Review Article

Obesity Hypoventilation Syndrome: A Systematic Review

Besharat Rahimi[1] and Ahmad Vesal[2]*

[1]Advanced Thoracic Research Centre, Tehran University of Medical Science, Tehran, Iran; [2]Department of Pediatric Cardiology, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical sciences, Tehran, Iran

Corresponding author:
Ahmad Vesal,
Department of Pediatric Cardiology,
Rajaie Cardiovascular Medical and Research Center,
Iran University of Medical sciences, Tehran, Iran,
Tel: 009891285895 93;
E-mail: Besharatrahimimd@yahoo.com

Abstract

Background: The accurate incidence of obesity-hypoventilation syndromes (OHS) in the general population remains unknown. OHS arises from an intricate interaction among sleep-disordered breathing, depauperate respiratory drive, obesity-related respiratory, metabolic, hormonal and cardiovascular impairments, and leading to a reduction in daily life activities. Currently, OHS information is extremely limited in the clinical and diagnostic predictors, and anesthesiology literature. This review will examine the epidemiology, clinical characteristics, and prevalence of OHS in different countries, and treatment available treatment modalities. **Methods:** A comprehensive literature search was conducted to identify studies focused on OHS through databases, including Google Scholar, PubMed, Medline, Scopus, Embase, Cochrane Library and Web of science. The articles in English published in index above were selected for the review. Data were extracted on the clinical outcome, prevalence and diagnosis features, epidemiology, and treatments. **Results:** Available data in this review article suggest that the high incidence of OHS, noninvasive ventilation (NIV) and continuous positive airway pressure therapy (CPAP) treatments were more effective than lifestyle modification with respect to the improvements in clinical symptoms, although bi-level PAP exhibited slightly greater respiratory functional improvements than CPAP with long-term treatment. **Conclusion:** NIV and CPAP therapies are the mainstay of treatment but the best approach for those who do not respond to this modality is unknown and may include a combination of PAP therapy and pharmacotherapy with respiratory stimulants or tracheostomy, with or without nocturnal ventilation.

Keywords: Obesity-hypoventilation syndromes; Prevalence; Treatment; Respiratory

Introduction

Obesity hypoventilation syndrome (OHS and or alveolar hypoventilation in the obese) was illustrated outset in 1955 [1-6] and currently, OHS is a modern name for an past syndrome, the term "pickwickian syndrome" that is as a respiratory outcome with higher morbidity and lower quality of life. [7-11]

On the other hand, International Classification of Sleep Disorders, OHS is distinguished by the combination of four defines: 1) obesity (body mass index (BMI) ≥ 30 or 40), 2) chronic daytime alveolar hypoventilation (PaO (2) <70 mmHg), 3) partial pressure of arterial carbon dioxide ($PaCO_2$) > 45 mmHg at sea level) during sleep and 4) wakefulness. [12-14]. In addition, OHS occurs from an intricate interaction among sleep-disordered breathing, depauperated respiratory drive, obesity-related respiratory, metabolic, hormonal and cardiovascular impairments, that leading to a reduction in daily life activities. [15-19]

A comprehensive literature search was conducted to identify studies that focused on OHS through databases, including Google Scholar, PubMed, Medline, Scopus, Embase, Cochrane Library and Web of science. The articles in English published in index above were selected for the review. Data were extracted on the clinical outcome, prevalence and diagnosis features, epidemiology, and treatments

Epidemiology and Clinical Presentation

Global epidemiology

The exact incidence of OHS in the general population remains unknown but OHS can be appraised using outbreak of obstructive sleep apnea(OSA), [20] and most reasonable findings of prevalence have focused on the topics of patients who referred to sleep centers for features of sleep-disordered breathing with OSA and its incidence has been estimated in various studies to range from 10% to 38% in multifarious groups or is computed to be between 0.15% and 0.3% or in the some studies, the estimated prevalence among the US obese population is estimated approximately 0.3%. [6,21-25]

Recent researches have been suggested a incidence of OHS among patients with OSA ranged from 9-20% as well as else studies containing a total of 1,326 patients, moreover, with investigation of patients presented to sleep centers with clinical signs of OSA the prevalence of OHS is estimated to range from 11–20% and also, another study with an throughout outbreak rate was nearly 16%. Furthermore, the prevalence of OHS increments remarkably on a other research as obesity increases

