

## Overview on Pediatric Obesity Hypoventilation Syndrome

Ahmed A. Fadl<sup>1</sup>, Mashaal A. Shahatah<sup>2</sup>, Atheer Y. Asiri<sup>2</sup>, Mohammed Y. Ogran<sup>3</sup>, Ali T. Alyami<sup>4</sup>, Ahmad M. Alasmari<sup>5</sup>, Alaa M. Albishri<sup>2</sup>, Albatul N. Alnasser<sup>6</sup>, Alaa M. Jادكاريم<sup>2</sup>, Renad A. Alrehaili<sup>7</sup>, Shooq A. Aljazzar<sup>7</sup>, Albatol T. Jifri<sup>2</sup>.

<sup>1</sup>Pediatric senior registrar at Doctor Samir Abbas Hospital, Department of pediatrics, Alazhar University hospitals, Cairo. <sup>2</sup>King Fahad armed forces hospital, KSA. <sup>3</sup>King Khalid University, KSA. <sup>4</sup>Najran University, KSA. <sup>5</sup>Ministry of health, KSA. <sup>6</sup>Sulaiman Alrajhi University, KSA. <sup>7</sup>Medical student, Fakeeh College For medical science, KSA.

### ABSTRACT

The relationship between obesity and the onset of persistent daytime alveolar hypoventilation is known as obesity hypoventilation syndrome. This illness results from a complicated interaction between sleep-disordered breathing, reduced respiratory drive, and obesity-related respiratory impairment, and is associated with considerable morbidity and mortality. Extreme obesity has become far more common in the United States and other nations during the past three decades. The prevalence of OHS will inevitably rise considering the global obesity pandemic. When compared to people with sleep apnea, patients with OHS have a poorer quality of life, incur higher medical costs, and are more likely to develop pulmonary hypertension and die young. Even though this illness is associated with severe morbidity and mortality, it is commonly overlooked, and treatment is typically postponed. Clinicians need to keep a high index of suspicion since this syndrome carries a heavy burden of morbidity and mortality, which is reduced by early diagnosis and treatment. The definition and clinical presentation of OHS, a brief overview of its prevalence, a review of current understanding of pathophysiology, and discussion of recent developments in therapeutics will all be included in this review.

**Keyword:** Obesity; hypercapnia; hypoventilation; obesity hypoventilation syndrome, sleep-disordered breathing; positive airway pressure.

### Introduction

The most prevalent nutritional disorder affecting children and adolescents in the US is pediatric obesity. According to growth standards established by the US Centers for Disease Control, the proportion of children in the US who were considered obese has increased by more than threefold during the 1970s [1]. The definition of "obesity" is the deposit and storing of additional fat, whereas "overweight" is defined as weightiness above a weight reference model.

There were no accepted principles for detecting pediatric obesity on the base of extreme body fat; classification regarding weight established on body mass index (BMI) has been often used for both epidemiologic and therapeutic objectives [2]. In America, obesity is now considered to be an epidemic. Despite national initiatives to encourage weight loss, the prevalence of pediatric obesity is rising. Now, 33% of adults are categorized as obese.

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**Address for correspondence:** Ahmed Abdelsamie Fadl, Pediatric senior registrar at Doctor Samir Abbas Hospital, Department of pediatrics, Alazhar University hospitals, Cairo.

