OHS. It is indicated in all patients with OHS and it should not be delayed during the weight reduction program.[1]

The different modes of PAP therapy are continuous positive airway pressure (CPAP), bilevel positive airway pressure (Bilevel PAP) or other advanced PAP such as auto adjusting Bilevel PAP. Although the criteria in choosing which treatment modality is indicated for a particular OHS is not consistently applied across the board, different panels have recommended that initiation of CPAP is the first line of treatment on patients with concomitant OSA. OSA usually occurs within 90% of OHS cases.[1,30,31,32,33]

CPAP is the initial treatment of choice for patients who are clinically stable and not in acute respiratory failure, with $PaCO_2$ levels at <55 mm Hg. For patients who do not satisfy these criteria

[28] Egea-Santaolalla C, Javaheri S. Obesity hypoventilation syndrome. Current Sleep Medicine Reports. 2016 Mar;2(1):12-9.
[29] Witmans M, MacLusky I, Zielinski D, Amin R. Section 10: Obesity hypoventilation in children. Canadian Journal of Respiratory, Critical Care, and Sleep Medicine. 2018 Aug 16;2(sup1):75-7.
[30] Pépin JL, Baillieul S, Tamisier R. Obesity hypoventilation syndrome: current status and future directions for optimizing care of a complex and diverse condition (a narrative review). Sleep Medicine. 2025 Mar 30:106491.
[31] Shetty S, Parthasarathy S. Obesity hypoventilation syndrome. Current pulmonology reports. 2015 Mar;4:42-55.
[32] Mokhlesi B, Kryger MH, Grunstein RR. Assessment and management of patients with obesity hypoventilation syndrome. Proceedings of the American Thoracic Society. 2008 Feb 15;5(2):218-25.
[33] Crummy F, Piper AJ, Naughton MT. Obesity and the lung: 2· Obesity and sleep-disordered breathing. Thorax. 2008 Aug 1;63(8):738-46.

and with evidence of primary non-obstructive hypoventilation, Bilevel PAP is recommended.[1,3,4,5,6]

Auto adjusting PAP titration has the advantage of eliminating laboratory-based titration in adult patients with uncomplicated OSA. However, there are disadvantages in this mode of titration, namely: it requires further studies to confirm its applicability and effectiveness amongst the pediatric population, and more importantly, auto adjusting PAP machines cannot determine hypercapnic and hypoxemic states in OHS. Thus, with these major limitations, auto adjusting PAP titration is not recommended in OHS patients.

PAP titration is a fundamental element in the management of OHS, therefore establishing a standard procedure is essential. It has also been recommended that laboratory-based titration of positive airway pressures and supplemental oxygen be done in managing OHS.[34]

Continuous Positive Airway Pressure (CPAP) Therapy

CPAP therapy enhances nocturnal gas exchange by preventing episodes of obstructive apnea and hypopnea while decreasing the respiratory effort associated with small airway closure and expiratory flow limitations.[4,7] CPAP prevents respiratory failure during awake states by reducing hypercapnia caused by sleep related obstruction.[4]

Studies have shown significant improvement in various physiologic parameters such as, gas exchange during wakefulness and ventilatory response to both hypoxia and hypercapnia. Overall, improvement of health-related quality of life has also been reported.[4] Studies on CPAP therapy have major limitations, specifically, only retrospective designs with limited sample size have been written to highlight its effectiveness in OHS.

Close monitoring of patients under CPAP treatment is recommended during the first 2-3 months after initiation of therapy. There should be a serious consideration of transitioning to Bilevel PAP if the patient is non responsive to initial CPAP treatment. CPAP treatment failure is characterized by persistent hypercapnia, hypoxemia and recurrent hospitalization secondary to acute on chronic respiratory failure.[3] However, patients with poor compliance or with poor adherence should not be classified as CPAP treatment failure.