How to Cite this Article: Rahimi B, et al. Obesity Hypoventilation Syndrome: A Systematic Review. Ann Med Health Sci Res. 2019;9: 564- 570

was around 10 to 20%. In parallel, a study shows in outpatients presenting to sleep clinics to approximately 50% of hospitalized patients with OSA. Current estimates of the articles published propose that around 0.3 to 0.4% of the population may have OHS. In a research prospective evaluated the clinical predictors of OHS in obese subjects with OSA and OHS prevalence in patients with OSA varies from 11 to 38%. In a previous study from the United Arab Emirates, the proportion of men with OHS was higher (77.4%) and, the outbreak of OHS among women diagnosed with OSA was lower (31.8%). The prevalence of OHS in obese individuals was found to be much higher at 19% to 31%. In 10 studies, the summation prevalence of OHS among OSA patients referred to a sleep disorder center is 17% (range 4%–50%). The greatest OHS study in the literature was retrospective, and the prevalence of OHS was 11%. [4,14,15,18,19,26-37]

On the other hand, Nowbar et al. revealed the incidence of OHS among hospitalized adult patients with BMI> 35 kg/m^2 was 31%. [35] In addition, a study indicated that the prevalence of OHS among patients referred to the Sleep Disorders Clinic with OSA was 8.5%. [20] In a great French retrospective study (n=1141), the prevalence of OHS was 11% among OSA patients. [23] Retrospective studies on investigation of 1,927 patients with a known diagnosis of OSA seen the outbreak of OHS ranged from 9–14%. [28-30] Macavei et al. reported the prevalence of OHS and predictors of OHS in patients with OSA. [13] Also, in 525 consecutive patients referred to the sleep medicine clinic prevalence of OSA among obese patients was 79.9% and OHS prevalence among OSAHS patients was 22.1%. [13] A recent prospective and observational study with an objective to determine the prevalence of OHS with 330 patients (3.4%) meeting the inclusion criteria were analyzed and 35.5% of patients had chronic hypoventilation which 24.6% was related to OHS. [31-34] Taken together, the incidence between sleep clinic patients was between 10% to 20% in various researches, and this rate was higher in patients with obstructive sleep apnea from 20% to 30%. [13,23,29] In parallel, BaHammam, with study on a large sample of Saudi patients with obstructive sleep apnea (1693 OSA patients) showed the prevalence and predictors of OHS was identified 144 (8.5%) (Women 66.7%). [4]

Plus, the incidence of OHS is increment with rising obesity; so, precise evaluation of outbreak of OHS is critical for planning health services to make preparation for this condition and obesity is now considered a worldwide epidemic. [16,38,39] In parallel, Mokhlesi et al. found an incidence of 20% in a sample of obese OSA patients with a mean BMI of 43 kg/m^2. [32-39] In Japan, Akashiba et al. reported higher outbreak of OHS among women (11.6%) compared to men (8.8%). [26] In other study, the prevalence of OHS among OSA patients with a BMI ≥40 kg/m^2 was 21%, which is similar to the previous studies on populations with BMI >40 kg/m^2. [40] Furthermore, in another research, OHS prevalence was 42.1% in OSA subjects with obesity, which is higher than previous studies. [7] A recent study of USA on obesity epidemic revealed a leveling off trend for 2009-2010 compared to 2003-2008, with an obesity incidence of 35.5% between adult men and 35.8% among adult women that this ascent in obesity is presumably that leads to a progress in respiratory consequences such as OHS. [13,41]

