Sleep apnea syndrome associated with gonadal hormone imbalance (Review)

CRISTIAN COJOCARU[1], ELENA COJOCARU[2], LUIZA-SIMONA POHACI-ANTONESEI[2*], CATALIN-ALEXANDRU POHACI-ANTONESEI[2*] and STEFAN DUMITRACHE-RUJINSKI[3,4*]

Departments of [1]Medical III and [2]Morpho-Functional Sciences II, Grigore T Popa University of Medicine and Pharmacy, 700115 Iasi; [3]Department of Cardiothoracic Pathology, Carol Davila University of Medicine and Pharmacy, 050471 Bucharest; [4]Department of Pneumology, Marius Nasta Institute of Pneumophtisiology, 050159 Bucharest, Romania

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Abstract. Patients with obstructive sleep apnea exhibit an increased risk of developing gonadal disorders. Because a notable number of people worldwide have sleep respiratory and reproductive disorders, it is essential to recognize the association between local upper airway dysfunction and its gonadal effects. Repeated breathing pauses cause sleep fragmentation, disorganization of sleep cycles and stages, sympathetic activation, intermittent hypoxemia and systemic inflammation. Nocturnal intermittent hypoxemia has a direct central effect on neurotransmitters, with disturbances in the normal production of hypothalamic-pituitary hormones. Awakenings and micro-awakenings at the end of apneic episodes produce a central stress responsible for hormonal changes and subsequent endocrine imbalances. The aim of the present study was to investigate the impact of obstructive sleep apnea syndrome (OSAS) on gonadal hormonal homeostasis and its consequences. Recognizing and understanding how local upper airway dysfunction causes gonadal imbalance may facilitate better care for patients with OSAS. Although there may be a direct relationship between sleep-disordered breathing and gonadal function mediated by hormones via the hypothalamic-pituitary-gonadal axis, to date, current therapies have not been effective.

Correspondence to: Professor Elena Cojocaru, Department of Morpho-Functional Sciences II, Grigore T Popa University of Medicine and Pharmacy, 16 University Street, 700115 Iasi, Romania
E-mail: elena.cojocaruu@umfiasi.ro

*Contributed equally

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Contents

1. Introduction

Sleep-disordered breathing is a notable health concern. About one billion people aged 30-69 are estimated to suffer from sleep-disordered breathing worldwide (1). Another study revealed that the prevalence of sleep-disordered breathing was 24.0-83.8% in males and 9.0-76.6% in females (2). As sleep-wake disorders affect homeostasis and metabolic disturbances underlie the onset of sleep disorder, the impact of these clinical situations is notable. Differences in sleep duration and pattern between sexes are already known. Sex hormones including progesterone, androgens and estrogens are also related to respiratory disorders. In addition, men are more likely to have obstructive sleep apnea syndrome (OSAS), although women are more likely to develop it after menopause. According with a study, postmenopausal patients had a prevalence of sleep disturbed breathing that was 3-6 times higher than it was in premenopausal women (2). Women generally get better sleep than men (3). They have twice as many sleep spindles, deeper deep sleep and a slower age-related decrease in delta activity, a sign of deep sleep (4). Only 26% of women report excellent or very good quality sleep (5). Women aged 40-65 years are more likely to experience sleep problems (6). Between the ages of 20 and 70 years, 50% of females develop OSAS. A total of 20% of females exhibit moderate sleep apnea and 6% develop severe cases (7). Male rats undergoing intermittent and chronic hypoxia have altered testicular morphology and lose spermatogenic cells throughout the spermatogenic cycle (8).

Increasing evidence of clinically significant differences between the sexes and genders correlates with the rise in obesity and its associated comorbidities (1,3,9). Although most research shows the impact of sleep disorder on the cardiovascular system, the effect on sexual function and fertility have received less attention (10,11). Disturbed breathing during sleep leads to repeated hypoxemia, activation of the sympathetic nervous system and excessive daytime sleepiness. Of mechanisms that can underlie breathing-associated sleep-disorders, OSAS is the most common (12,13). OSAS is a heterogeneous disorder that includes anatomical compromise of upper airway patency, loss of tone of the pharyngeal dilator muscles and a reduced threshold for respiratory stimulus. Due to repeated interruptions of breathing during sleep, repeated episodes of hypoxemia and disturbances of normal sleep architecture appear such as decreased time in the deeper stages of sleep, poor sleep quality and microawakenings lasting up to several minutes (14). Consequently, sympathetic activation, cortical excitation, and circadian disturbance of hormonal secretions occur, generating cardiovascular disease and endocrine and reproductive disorder (15).

