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REVIEW

Gender differences in obesity hypoventilation syndrome

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ABSTRACT

Sleep-disordered breathing (SDB) is a group of sleep-related breathing disorders which includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and obesity hypoventilation syndrome (OHS). OHS is characterized by a combination of obesity, daytime hypercapnia and hypoxemia, and sleep-disordered breathing without other known hypoventilation causes, such as severe obstructive or restrictive parenchymal lung disease, kyphoscoliosis, severe hypothyroidism, neuromuscular disease, or congenital central hypoventilation syndrome. Four hundred ninety potentially eligible references were identified; of these, 462 abstracts or full texts were excluded because they did not fulfil inclusion criteria. We reviewed the full text of the remaining 38 papers which fulfilled the inclusion criteria. The role of gender in SDB and particularly in OHS is not well known. In general, the diseases are under-recognized in women and only a few studies have reported the impact of gender on clinical presentation and treatment outcome. On the other hand, there is often a delay in diagnosing these diseases in women as compared to men; therefore, they are often more advanced when diagnosed in women. Better understanding and clinical awareness of the higher OHS prevalence in postmenopausal women may lead to earlier diagnosis and a more timely and appropriate treatment. Further studies are needed to assess the prevalence of OHS in women, the effect of menopause on OHS, and the increased risk of OHS, which will hopefully lead to optimizing OHS patient care.

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KEY WORDS: Sex characteristics; Sleep disorders, intrinsic; Sleep apnea, obstructive; Obesity hypoventilation syndrome.

Sleep-disordered breathing (SDB) includes a group of sleep-related breathing disorders, such as obstructive sleep apnea (OSA), central sleep apnea (CSA), and obesity hypoventilation syndrome (OHS). In general, as is the case in many other diseases, SDB is under-recognized in women.[1] SDB is a common, under-diagnosed, and treatable syndrome. In developed countries, it is reported that it affects between 3-7% of middle-aged men and 2-5% of women.[2, 3] Studies assessing gender differences in patients with SDB have reported differences in prevalence, clinical presentation, polysomnographic features, and treatment of SDB.[4] OHS and OSA are often comorbid conditions.[3, 4] Compared with patients with either OHS or OSA alone, those with both diseases commonly experience higher levels of hypoxemia and CO_2 retention, as well as an accelerated onset of pulmonary artery hypertension and cor pulmonale development.[1, 3]

OHS is not as commonly prevalent in men, and several previous sleep clinic studies have found that women appear to be more affected by OHS.[5] In fact, OHS may be more prevalent in women than in men (15.6% and 4.5%, respectively), even after adjusting for Body Mass Index (BMI) differences. However, these data have generally not been confirmed with statistical analyses.[6] It is also unclear whether there are differences in the clinical presentation and treatment outcomes between men and women with SDB. Studies dealing with the gender perspective in OHS are sparse, and many of them have been performed at sleep clinics on participants with SDB, where men are over-represented.[7] Similar to other SDB conditions, it has been hypothesized that gender plays a role in OHS prevalence and clinical presentation. The aim of this review was to identify and analyze gender differences in patients with OHS, in order to help reduce the occurrence of poor clinical outcomes.

Literature search

Data source

We searched the following electronic databases from January 1990 to March 2022: Medline, Embase, CINHAIL, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, and the American Journal of Physicians Journal Club database. No language restriction was applied: non-English publications were professionally translated into English. We identified "sex differences, gender differences, sleep related breathing disorders, obesity hypoventilation syndrome" as key words, which had to be present in the article title or abstract.

Study selection

We found 1994 papers, including clinical trials, comparative studies, controlled clinical trials, reviews and case reports. Through reviewing abstracts, we excluded articles which were clearly not relevant to the purpose of this review and identified other useful studies for our analysis among the references of the selected works. We identified 490 potentially eligible references; of these, 462 abstracts or full texts were excluded because they did not fulfil our inclusion criteria. We reviewed the full text of the remaining 38 papers which fulfilled the inclusion criteria. Figure 1 shows the study flow chart.

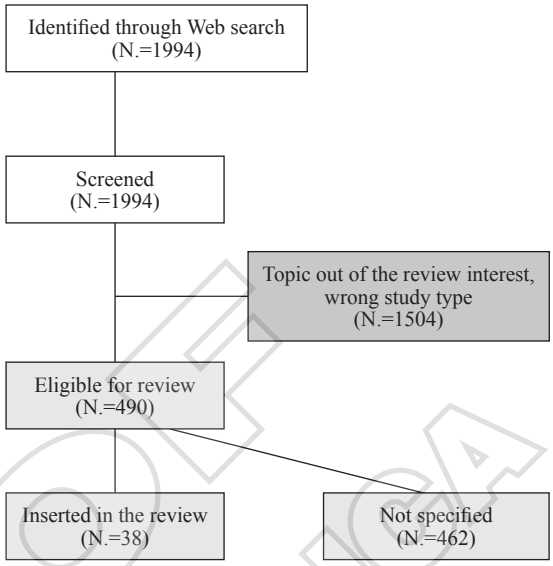

Figure 1.—Study flow chart.