Bilevel Positive Airway Pressure (Bilevel PAP) Therapy

Bilevel PAP is recommended for patients who are classified as CPAP non responders. The risk factors contributing to non-responsive CPAP treatment are: BMI >40, higher carbon dioxide

[34] Fadl AA, Shahatah MA, Asiri AY, Ogran MY, Alyami AT, Alasmari AM, Albishri AM, Alnasser AN, Jadkarim AM, Alrehaili RA, Aljazzar SA. Overview on Pediatric Obesity Hypoventilation Syndrome. Saudi Medical Horizons Journal. 2023 Oct 29;3(3):110-7.

levels, lower nocturnal oxygen saturation, and hypoxemia.[1,35] Although Bilevel PAP is the initial recommendation in treating CPAP non responders, a potential shift to CPAP on a long-term management of OHS can be considered.[1,6]

The benefits of Bilevel PAP over CPAP therapy are: additional inspiratory support which increases the tidal volume, and provision of "back-up" respiratory rate, particularly when inspiratory efforts are decreased in REM stage.[4,6,7] Moreover, Bilevel PAP therapy reduces the inspiratory muscles workload by decreasing the diaphragmatic strain by 40%.[4]

In Bilevel PAP therapy, regulated and distinct pressures are applied during inspiratory phase (IPAP) and expiratory phase (EPAP). IPAP is higher than EPAP to facilitate alveolar aeration, while EPAP prevents obstructive events. A common target difference of at least 6 to 7 cm H_2O between IPAP and EPAP is necessary for Bilevel PAP therapy to be optimally effective in managing OHS.[4]

In summary, Bilevel PAP is strongly considered as primary treatment amongst OHS patients with the following conditions: failure to initial CPAP therapy, primary component of non-obstructive hypoventilation, and severe hypercapnia with ineffective CPAP treatment.[3,4,5]

PAP Adherence

PAP adherence is an important modifiable factor that can greatly affect treatment efficacy. Research conducted on adult populations revealed that patients using PAP device for more than 4.5 hours have substantial improvement on $PaCO_2$ and PaO_2 levels comparing to patients with lower adherence.[36] In the research study done by Sullivan et al., positive effects of CPAP such as reduction in daytime sleepiness and mental dysfunction, and resolution of right heart failure were evident a few days after initiation of treatment.[37]

Another study reported that after 3 to 6 months of CPAP therapy, patients with OHS experienced an improved quality of life. Further studies have shown notable improvements in daytime sleepiness, and other objective parameters such as arterial blood gases, lung volumes, and pulmonary function test results.[9]

Oxygen Therapy

Obesity Hypoventilation Syndrome is characterized by extended periods of sustained hypoxemia during sleep and wake periods. Supplemental oxygen in conjunction with PAP therapy

[35] McKim D, Road J, Avendano M, Abdool S, Côté F, Duguid N. (2011). Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J, 18:197–215.
[36] Al Dabal L, BaHammam AS. Obesity hypoventilation syndrome. Annals of thoracic medicine. 2009 Apr 1;4(2):41-9.
[37] Sullivan C, Berthon-Jones M, Issa F, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. The Lancet. 1981 Apr 18;317(8225):862-5.

may be required in some patients to maintain oxygen saturation levels above 90%.[7] Administration of supplemental oxygen may prove beneficial in patients with persistent hypoxemia despite relief from upper airway obstruction with PAP therapy. This will prevent long-term adverse effects of hypoxemia in the pulmonary vasculature, and other vital organs. It is important to note that oxygen therapy alone cannot resolve the underlying hypoventilation and upper airway obstruction. Therefore, it is not recommended as a single therapy for OHS, due to its clinical insufficiency.[1,3,6,9,38]

Oxygen as a single therapy decreases ventilation, increases apnea-hypopnea index, particularly during REM sleep, and increases nocturnal CO_2 levels. This state of nocturnal hypercapnia leads to impairment of sleep quality. Moreover, oxygen treatment alone has detrimental effects by increasing the risk of decompensated respiratory failure.[1,3,6,9,11]

Hypercapnia can be worsened by high oxygen concentration through several mechanisms. An increase in the fraction of inspired oxygen can lead to reduced minute ventilation and subsequently lower tidal volume due to the inhibition of peripheral chemoreceptors activity. The oxygenation of hypoxic regions in the lungs leads to vasodilation, which alters blood flow to previously poorly ventilated areas, causing an increase in dead space. The Haldane effect reduces the affinity of hemoglobin to carbon dioxide and decreases correction of hypoxia, resulting to a greater release of CO_2 into the plasma, thus exacerbating hypercapnia.[11]

Weight Reduction

Obesity causes changes in the mechanical properties of the lungs and chest wall. It substantially alters pulmonary function by decreasing lung volumes, increasing the airway resistance, and affecting the gas exchange. Given these primary pulmonary effects of obesity, it is therefore recommended that weight reduction and lifestyle modification are one of the main approaches to treatment of OHS.