**E-mail:** [Dr\\_fadl844@yahoo.com](mailto:Dr_fadl844@yahoo.com)

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Every year, obesity is to blame for 300,000 fatalities as well as a great deal of sickness, lost workdays, and disability. Obese adolescents become obese adults in 80% of cases. After 55 years of follow-up, adolescent obesity predicts a wide variety of unfavorable health outcomes independent of adult weight [3, 4]. Insufficient ventilation is referred to as alveolar hypoventilation. Infants and children with hypoventilation syndromes have a rare but significant range of respiratory control problems [5]. The term "obesity hypoventilation syndrome" (OHS) is used when awake hypercapnia ( $\text{PaCO}_2 > 45 \text{ mm Hg}$ ) first manifests in an obese individual and other probable causes of hypoventilation, have been ruled out. Although the definition of OHS does not currently include sleep-disordered breathing, the sleep breathing of these patients typically exhibits a variety of polysomnographic phenotypes, such as flow restriction leading to obstructive hypoventilation, recurrent frank OSAS with hypercapnia, and eventually hypoventilation throughout all sleep phases [6]. OHS cannot be diagnosed by sleep hypoventilation alone without the presence of daytime hypercapnia. Obese people who experience hypoventilation while sleeping but not awake hypercapnia may really be experiencing a "prodromal" form of OHS that eventually leads to persistent hypercapnia. This may resemble the clinical picture seen in patients with neuromuscular illness and sleep disordered breathing [7- 9]. Ventilatory control in children with the obesity-hypoventilation syndrome has not been examined, but subnormal ventilatory response to hypercapnia is regarded as a component of the condition in adults. In the families of two obese 13-year-old girls with Prader-Willi syndrome, one of whom had recovered from the obesity hypoventilation syndrome and the other of whom had never had hypoventilation, a study investigated the ventilatory response to hypercapnia. Obesity and a family reduced response to hypercapnia are likely two distinct causes of respiratory failure in the child with obesity-hypoventilation syndrome. Only a tiny number of obese patients experience the obesity-hypoventilation syndrome, which may be explained by the hereditary aspect [10- 12]. Although the obesity-hypoventilation syndrome in children is uncommon, it can have catastrophic consequences and has a high death rate. This paper describes a child who had this syndrome and whose condition got better after having an intestinal bypass. According to a review of the literature, this condition requires aggressive treatment if fatalities are to be avoided [13- 15].

### **Obesity Hypoventilation Syndrome**

An important group of respiratory disorders in children and adolescents are hypoventilation syndromes; nevertheless, they are rare to occur but important due to their morbidity. Alveolar hypoventilation is related to hypercapnia. This typically indicates generalized hypoventilation (ventilation at the mouth and nose is also decreased) in the absence of lung illness. From a conceptual standpoint, even brief decreases in ventilation (such those caused by isolated episodes of apnea and hypopnea during sleep) must result in acute hypercapnia during the time of low ventilation [16- 23]. Although the definition of OHS does not currently include sleep-disordered breathing, the sleep breathing of these patients typically exhibits a variety of polysomnographic phenotypes, such as flow restriction leading to obstructive hypoventilation, recurrent frank OSAS with hypercapnia, and eventually hypoventilation throughout all sleep phases [24- 27]. The equilibrium between  $\text{CO}_2$  assembly and dismissal determines the  $\text{PaCO}_2$ . Since short-term PAP therapy relieves hypercapnia without significantly changing body weight,  $\text{CO}_2$  generation, hypercapnia in OHS was completely the result of hypoventilation [28]. However, the precise mechanisms that cause obesity-related hypoventilation in people are complex. There are many different physiologic differences between people with OHS and those who have obesity and/or OSA: Risk factors for pulmonary edema include elevated upper airway resistance, pulmonary edema-related ventilation-perfusion mismatch, low lung volume/atelectasis, reduced vital rejoiner to hypoxemia and hypercapnia, impaired neurohormonal responses, sleep-disordered breathing, and excessive mechanical consignment on the respiratory system [16- 20]. Even while these are clearly present, sleep disturbed breathing and a weakened brain response to hypoxia and hypercapnia provide the strongest evidence for etiology. To explain the onset of this illness, Norman and associates suggested a mathematical model that incorporates sleep disturbed breathing, renal buffering, and central respiratory drive [7].