Prevalence in different countries on both sexes

Less is known about incidence of OHS in the obese population. Weitzenblum et al., have shown that with study on 4,332 admissions of referred patients, 6% of patients were severely obese and 31% (n = 47) of the patients related to obesity-associated hypoventilation with subjects who did not have other reasons for hypercapnia and in other section of study authors have noticed that at 18 months following hospital discharge, mortality was 23% in the OHS group as compared to 9% in the simple obesity group, so they concluded that hypoventilation mostly entangles intense obesity between hospitalized adults and is related to excess morbidity and mortality. [40] In a another study, Chau et al., with research on a review of epidemiology of OHS reported whom the incidence of OHS is estimated between 10-20% in obese patients with OSA and 0.15-0.3% in the general adult population. [9] Moreover, with a study on OHS, sleep apnea, and overlap syndrome by Raveendran et al., 2017 demonstrated that OHS and overlap syndrome are related to considerable comorbid situations and more perioperative morbidity than OSA alone, also, this study showed that 90% of OHS patients have OSA. In patients with OSA, OHS, and overlap syndrome, development in the perioperative consequence has been shown by initiating positive airway pressure therapy. Taken together, their study revealed that anesthesiologists have a key role in the management of patients with sleep disordered breathing. [41] In addition, Almeneessier et al., in a study with subject of the prevalence of pulmonary hypertension in patients with OHS on 77 patients with a mean age of 60.5 ± 11.7 years using echocardiographic data have been indicated no significant differences between the OHS patients with pulmonary hypertension. Almost 71.4% of women and 61.9% of men with OHS also had pulmonary hypertension. Intense pulmonary hypertension was diagnosed in 28.6% of the women and 14.3% of the men. In summary, this study suggested that pulmonary hypertension is extremely usual between patients with OHS who have been presented to sleep disorders clinics. [42,43] On the other hand, Alawami et al., by research in 47 patients with OHS have shown a great outbreak of right ventricular impairment, pulmonary hypertension, left ventricle hypertrophy, diastolic dysfunction and arrhythmias in patients with OHS as well as available data would appear to be higher than expected in obese patients without OHS and it is needed to confirm the clinical significance of these results. [44] Furthermore, Borel et al., in a study of prevalence of OHS on population of 241 obese patients undergoing sleep and respiratory assessments. The prevalence of OHS was 1.10, they expressed that the incidence of OHS in our obese population was lower than previous estimations based on hospitalized patients or clinical cohorts with sleep breathing disorders. [45] In a paper on OHS in obese subjects by Bingol et al., reported that of 152 obese subjects with OSA (79 females/73 males), 51.9% with severe OSA, and 42.1% (n = 64) had OHS [7]. Harada et al., in Japan on OHS showed that the prevalence of OHS in OSA and obese OSA were 2.3% and 12.3%, respectively. Totally, it was announced the prevalence of OHS in OSA in Japan was 2.3%. [46] Ojeda Castillejo et al., with study on 83 patients exhibited 60 women (72.3%) and 23 men (27.7%), with a mean survival time of 8.47 years. 50 patients (60.2%) were included in the group without obstructive sleep apnea-hypopnea syndrome (OHS) and 33 (39.8%) in the

obstructive sleep apnea-hypopnea syndrome-associated OHS group. [47]

Old and new treatments

Currently there are no appointed guidelines on treatment of OHS as well as based on the studies, no medications that effectively treat OHS are usually available. Clearly treatment of OHS will depend on the state of the patient at presentation. In excessive cases patients with OHS may present with decompensated respiratory failure. [14,48]

Remedy modalities or common treatment approaches for OHS are each based on various perspectives of the underlying pathophysiology of the condition and these methods can be broadly categorized into several areas: reversal of sleep-disordered-breathing, improve nocturnal gas exchange, weight loss, oxygen therapy, surgical intervention to promote likewise bariatric surgery, strategies for reversing upper airway obstruction, such as tracheostomy and nasal continuous positive airway pressure therapy (CPAP), noninvasive ventilation (NIV) and pharmacotherapy methods to stimulate breathing such as, medroxyprogesterone acetate and acetazolamide. [49,50]

Discussion

In multiple reports by Sullivan et al., Stasche et al., Epstein et al., Spicuzza et al., Cortese et al., have been revealed that current gold standard therapy for OHS includes in the application of positive airway pressure (PAP) during sleep [51-55] as well as, in a study by Shivaram et al., reported that nasal CPAP may be effective in these situations. [48] Moreover, Masa et al., and Howard et al., with longer-term comparative studies suggest that PAP will provide significant information to guide clinical decisions around longer-term PAP management in OHS and regardless of the results of these reports, it is obvious that PAP treatment addresses only two perspectives of OHS, namely, sleep disordered breathing and awake hypercapnia. [56-58] In another research by Masa et al., have been demonstrated that NIV and CPAP were rather effective than lifestyle amendment in ameliorating clinical indications and polysomnographic parameters, however NIV yielded better respiratory functional developments than did CPAP. In addition, Ayappa et al., and Chau et al., have been proposed that with short interevent periods. Although, it is avowed that the advanced accumulation of CO_2 effected by repetitive obstructive events and can contribute to increased daytime $PaCO_2$. [59,60] Furthermore, In a prospective randomized study by Piper et al., with selection of 18 patients with OHS to receive CPAP treatment for 3 months, have shown an improvement in daytime sleepiness, subjective sleep quality and psychomotor vigilance performance and they have been concluded an effective method in improving daytime hypercapnia of patients with obesity hypoventilation syndrome without severe nocturnal hypoxaemia. On the other hand, more recent data by De Miguel Diez et al., Perez de Llano et al., and Mokhlesi et al., suggest that a four-week period may be sufficient to achieve the full benefits of treatment with regard to modifications in blood gases, irrespective of the type of PAP remedy utilized. They have elucidated 3 months of treatment appeared to be a sufficient time period to allow improvements in nocturnal breathing and have also reported the long-term use of CPAP therapy. [60-62] Although more studies confirmed its efficacy, in contrast, some authors such as Rapoport et al., Schafer et al., and Laaban et al., have been indicated that failure of CPAP therapy in some cases has led to dubiety whether CPAP should be attempted initially. [63-66] In one study, mokhlesi and colleagues showed eight patients (23%) between the thirty-four patients who utilized PAP for at least 4.5 h/d, did not have an important progress in their $PaCO_2$—reduction in $PaCO_2$ of less than 4 mm Hg. [61]