An important component in the multidisciplinary approach to weight reduction is professional counseling. This entails providing information on healthy eating habits, balanced and nutritious diet, weight loss exercise programs, healthcare risks associated with obesity, and importance of a healthy lifestyle and maintenance of ideal body weight.

Several studies have reported positive outcomes of weight loss, highlighting its significant improvements in lung function and gas exchange.[1,4,7]

A systematic review by Kakazu et al. conditionally recommended that a target of sustained weight loss between 25-30% of actual body weight should be followed in weight reduction

[38] Athayde RAB, Oliveira Filho JRB, Lorenzi Filho G, Genta PR. Obesity hypoventilation syndrome: a current review. J Bras Pneumol. 2018 Nov-Dec;44(6):510-518. doi: 10.1590/S1806-37562017000000332. PMID: 30726328; PMCID: PMC6459748.

programs amongst OHS patients.[39] This recommendation was based on low quality evidence conducted on adult populations. At present, high quality research studies are necessary to determine the extent of weight loss required to achieve clinically relevant outcomes in patients diagnosed with OHS. Likewise, clinically important researches on weight reduction should be conducted in pediatric populations.

Surgery is a treatment option in patients whom lifestyle modification is inadequate to manage obesity.[1] Bariatric surgery is considered the most effective method in achieving significant sustainable weight loss over time particularly those with morbid obesity (BMI >40 kg/m²).[40]Although several studies revealed surgical weight loss can lead to substantial increase in lung volumes, specifically on expiratory reserve capacity and showed improvements in gas exchange, only few studies have investigated the surgical outcomes in OHS cases.[7] In bariatric surgery, potential risk versus favorable outcome on weight loss should be considered in making a clinical decision. However, even after successful resolution of OHS following surgical intervention, OSA may be a continuing problem.[13]

In the pediatric population, especially those in the younger years, bariatric surgery is not recommended as first-line of treatment. It is a viable alternative if other therapies have proven ineffective or when substantial comorbidities exist. Upon consideration of this option, a holistic and multidisciplinary approach is advised.[41]

Tracheostomy

Tracheostomy can effectively alleviate obstructive events associated with sleep-disordered breathing by bypassing the upper airway obstruction.[4] While upper airway obstruction is a contributor to chronic hypoventilation in OHS patients with co-existing OSA, not all patients achieve eucapnia post tracheostomy. Other contributing factors of OHS include obesity, which leads to ongoing CO_2 production, and potentially weakens the respiratory muscles.[1]

Currently, tracheostomy is reserved for managing refractory OHS in the presence of treatment failure. This is primarily due to the risks and complications associated with this procedure, particularly in obese patients.[4,11]

[39] Kakazu MT, Soghier I, Afshar M, Brozek JL, Wilson KC, Masa JF, Mokhlesi B. Weight Loss Interventions as Treatment of Obesity Hypoventilation Syndrome. A Systematic Review. Ann Am Thorac Soc. 2020 Apr;17(4):492-502. doi: 10.1513/AnnalsATS.201907-554OC. PMID: 31978317.

[40] Ramírez Molina VR, Masa Jiménez JF, Gómez de Terreros Caro FJ, Corral Peñafiel J. Effectiveness of different treatments in obesity hypoventilation syndrome. Pulmonology. 2020 Nov-Dec;26(6):370-377. doi: 10.1016/j.pulmoe.2020.05.012. Epub 2020 Jun 16. PMID: 32553827.

[41] Mazur A, Zachurzok A, Baran J, Dereń K, Łuszczki E, Weres A, Wyszyńska J, Dylczyk J, Szczudlik E, Drożdż D, Metelska P. Childhood obesity: position statement of polish society of pediatrics, polish society for pediatric obesity, polish society of pediatric endocrinology and diabetes, the college of family physicians in Poland and polish association for study on obesity. Nutrients. 2022 Sep 15;14(18):3806.

Pharmacotherapy

In pediatric OHS, pharmacological treatment options are limited, with respiratory stimulants such as medroxyprogesterone and acetazolamide. These are being regarded as supplementary treatment. Nevertheless, their use is not broadly endorsed owing to insufficient data and associated risks.