### **OHS Comorbidities**

The most severe stage of cardiometabolic comorbidities should be considered when defining OHS, according to a recent task force of the European Respiratory Society. After excluding out other potential causes of alveolar hypoventilation, hypercapnia while awake is used as the basis for the

## Overview on Pediatric Obesity Hypoventilation Syndrome

current definition of OHS. Such a claim implies that comorbidities were extremely important since they affect how healthcare resources were used and degrade the treatment outcomes of these patients [23]. Between 55% and 88% of OHS patients have hypertension, which is a fairly high prevalence. Cardiovascular and metabolic disorders are the most frequent associated morbidities, and they are frequently found before OHS is acknowledged. In fact, those diagnosed throughout an acute aggravation of chronic respiratory catastrophe—one of the two clinical presentations of OHS—present with heart failure, pulmonary hypertension, and coronary heart disease, with greater frequency than patients who are referred to a sleep specialist for alleged OSA. These coexisting conditions emphasize how vulnerable OHS patients are even more [24, 26]. The disorder most likely to have a direct relationship with chronic hypoventilation is pulmonary hypertension, which affects nearly half of OHS patients. NIV may be superior to CPAP for treating pulmonary hypertension [28, 29]. According to Corral et al.'s theory, NIV may provide better nighttime hypoventilation regulation than CPAP, resulting in a more pronounced decrease in pulmonary hypertension. With NIV alone, they saw a significant reduction in pulmonary hypertension, which was followed by a concurrent decrease in left ventricular hypertrophy and an upgrade in exercise capacity. Day blood pressure, however, remained unchanged [30, 32]. Plus having major comorbidities, patients diagnosed with OHS also have increased fatality rates. Numerous studies found that untreated OHS patients had an all-cause mortality of 24% at 1.5–2 years. Two observational studies that included individuals with acute-on-chronic hypercapnic respiratory failure found that 1-year death was 18% and 3-year mortality was 31.3% [14, 25].

### Diagnosis and Screening

Great awake PaCO<sub>2</sub> is required to diagnose OHS. Though, since arterial blood gases aren't regularly measured in sleep hospitals and labs and chronic symptoms can resemble uncomplicated OSAS, the illness may go undetected unless physicians have a high catalog of doubt. A formal respiratory evaluation, including arterial blood gases, should be performed as part of the preoperative evaluation in individuals with sleep disorders and individuals who are super obese (BMI > 50) considering this issue, according to available therapeutic guidelines for people experiencing bariatric surgery [33]. Despite these suggestions, the ideal clinical screening approach for identifying OHS in patient populations remains

unknown [7]. Due to costs and a lack of facilities in many countries, simple respiratory observing and auto titrating pressure strategies are being used more and more for the diagnosing and management of OSAS. Though the unmanaged titration of CPAP in OHS is discouraged by current clinical guidelines, it is likely that some patients will be treated in this fashion simply because the disease is not acknowledged. Although some patients may benefit from CPAP, others may continue to experience continuous nocturnal desaturation and hypoventilation, which could lead to a partial or worsening response to therapy [31- 34]. Transcutaneous CO<sub>2</sub> monitoring during sleep is not commonly used in most clinical settings, however the technique can be useful for determining how much CO<sub>2</sub> is stored, particularly during REM sleep. This makes it potentially beneficial for identifying prodromal OHS in obese people. Although thorough calibration is necessary to maintain measurement accuracy, also in very obese patients receiving positive-airway-pressure (PAP) therapy, displaying good agreement with PaCO<sub>2</sub> obtained from arterial blood sampling. But there is not enough data from randomized controlled studies to say whether diagnosing and treating OHS patients with continuous transcutaneous CO<sub>2</sub> monitoring has any clinical advantages beyond only measuring oxygen saturation and awake arterial blood gases [35].