OHS and OSA: similarities and differences and the obesity related sleep hypoventilation

OHS is defined as the combination of obesity (BMI≥30 $kg \cdot m^{-2}$), sleep disordered breathing, and daytime hypercapnia (arterial carbon dioxide tension [$PaCO_2$]≥45 mmHg at sea level) during wakefulness, occurring in the absence of an alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation. OHS is typically diagnosed during an episode of acute-on-chronic hypercapnic respiratory failure or when symptoms lead to pulmonary or sleep consultation in stable conditions.[8] Approximately 90% of patients with OHS have OSA, which is defined by an Apnea-Hypopnea Index (AHI)≥5 events/hour. Nearly 70% of patients have concomitant severe OSA (AHI≥30 events/hour).[8, 9] The remaining patients have non-obstructive sleep hypoventilation with no or mild OSA. The American Academy of Sleep Medicine has arbitrarily defined sleep hypoventilation in adults with the following criteria: $PaCO_2$ (or a $PaCO_2$ surrogate,

such as end-tidal carbon dioxide tension or transcutaneous carbon dioxide) >55 mmHg for >10 minutes or an increase in $PaCO_2$ (or surrogate) >10 mmHg compared to an awake supine value >50 mmHg for >10 minutes.[7] OHS is considered to be the most severe form of SDB.[7, 10] Recent developments in defining OHS include proposed classification systems of severity and demonstrating the value of using serum bicarbonate to exclude OHS in patients with a low index of suspicion.[11-13] The exact prevalence of OHS in the general population remains unknown; the incidence of OHS increases significantly as obesity incidence increases. In the USA, the estimated prevalence of OHS is 0.15-0.30% of the adult population;[10] however, its prevalence among patients who are referred to sleep clinics is reportedly from 10- 31% in hospitalized patients with a BMI>35 kg/m.[2, 10, 14, 15] OHS is a disease entity distinct from simple obesity and OSA. Patients in whom OHS is diagnosed consume greater levels of healthcare resources than eucapnic patients with OSA[14] due to, among other reasons, the associated comorbidities. OHS is usually associated with OSA, pulmonary hypertension, and right heart failure. Major clinical features are hypersomnia, dyspnea, and headache combined with polycythemia.[15] There are many similarities between OHS and OSA, and the clinical presentations are similar as well: excessive daytime sleepiness, fatigue, or morning headaches. Furthermore, 11-15% of obese OSA patients present with hypercapnia, and a majority of the hypercapnic obese patients manifest OSA. Hypercapnia is more frequent in obese than in non-obese OSA patients.[7, 14-16] A transition from OSA to Ohs has been studied by Treml *et al.* but the preliminary data obtained did not allow a characterization of different stages in the development from OSA to OHS although a small fraction of patients showed indication of being in a transitory state.[17] Further studies identified isolated hypoventilation during sleep in obese patients (obesity related sleep hypoventilation, ORSH) is now considered as an early stage of OHS.[9, 13] ORSH has a similar prevalence of OHS. Awake oxygen saturation and partial pressure of carbon dioxide performed in the supine position may help predict obese patients with sleep hypoventilation without awake hypercapnia. ORSH had a prevalence of 13% in an outpatient setting which included a population of 94 subjects with a Body Mass Index >40 kg/m.[2, 13] Gender differences in OSA have been studied. As we have previously mentioned, OSA is approximately three times more prevalent in men than in women.[16] This difference between women and men has been attributed to differences in anatomical and functional factors, such as variations in craniofacial morphology, fat deposition, hormones, and ventilatory responses.[17, 18] The different distribution of fat in women, namely peripheral deposition, may protect them from developing OSA.[19] In addition, upper airway collapsibility is greater in men than in women. The female airway is short and wide, with a lower critical closing pressure, and is therefore less collapsible. Some reports support the hypothesis that upper airway resistance during sleep is higher in men than in women.[20, 21] Hormonal status may also have an impact on sleep apnea susceptibility, particularly in women. Progesterone and estrogens protect against OSA, and previous studies have shown that menopause is a major risk factor for OSA in women.[18, 22] Indeed, postmenopausal women demonstrate an increase in sleep apnea prevalence and severity compared with premenopausal women.[23] Regarding ventilatory control, men appear to be more susceptible to the influence of certain chemical factors, with a greater hypoxic and hypercapnic response (a higher loop gain). The polysomnographic profile also differs according to sex. Women have a lower AHI with a predominance of REM episodes and less desaturation.[24] They have more partial obstruction and more airflow limitation, while in men there is a predominance of positional OSA and a higher AHI. The symptoms in men and women with OSA are also different. Overall, women appear to be more symptomatic, with lower AHI scores than men. Women are more likely to complain of daytime fatigue, lack of energy, insomnia symptoms, morning headaches, mood disturbances, and nightmares compared to men.[18, 20, 24-26] Men present with "typical" symptoms, namely snoring, excessive daytime sleepiness and apnea.[26, 27] In fact, even the Epworth score for assessing excessive daytime sleepiness has not been validated