Medroxyprogesterone, a synthetic analogue of progesterone, improves respiration by increasing the ventilatory response to hypercapnia. It may be advantageous for managing OHS patients by reducing the AHI and enhancing the ventilatory response to hypercapnia. Treatment results for OHS patients have been inconsistent, with some individuals exhibiting a reduction in $PaCO_2$ while others show no improvement in $PaCO_2$, minute ventilation, or the ventilatory response to hypercapnia. Most OHS patients may normalize $PaCO_2$ with forced hyperventilation; however, mechanical complications may hinder this process. Medroxyprogesterone is reported to increase the risk of venous thromboembolism, hence restricting its use.[7]

Acetazolamide is a diuretic that inhibits carbonic anhydrase, enhances HCO_3 excretion, and induces metabolic acidosis, hence stimulating ventilation. This is due from a leftward shift in the CO_2 response curve, rather than an alteration in the slope of the ventilatory response to hypercapnia. Acetazolamide may be useful in treating OHS to prevent the start of metabolic alkalosis, correct the right shift in the CO_2 response curve, and reduce the frequency of obstructive events, similar to how it manages moderate-to-severe OSA patients.[7]

Pediatric Obesity Hypoventilation Syndrome: Follow-up care

Patients with OHS should be followed clinically to assess their response to noninvasive positive airway pressure (PAP) therapy and/or weight loss, typically at intervals such as every six months. This guidance applies to adults and is not specific to pediatric cases. Because the duration of therapy is usually indeterminate and often lifelong, follow-up must remain ongoing. The required level of support may change over time depending on factors such as weight loss or gain, medication changes, and the development or treatment of comorbidities.

Follow-up after noninvasive PAP – Follow-up for patients on PAP focuses on ensuring that device settings are appropriate and that adherence is adequate. Visits should include assessment of symptoms, repeat arterial blood gases (ABG), and, in selected cases, repeat polysomnography to reassess ventilatory requirements and optimize therapy.[42]

Follow-up after weight loss – Even substantial weight loss rarely eliminates the need for nocturnal ventilatory support. Long-term PAP is usually still required, although many patients can be managed with lower pressure settings or transitioned from bilevel PAP to continuous PAP. Reassessment of OHS is recommended after significant weight loss (for example, within one to two years after bariatric surgery). Evaluation should include ABG to measure awake $PaCO_2$ and arterial oxygen tension, as well as in-laboratory polysomnography to confirm appropriate PAP and supplemental oxygen settings. Early, rapid postoperative weight loss (typically 45–70% of excess body weight in the first year) is often associated with improvement in OHS. However, this is not universal, and some patients have residual OSA despite symptomatic improvement. PAP therapy should not be discontinued after weight loss unless polysomnography confirms the absence of clinically significant OSA or hypoventilation.[1]

The therapeutic goals for patients with OHS include[43]:

- Normalization of $PaCO_2$ during wakefulness and sleep (target < 45 mmHg).
- Elimination of oxyhemoglobin desaturation during wakefulness and sleep, using the lowest supplemental oxygen flow needed to maintain saturation ≥ 90% while avoiding worsening hypercapnia.
- Relief of OHS symptoms, typically daytime hypersomnolence.
- Prevention of complications such as erythrocytosis, pulmonary hypertension, and right heart failure.
- Treatment of underlying OSA (eliminating obstructive apneas and hypopneas) or sleep-related hypoventilation.
- Improvement of sleep architecture and quality, reduction of nocturnal work of breathing, and provision of respiratory muscle rest.

[42] Fujita Y, Yamauchi M, Muro S. Assessment and management of continuous positive airway pressure therapy in patient with obstructive sleep apnea. Respiratory Investigation. 2024 Jul 1;62(4):645-50.

[43] Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, Buyse B, De Backer W, Eckert DJ, Grote L, Hagmeyer L, Hedner J, Jennum P, La Rovere MT, Miltz C, McNicholas WT, Montserrat J, Naughton M, Pepin JL, Pevernagie D, Sanner B, Testelmans D, Tonia T, Vrijsen B, Wijkstra P, Levy P Eur Respir J. 2017 Jan;49(1)

Pediatric Obesity Hypoventilation Syndrome: Complications

Obstructive Hypoventilation Syndrome (OHS), if left untreated, has the potential to result in significant long-term complications that affect multiple organ systems thus impacting the overall health of the patient. Recognizing and managing OHS early is essential to prevent these complications. These complications include:

Respiratory Complications

Inadequate ventilation can result in severe nocturnal hypoxemia which eventually lead to increased daytime lethargy. This can have a negative impact on quality of life and cognitive function. Additionally, co-existing pulmonary conditions like bronchial asthma and/or having respiratory infections may worsen lung function resulting in more frequent exacerbations and hospitalizations.