### Management

It is still unclear how best to treat patients with OHS. Medical approaches have classified treatment into two main categories: 1) medical therapies to manage sleep-disordered breathing like PAP, and 2) surgical procedures to support weight loss [36]. Numerous studies have demonstrated benefits in chronic daytime hypoxia and hypercapnia with PAP therapy (CPAP or bi-level PAP). Nearly half of OHS patients require oxygen therapy in addition to PAP therapy when their treatment is initiated. Even though PAP titration is the cornerstone of treatment for patients with OSA and OHS, there is no recognized approach for it. Even while auto adjusting PAP technology can be utilized to avoid laboratory-based titration tests in patients with uncomplicated OSA, this technology cannot be advised for patients with OHS since it is unable to distinguish between hypoventilation and hypoxemia. Therefore, PAP treatment and oxygen titration in a laboratory are necessary for OHS patients [32, 37]. Phlebotomy's application in OHS patients who develop secondary erythrocytosis has not been well investigated. A physiological response to tissue hypoxia that improves the tissue's capacity to carry

## Overview on Pediatric Obesity Hypoventilation Syndrome

oxygen is called secondary erythrocytosis. On the other side, hyperviscosity inhibits oxygen distribution and can offset the benefits of erythrocytosis. Phlebotomy has been recommended if the hematocrit is greater than 65% in adults with congenital cyanotic heart disease, but solely if hyperviscosity complaints were evident [37]. The fact that many hyperviscosity symptoms overlap with OHS symptoms makes it challenging to apply this advice to people with OHS. Secondary erythrocytosis eventually improved with PAP therapy to correct hypoventilation and hypoxemia, and patients with OHS rarely require phlebotomy [38].

### **PAP therapy**

When chronic hypercapnia is primarily caused by upper airway obstruction, morning CO<sub>2</sub> may be reversed with CPAP unaccompanied. If sufficient pressure is used, flow limitation can also occur, which causes protracted hypoventilation and once more responds to CPAP therapy [12]. Titration of CPAP will likely be the main mode of action to restore oxygen capacity and reduce rises in night-time CO<sub>2</sub> levels [39]. The pressure was increased to stop apneas, snoring and hypopneas, and to maintain oxygen inundation. Bilevel treatment was then utilized if continuous desaturation and rising CO<sub>2</sub> levels persist [17]. The amount of airway burden used for inspiration (IPAP) and expiration (EPAP) may be regulated distinctly during bilevel therapy. While EPAP is increased to stop obstructive episodes, IPAP is raised overhead the level of EPAP to encourage alveolar aeration. Between IPAP and EPAP, there should typically be a pressure difference of at least 6 to 7 cm H<sub>2</sub>O [40]. Trials with bilevel treatment have repeatedly demonstrated enhanced awake blood gases, morning sleepiness, and ventilatory response to CO<sub>2</sub>, as well as decreased hospitalisations and improved quality of life when equated to baseline dealings [30-38]. However, randomized trials that compare the clinical results of various treatment methods have produced only a small amount of evidence. These trials have several limitations, including a small sample size (10–36 patients), a short follow-up period (one night to three months), and comparisons that were only made between two types of PAP, in groups with relatively mild OHS based on daytime CO<sub>2</sub> levels. To confirm if the findings of these modest, randomized trials may be extrapolated to the larger OHS population, larger multicenter studies are required. Although the reasons for this are not apparent, several studies have found that girls with OHS had higher discontinuation rates than males do [40, 41]. Finding

the root causes and making sure alternative therapeutic choices were provided to noncompliant PAP patients are crucial, especially in light of the much higher death rate observed for patients with unmanaged OHS compared with those ongoing on treatment [33]. In order to maintain SpO<sub>2</sub> above 90%, a large majority of patients may initially require oxygen therapy in addition to PAP [27]; however, once excellent nighttime breathing is achieved, this demand significantly decreases. Some persons may still have inadequate oxygenation, which is measured as the proportion of recording time with SpO<sub>2</sub> 90%, both when awake and while sleeping, despite improvements in daytime blood gases. Even though daily hypoxemia has been shown to neither increase dyspnea nor daytime sleepiness in one experiment, it has been shown to be an independent predictor of poor survival in OHS both before and after the start of PAP therapy [4, 42]. Consensus on treatment endpoints has not been reached, which has hindered OHS outcomes research up to this date. We don't fully understand what a typical waking PCO<sub>2</sub> level in these individuals looks like, nor do we know how much oxygen desaturation is tolerable or safe while they sleep. An important part of the investigation schedule for the future was to identify and support therapy goals in OHS patients with data [38]. Up to 25% of patients may continue to be hypercapnic with an awake CO<sub>2</sub> greater than 45 mm Hg even when they are compliant with PAP therapy. This needs to be clarified because adherence is generally thought of as using PAP therapy for more than 4 or 4.5 hours while sleeping. Given that most people sleep for at least 6 to 7 hours on average each night, some adherent patients may experience residual hypoventilation, which could lead to a partial reversal of awake hypercapnia. Alternative treatment options should be taken into consideration when significant daytime gas exchange problems continue, or the patient is unable to tolerate mask PAP therapy [43].