Indeed, the most recent studies such as Waldhorn et al., Masa et al., Aloia et al., Marin et al., Perez de Llano et al., Zimmerman et al., Dorkova et al., Bradley and Floras, Montesi et al., Iftikhar et al., Nadeem et al., Chen et al., Jullian-Desayes et al., Pamidi et al., Salord et al., and Cortese et al., have been suggested that there is current abundant evidence showing the favorable impact of PAP remedy on the outcome of approximately whole of the associated morbidities, such as neurocognitive changes, cardiovascular diseases, blood pressure, serum lipid profiles, insulin sensitivity, dyspnea, pulmonary hypertension, leg edema, secondary erythrocytosis, glucose metabolism and increase in DNA methylation, Although, the cellular signaling pathway mechanisms that underlie PAP treatment useful effects remain to be distinguished. [37,64,54,67-80]

Previous data indicated by Olson et al., and Powers et al., that the alone impressive treatment is weight loss. However, weight loss is slow to occur, and patients with OHS experience quick deterioration until respiratory failure develops. In these patients, noninvasive positive-pressure ventilation or invasive mechanical ventilation may be beneficial strategies, they have concluded that weight loss is the favorable long-term treatment for OHS, so it is critical that physicians are able to identify and treat obesity-associated diseases. [17,81] In a study, Umei and Ichiba, have reported that weight loss is a the essential treatment for obesity hypoventilation syndrome in morbidly obese patients. In another study, Piper et al., have demonstrated that encourage long-term weight loss because to increase physical activity, and decrease daily sedentary behavior are also needed to manage those perspectives of the disorder arising from obesity and its complications. [81] Furthermore, Mart-Valeri et al., reported that 14% of OHS patients still need to be PAP therapy after weight loss. Therefore, OHS patients should undergo re-investigation post-bariatric surgery before interrupting PAP treatment. [82] Moreover, Sugerman et al., Lin et al., Lumachi et al., and Borel et al., at different reports have been revealed that body weight loss clearly seems to be the etiological therapy in OHS. [8,83-85] In addition, Peppard et al. have studied a cohort of 690 subjects and indicated that 10% weight gain or weight loss were respectively related to a 32% increment or a 26% decrement in the apnoea/hypopnoea index as well as from weight loss, acting synergistically to ameliorate the respiratory disturbances and comorbidities of OHS. [86]

Sutton et al., in a study on 10 men with OHS treated for one month with high doses of oral medroxyprogesterone (60 mg/dl), have observed the reduction of $PaCO_2$ from 51 mm Hg to 38 mmHg and the P aO_2 increased from 49 mm Hg to 62 mm Hg (an increase in $PaCO_2$ and a decrease in $PaCO_2$ in OHS patients). They conclude that reinstitution of medroxyprogesterone

acetate caused improvement in both the oxygen and carbon dioxide tensions. [87] In one study else, Skatrud et al., the capability to drop the $PaCO_2$ by at least 5 mm Hg with voluntary hyperventilation was the principal predictor of a desirable repercussion to medroxyprogesterone as well as their findings showed that four weeks of medroxyprogesterone acetate treatment caused significant reductions in $PaCO_2$. [88] In contrast, Rapoport et al., have recommended that medroxyprogesterone did not improve $PaCO_2$, or ventilatory response to hypercapnia in OHS patients who remained hypercapnic after tracheostomy. In parallel, high doses of medroxyprogesterone in women can lead to breakthrough uterine bleeding and in men can lead to decreased libido and erectile dysfunction. [64] Poulter et al., showed that medroxyprogesterone acetate increases the risk of venous thromboembolism. On the other hand, one other research, [89] Bayliss and Millhorn, have been reported that medroxyprogesterone acetate motivates respiration at the hypothalamic level and its role in OHS is unknown. [90]

Conclusion

Available data in this review article suggest that the high incidence of OHS, therefore, it should be considered in the arranged clinical evaluation of whole patients with OHS. NIV and CPAP treatments were more effective than lifestyle modification with respect to the improvements in clinical symptoms, although Bi-level positive airway pressure exhibited slightly greater respiratory functional improvements than CPAP with long-term treatment. These therapies are the mainstay of treatment but the best approach for those who do not respond to this modality is unknown and may include a combination of PAP therapy and pharmacotherapy with respiratory stimulants or tracheostomy, with or without nocturnal ventilation.

Conflict of Interest

The authors disclose that they have no conflicts of interest.

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