Cardiovascular Complications

One of the most prevalent cardiovascular complications of pediatric OHS is the development of pulmonary hypertension. This results from chronic hypoxia and increased vascular resistance. Chronic hypoxia and increased vascular resistance raise pressure on the right side of the heart. Over time, this can lead to right ventricular enlargement and eventually heart failure if left untreated. This significantly increases morbidity, and has overall early mortality compared to non-hypercapnic patients with sleep-disordered breathing alone.[44] Moreso, children with OHS have an elevated risk of cardiac arrhythmias, congestive heart failure (CHD) and ischemic heart disease (IHD).[45] In general, cardiovascular diseases are reported to be the leading cause of mortality in OHS populations.

Metabolic Complications

Children with OHS face an increased risk of insulin resistance due to chronic metabolic dysfunction. The persistent hypercapnia and hypoxia can impair glucose metabolism leading to reduced glucose tolerance. Concurrently, obesity, particularly with considerable visceral fat deposition, strongly correlates to insulin resistance—a critical component in metabolic syndrome.

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[44] Umer A, Kelley GA, Cottrell LE, Giacobbi P Jr, Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health. 2017 Aug 29;17(1):683. doi: 10.1186/s12889-017-4691-z. PMID: 28851330; PMCID: PMC5575877.

[45] Zheng Y, Phillips CL, Sivam S, Wong K, Grunstein RR, Piper AJ, Yee BJ. Cardiovascular disease in obesity hypoventilation syndrome - A review of potential mechanisms and effects of therapy. Sleep Med Rev. 2021 Dec;60:101530. doi: 10.1016/j.smrv.2021.101530. Epub 2021 Aug 3. PMID: 34425490.

Studies show that metabolic syndrome components, particularly higher fasting glucose levels, are frequent among obese children with OHS.[46],[47]

Additionally, dyslipidemia is another prevalent metabolic issue in children with OHS. The combination of obesity and hypoventilation may lead to increased triglycerides and reduced high-density lipoprotein (HDL) cholesterol levels. This condition leads to the risk of cardiovascular illnesses later in life.[48]

Other Adverse Events

Long-standing systemic inflammation and metabolic dysfunction may contribute to neurodegenerative processes and cognitive deterioration.[49] Metabolic abnormalities might adversely affect brain health and function. Persistent low oxygen levels may result in neuronal injury and disrupted brain development, leading to learning difficulties and behavioral problems.[50,51]

[46] Weiss R, Caprio S. The metabolic consequences of childhood obesity. Best Pract Res Clin Endocrinol Metab. 2005 Sep;19(3):405-19. doi: 10.1016/j.beem.2005.04.009. PMID: 16150383.
[47] Yeste D, Carrascosa A. Obesity-related metabolic disorders in childhood and adolescence. InAnales de pediatria (Barcelona, Spain: 2003) 2011 May 14 (Vol. 75, No. 2, pp. 135-e1).
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[49] Bhat ZF, Morton JD, Mason S, Bekhit AEA, Bhat HF. Obesity and neurological disorders: Dietary perspective of a global menace. Crit Rev Food Sci Nutr. 2019;59(8):1294-1310. doi: 10.1080/10408398.2017.1404442. Epub 2017 Dec 19. PMID: 29257910.
[50] Logan NE, Ward-Ritacco CL. The Developing Brain: Considering the Multifactorial Effects of Obesity, Physical Activity & Mental Wellbeing in Childhood and Adolescence. Children (Basel). 2022 Nov 24;9(12):1802. doi: 10.3390/children9121802. PMID: 36553249; PMCID: PMC9776762.
[51] Logan NE, Raine LB, Drollette ES, Castelli DM, Khan NA, Kramer AF, Hillman CH. The differential relationship of an afterschool physical activity intervention on brain function and cognition in children with obesity and their normal weight peers. Pediatr Obes. 2021 Feb;16(2):e12708. doi: 10.1111/ijpo.12708. Epub 2020 Aug 16. PMID: 33249759.