### **Surgical intervention**

Weight loss is the best course of action for obesity hypoventilation syndrome since it corrects most physiologic issues thought to be contributing to etiology and ultimately results in the restoration of daytime eucapnia. A minimum of 10 kg of weight loss leads to a considerable increase in maximum voluntary ventilation and vital capacity as well as a large decrease in daytime PaCO<sub>2</sub>. Weight reduction has also been demonstrated to dramatically improve central ventilatory drive as determined by the diaphragmatic electromyogram response to carbon dioxide

## Overview on Pediatric Obesity Hypoventilation Syndrome

inhalation; however the amount of available data is restricted [22]. The most efficient way to lose weight more significantly and keep it off for longer periods of time is through bariatric surgery. Few research particularly investigated outcomes in OHS patients, despite the fact that several studies have shown that surgical weight loss can considerably increase lung sizes, notably expiratory reserve capacity and gas exchange [33, 39]. Since OHS is less prevalent in severely obese women than in men, bariatric surgery is more frequently performed on them. Information on surgical complications and long-term results was omitted. Even though surgical weight loss significantly improves sleep disordered breathing, many people still have high apnea-hypopnea indices, according to a recent meta-analysis [40]. If a patient feels their sleep issues have been resolved or if there is still persistent sleep-disordered breathing present, they can be reluctant to engage in evaluation of breathing after surgery. This could cause a sizable number of patients to discontinue PAP therapy before recovery after surgery [22]. In morbid obese and highly morbid obese people, surgical weight loss is being employed more frequently [42]. Even though these groups saw significant and long-lasting weight loss, only one out of every three patients saw their BMI drop below 40 kg/m<sup>2</sup> [19]. The adherence to PAP therapy in these highly obese individuals following surgery was not addressed, and long-term cardiovascular results were not carefully monitored. Allocated the over-all data on the generally low level of issues connected with bariatric surgery in qualified institutions, more in-depth research examining this method in the long-term managing of OHS should be taken into consideration [43].

### **Tracheostomy**

There have not been any sizable studies looking at tracheostomy patients' long-term outcomes. Two weeks after having a tracheostomy for the treatment of OHS, three out of seven patients had their PaCO<sub>2</sub> return to normal. Minute ventilation stayed at the baseline level in the four individuals in whom PaCO<sub>2</sub> did not normalize. Responders and non-responders were similar in terms of physiologic dead space, FVC, FRC, FEV1/FVC ratio, and other factors [44]. Tracheostomy can provide a complete remission of obstructive respiratory episodes in people with simple OSA. Though, patients with OHS may continue to have breathing problems when sleeping after tracheostomy. A review of thirteen patients with OHS revealed that tracheostomy was related with a considerable enhancement in OSA. When the

tracheostomy was closed, the mean NREM AHI and REM AHI were 64 and 46, respectively; when it was open, these values decreased to 31 and 39, correspondingly. An AHI of greater than 20 was still present in seven cases. These residual respiratory episodes were associated with persistent respiratory effort. The majority of patients' hypercapnia did, however, go away as a result of the tracheostomy's general decrease in the degree of sleep disordered breathing [25, 45].