in women. In view of these differences between men and women in OSA and its association we should consider whether the same factors could influence OHS. The pathophysiology of OHS is known to be more severe than that of OSA. Patients with OHS have significantly impaired respiratory system mechanics with a restrictive ventilatory pattern, and the ventilation-perfusion mismatch secondary to pulmonary atelectasis contributes to hypoxemia. There are three leading hypotheses for the pathogenesis of chronic daytime hypoventilation in OHS: 1) impaired respiratory mechanics due to obesity; 2) leptin resistance leading to central hypoventilation; and 3) impaired compensatory response to acute hypercapnia in OSA. Multiple mechanisms contribute to the development of OHS and include abnormal pulmonary mechanics, altered hypoxic and hypercapnic ventilatory responses due to chronic hypoxemia and poor sleep quality, upper airway obstruction, and possibly the influence of leptin.[28] Patients with OHS may clinically present with unexplained hypoxemia or with symptoms similar to those of OSA, such as excessive daytime sleepiness, fatigue, loud habitual snoring, nocturnal choking episodes, and morning headaches. In contrast to patients with OSA, dyspnea, lower extremity oedema, and low oxygen saturation measured by pulse oximetry during wakefulness are common in OHS. A restrictive defect is often seen on pulmonary function tests and is caused by obesity.[29] If left untreated, pulmonary hypertension and right-sided congestive heart failure can develop in patients with OHS.[28, 30-32]

Comparison of women and men with OHS

The diagnosis of OHS is often delayed in women compared to men, and the disease is more advanced when diagnosed.[1, 3, 5, 33] In the Swedish National Registry, women with OHS were older, more obese, and had a higher incidence of comorbid chronic obstructive pulmonary disease and pulmonary disease than men. Furthermore, women had greater changes in blood gases at the time of long-term mechanical ventilation (LTMV) initiation and were subjected to non-elective LTMV more frequently than men. Despite this, improvements in blood gases and survival rates were similar to that of men.[5] After comparing postmenopausal women with age-matched men with OHS, it was observed that the prevalence of OHS remained significantly higher (four times higher) in postmenopausal women, with no significant differences observed in age, AHI, or BMI. In Bahammam *et al.*'s prospective study, differences in the clinical characteristics of women and men with OHS were assessed in a large cohort of 1973 patients with OSA who were referred to a sleep clinic. Women with OHS were significantly older than men with OHS (mean age 61.5 *vs*. 49.1 years; P<0.001), and women were found to suffer from significantly more comorbidities, with a higher prevalence of hypertension, diabetes, and hypothyroidism. Importantly, the prevalence of hypertension (83% *vs*. 47%, P=0.003) and diabetes (64.1% *versus* 31.6%, P=0.03) remained significantly higher in women than in age-matched men.[29] The underlying cause of the higher prevalence of OHS among women is not known. To explain this difference, several potential mechanisms have been proposed. Some authors have postulated a theory on leptin resistance. Leptin acts as a powerful respiratory stimulant, and obese individuals have significantly higher serum leptin levels than lean individuals.[34] Recent advances shed light on the molecular pathways related to the central chemoreceptor function in health and disease Leptin signaling in the nucleus of the solitary tract retrotrapezoid nucleus, hypoglossal nucleus, and dorsomedial hypothalamus, and anatomical projections from these nuclei to the respiratory control centers, may contribute to OHS[35].Gender differences in leptin concentration in obese patients have been reported .Recent human studies suggested a role of leptin in the modulation of neural compensatory mechanisms at the level of the upper airway.[36] Since obese women have been reported to have up to four times higher leptin levels than obese men,[30] leptin represents a potential protective factor against upper airway obstruction in obese women.[37] The therapeutic use of intranasal leptin has been successfully tested in obese animals.[38] It is possible that obese women develop a greater resistance to the central effects