Pediatric Obesity Hypoventilation Syndrome: Prognosis

Current literature provides limited insights into the morbidity and sequelae associated with Obesity Hypoventilation Syndrome (OHS) in pediatric populations. Conversely, in adults diagnosed with OHS, there is a notable increase in mortality rates, higher hospitalization frequency, diminished health-related quality of life, reduced vigilance, and a heightened incidence of complications such as heart failure, angina, and pulmonary hypertension.[1] Although it is anticipated that children with OHS will similarly face elevated morbidity and mortality rates, potentially leading to a reduced life expectancy, there is a lack of research specifically evaluating outcomes and prognostic factors in this demographic.[52]

Quality of Life Considerations

Reports indicate that both caregivers and children have observed improvements in quality of life following treatment with positive airway pressure therapy in obese children. However, it is important to note that the study assessing these outcomes was not specifically designed to evaluate the effects in children with OHS.[1]

Morbidity Risks

Patients with obesity who also present with hypercapnia are at an increased risk for morbidity compared to their counterparts without hypercapnia. Those with OHS frequently require more medical consultations, increased use of emergency services, longer hospital stays, a higher incidence of intensive care unit (ICU) admissions, greater reliance on invasive mechanical ventilation, and a higher rate of perioperative complications.2

Specifically, compared to obese individuals who do not experience hypoventilation, patients with OHS are at significantly elevated risk for heart, angina pectoris and corpulmonale. The prevalence of pulmonary hypertension in OHS patients has been reported to be as high as 88%, compared to only 15% in those suffering from OSA. Timely diagnosis and treatment of OHS can significantly decrease hospital stay durations from an average of 7.9 days to just 2.5 days annually.2

Mortality Rates

The primary causes of mortality in individuals with OHS include hypercapnic respiratory failure, exacerbated cor pulmonale and pulmonary thromboembolism. Research indicates that patients with OHS who refuse continuous positive airway pressure (CPAP) management have a

[52] Manisha Witmans, Ian MacLusky, David Zielinski & Reshma Amin on behalf of the CTS Pediatric Home Ventilation Guidelines Panel (2018) Section 10: Obesity hypoventilation in children, Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 2:sup1, 75-77

concerningly high mortality rate, reaching up to 46% within 50 months of follow-up. Furthermore, hospitalized patients who do not receive appropriate treatment exhibit a mortality rate of 23% at 18 months, in stark contrast to the 6% mortality rate observed in obese individuals without hypercapnia. However, when patients receive treatment with noninvasive ventilation (NIV), the mortality rate at 18 months drops to just 3%, with rates of 8% and 30% at 2 and 5 years, respectively. Early detection and intervention are crucial in preventing hospital admissions, ICU stays, the need for mechanical ventilation, and ultimately, death.[2]

Limitations

A state-of-the-art review on Obesity Hypoventilation Syndrome (OHS) reveals significant limitations, particularly concerning the scarcity of information and research focused on pediatric populations. While substantial studies have been conducted on OHS in adults, understanding of the syndrome's implications for children remains limited. Most existing literature emphasizes the morbidity and mortality associated with OHS among adults, leaving a notable gap in knowledge regarding the pediatric demographic. This oversight is concerning, as children with OHS may experience different physiological responses and long-term outcomes than adults, potentially leading to severe health consequences if undiagnosed or untreated.

The lack of targeted research and clinical studies on OHS in children restricts the ability to develop age-appropriate diagnostic criteria, effective treatment protocols, and preventive measures tailored to this vulnerable group. Consequently, there is an urgent need for comprehensive studies that explore the prevalence, clinical presentation, and long-term effects of OHS in children, as well as the effectiveness of various therapeutic interventions. Addressing these gaps is crucial to improving the quality of care and health outcomes for pediatric patients suffering from OHS.

Conclusions

Given the current global obesity epidemic, the prevalence of OHS is expected to rise, accompanied by high rates of morbidity and mortality. Despite this, the condition often goes undiagnosed and treatment is frequently delayed. Therefore, maintaining a high index of suspicion is essential for clinicians, as early detection and intervention are critical for enhancing patient outcomes.

This review accentuates the importance of early identification and targeted management strategies, including weight loss, PAP therapy, and oxygen therapy to improve the prognosis of OHS. Given the significant healthcare burdens associated with this condition, it is imperative to address the rising impact of OHS on public health through comprehensive research aimed at refining diagnostic criteria and developing more effective treatment modalities.

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