### **Pharmacotherapy**

A) Medroxyprogesterone: The progesterone-induced respiratory response is facilitated at the hypothalamus by an estrogen-dependent progesterone receptor, similar to the system governing progesterone's effects on reproduction [27]. Medroxyprogesterone may be beneficial for treating OHS patients since it lowers the AHI in OSA patients and increases the ventilatory response to hypercapnia. Treatment outcomes for OHS patients have been conflicting [46]. PaCO<sub>2</sub> fell from 51 to 38 mm Hg in a group of 10 patients who received medroxyprogesterone treatment, while Pao<sub>2</sub> rose from 49 to 62 mm Hg. On the other hand, medroxyprogesterone did not improve PaCO<sub>2</sub>, minute ventilation, or the ventilatory response to hypercapnia in three patients who remained hypercapnic after tracheostomy. Most OHS patients, though not all, can get their PaCO<sub>2</sub> back to normal by choosing to induce hyperventilation. A mechanical issue could prevent deliberate hyperventilation from successfully releasing CO<sub>2</sub> into the atmosphere [46]. According to one study, the primary indicator of a positive response to medroxyprogesterone was the capacity to lower the PaCO<sub>2</sub> with voluntary hyperventilation by at least 5 mm Hg. It is therefore likely that before starting treatment with respiratory stimulants, patients should be evaluated for their capacity to lower PaCO<sub>2</sub> by at least 5 mm Hg through voluntary hyperventilation. Medical providers must understand that medroxyprogesterone can increase the risk of venous thromboembolism, though [47].

B) Acetazolamide: In contrast to loop diuretics, which cause metabolic alkalosis, acetazolamide, a carbonic anhydrase inhibitor, induces metabolic acidosis. The blood bicarbonate level decreases by 4 to 6 mEq/L and the pH decreases by 0.05 to 0.1 within 24 hours after taking a medication. This metabolic acidosis causes a 15% increase in minute breathing and a 5–6 mm Hg decrease in PaCO<sub>2</sub>. The drop in PaCO<sub>2</sub> is caused by a shift of the CO<sub>2</sub> response curve to the left of 7.3 mm Hg rather than a change in the ventilatory response to hypercapnia's slope [33].

## Overview on Pediatric Obesity Hypoventilation Syndrome

For three reasons, acetazolamide might be useful in the treatment of OHS. First of all, it may be a helpful medicine for treating people with severe OSA to prevent the start of metabolic alkalosis because we now understand how metabolic recompense for abrupt respiratory acidosis throughout sleep contributes to the advance of hypercapnia. Second, in OHS patients, it corrects the right shift in the CO<sub>2</sub> response curve [34]. Third, in people with moderate-to-severe OSA, it can lessen the frequency of obstructive events. In fact, three patients who had a tracheostomy but remained hypercapnic underwent eucapnia after receiving 250 mg of acetazolamide daily for two weeks [48]. Alternative therapies to PAP therapy have received little study. Therefore, it is crucial to actively promote PAP therapy compliance to avoid the severe detrimental effects of OHS. Physicians should think about tracheostomy, weight loss surgery, and respiratory stimulant medication if PAP therapy does not produce the required results. These therapeutic approaches will not totally cure hypoventilation, so the patient might need to combine therapies, including tracheostomy along with mechanical ventilation or acetazolamide medication [49].

### Limitation

There is a shortage of information and studies regarding obesity hypoventilation syndrome (OHS) in the pediatric age range, and most of the research focused on adults. Studies concerning this topic in Saudi Arabia specifically and the Middle East generally are very limited.

### Conclusion

OHS prevalence is predicted to rise considering the global obesity pandemic. OHS has a high rate of morbidity and mortality, although treatment is routinely postponed and frequently goes undiagnosed. Maintaining a high index of suspicion is crucial for clinicians, especially since early detection and treatment improve results. To comprehend the pathogenesis and long-term treatment outcomes of OHS patients, more research is required.

### Conflict of Interest

None

### Funding

None

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## Overview on Pediatric Obesity Hypoventilation Syndrome

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## Overview on Pediatric Obesity Hypoventilation Syndrome

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