of leptin than men and therefore have a higher risk of hypoventilation and hypercapnia, resulting in an increased OHS prevalence. A previous study that assessed the effects of postmenopausal hormone replacement therapy (pHT) on a large sample of healthy postmenopausal women demonstrated that leptin concentrations were significantly higher in obese postmenopausal women than in counterparts with normal weight, and that neither pHT nor serum estradiol concentrations influenced leptin concentrations, even after adjustment for BMI.[36] Another possible explanation for the gender differences in OHS is the difference in hormonal profiles between men and women. Similar to previously reported findings for OSA, female hormones could play a critical role in OHS. Progesterone is a known respiratory stimulant,[39] and previous studies have shown that it increases alveolar ventilation, lowers $PaCO_2$, and augments hypercapnic and hypoxic ventilatory responses.[40] Therefore, it is possible that the withdrawal of progesterone during menopause may contribute to the increased prevalence of hypoventilation in postmenopausal women with OHS, compared with premenopausal women with OHS, through a reduced respiratory drive and respiratory pathway relaxation. In a placebo-controlled, double-blind trial of postmenopausal women with OSA on continuous positive airway pressure (CPAP) therapy, women were randomly assigned either medroxyprogesterone acetate (MPA) or a placebo for two weeks after CPAP discontinuation. Fourteen days after discontinuing the use of CPAP, nocturnal oxygen saturation remained higher and $PaCO_2$ remained lower ($P<0.001$) in the MPA treated group.[41] These results may support the theory of the role of progesterone in the development of hypercapnia.[17] However, a randomized controlled trial is necessary to determine whether treatment with progesterone can reverse hypercapnia. The possible protective role of hormone replacement therapy (HRT) in post-menopausal women with OSA was assessed in studies with small numbers of subjects.[17] The available data do not clearly support the hypothesis that sex hormone changes during menopause are an independent cause of SDB, and, in peri- and postmenopausal women, HRT has not been unambiguously proven to alleviate OSA. Therefore, there is no evidence that menopause has a direct effect on SDB. Due to the strong association of age and SDB prevalence, it is a real challenge to further investigate the role of menopause, since the age range for premenopausal women is biologically limited.[42] Gender-affirming treatment can add additional complexity to understanding the role of sex hormones.[17, 43] Another potential hypothesis for the underlying cause of gender differences in OHS is associated with the functional status of the thyroid. The prevalence of hypothyroidism is significantly higher in women than in men with OHS. Hypothyroidism suppresses the ventilatory response to hypercapnia and hypoxia. Therefore, hypothyroidism may impair ventilatory responses, which could in turn predispose patients to hypoventilation.

On management and treatment of OHS

There are only a few studies which primarily aimed to investigate the sex differences in treatment responses in OHS and OSA patients.[44] The goals of care should be to treat respiratory sleep disturbances, diurnal hypercapnia and hypoxemia, which may persist after correcting alveolar hypoventilation. According to the Pickwick study, which is the largest multicenter study with the longest follow-up period of patients with severe OHS and OSA, in the stable phase of hypercapnic respiratory failure,[8, 45] non-invasive ventilation (NIV) and CPAP seem to have a similar long-term effect. As CPAP is cheaper and easier to manage, it may be preferable as a first-line treatment in stable patients with OHS and severe OSA.[46] In the OHS specific phenotype without severe OSA, NIV was the most effective treatment for reducing $PaCO_2$.[47-49] In the Pickwick study, there were no statistically significant differences between the two treatment groups (CPAP and NIV) between men and women.[47]The study which used the data from the National registry in Sweden for assessing gender differences in patients undergoing long-term home NIV for OHS, showed that OHS diagnosis in women is more delayed and the disease is more advanced at the time of LTMV initiation. Approximately 40% of OHS patients initially present with acute

decompensation and hypercapnic respiratory failure. This acute presentation is more common in women, indicating that OHS is underrecognized in women until acute decompensation develops. Indeed, more women than men start treatment with long-term mechanical ventilation in an acute setting. Furthermore, in the aforementioned study, the five-year survival rate was found to be 68.2% (95% CI: 63.6-72.3%) in men *vs*. 59.3% (95% CI: 54.2-64.0%) in women; these data collectively indicate increased disease severity in women. Conversely, another French study reported that women with OHS had better survival rates than men, however, after adjusting for potential confounders, the gender differences in the survival rate disappeared.[8] Therefore, presently there is no clear evidence that gender drives the differences in survival rates among patients with OHS treated with long-term NIV.[45, 47-49] Other treatment options, such as mandibular repositioning splints (MRS), have been studied in both men and women. In mild OSA and OHS, MRS use is higher in women compared to men, although the percentage of women is generally low in published studies.[32]

Conclusions

Better understanding and clinical awareness of the higher OHS prevalence in postmenopausal women may lead to earlier diagnosis and a more timely and appropriate treatment. Further studies are needed to assess the prevalence of OHS in women, the effect of menopause on the pathophysiology of OHS, and the increased risk and comorbidities of OHS, which will hopefully lead to optimizing OHS patient care.

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