In patients with OSAS, a decrease in minute-ventilation during sleep, an increase in upper airway resistance and a decrease in the response of the respiratory centres to stimuli induced by hypoxia and hypercapnia are present (16,17). In response to respiratory changes during sleep, microtremors, erectile dysfunction or fertility disorders frequently emerge (18).

Large-scale epidemiological studies have estimated that ~4% of males and 2% of women suffer from OSAS (12,19). Additionally, it is estimated that 80-90% of OSAS cases remain undiagnosed (20).

Infertility is a notable issue for public health. According to the World Health Organization, infertility affects 48 million couples and 186 million individuals worldwide (21). To the best of our knowledge, the association between OSAS and infertility has rarely been studied (22,23). Infertility due to sleep-disordered breathing has been proposed to occur via direct mechanisms such as impaired spermatogenesis as well as indirect mechanisms, such as altered gonadal hormone secretion and decreased libido (22,23).

The present review aimed to describe the main mechanisms that alter the sex hormone homeostasis and fertility status in patients with OSAS and whether continuous positive airway pressure (CPAP) therapy can improve these.

2. OSAS pathogenesis

OSAS is characterized by repeated episodes of apnea and hypopnea with a frequency of at least five episodes/h, caused by partial or total obstruction of the pharynx. The pharynx is a duct that is kept open due to pharyngeal dilator muscle activity. Under normal conditions, when the tonus of the pharyngeal muscles decreases (as during sleep), there are no notable airflow changes. However, certain factors, including obesity and facial features (retrognathia, acromegaly, dental malocclusion, longer distance from the hyoid bone to the mandibular plane, relaxed pharyngeal soft tissue and large tongue base), may result in airflow disturbances due to increased upper airway resistance leading to severe apnea (24).

Following episodes of apnoea and hypopnoea, nocturnal hypoxemia is initially associated with impaired respiratory flow; when recovery capacity is exceeded on resumption of pulmonary ventilation, continuous hypoxia occurs due to carbon dioxide retention (25). In addition, at the end of apnea hypopnea episodes, due to increased respiratory effort, microtremors appear, which may produce a transition from sleep to wakefulness, with stage N1 increase and stage N3 and rapid eye movement (REM) decrease (26). Chronic nocturnal hypoxemia stimulates both hematopoiesis, causing polyglobulia and increased blood vascularity, and the gonadal glands, increasing hormone synthesis (27).

OSAS during infancy has been shown to influence normal growth and development by impairing the secretion of growth hormone (28). Data showing increased cortisol and adrenocorticotropic hormone levels associated with sleep-wake cycle disruption reflect the effort to maintain wakefulness (29,30). It is unclear whether apnea control via CPAP treatment normalizes testosterone levels. Testosterone therapy in patients with OSAS may generate notable adverse effects like increased cardiovascular morbidity, increase serum prostate-specific antigen levels, erythrocytosis. Thus, it should not be introduced without careful consideration (31). To the best of our knowledge, there is limited analysis of the impact of OSAS on female gonadal function (32-34).

The association between CPAP therapy and estrogen levels may depend on several factors (Fig. 1). Effective CPAP treatment can reduce hormonal problems related to OSAS, menstrual irregularities and PCOS risk, potentially increasing fertility and alleviating menopausal symptoms by enhancing sleep quality and managing weight problems (32).

3. Hypothalamic-pituitary-gonadal axis

Gonadal function is controlled by gonadotropins secreted by the anterior pituitary, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In turn, the pituitary gonadotropins controlled by gonadotropin-releasing hormone (GnRH) released by the median eminence of the hypothalamus into fenestrated capillaries of portal circulation and carried to the anterior pituitary (35). The ovarian follicle granulosa cells are stimulated by FSH to release aromatase, which converts androgens produced by thecal cells into estradiol (E2). FSH stimulates ovarian follicles to grow and mature; in combination with intratesticular testosterone, it supports spermatogenesis. LH stimulates ovulation and corpus luteum development and controls the androgen synthesis by the Leydig cells. The loss of negative estrogen feedback to the hypothalamus and pituitary gland due to androgens leads to increased FSH and LH levels (36,37). Depending on the serum values of gonadotropin and sex steroids, it is possible to differentiate between gonadal or hypothalamic/pituitary reproductive deficiency. Gonadal dysfunction is characterized by elevated FSH levels and reduced sex steroid levels, indicating primary dysfunction of the ovaries or testes. Hypothalamic/pituitary dysfunction is marked by low FSH and LH levels with decreased or normal sex steroid levels, signaling a problem in the regulatory signals from the brain to the gonads (38).

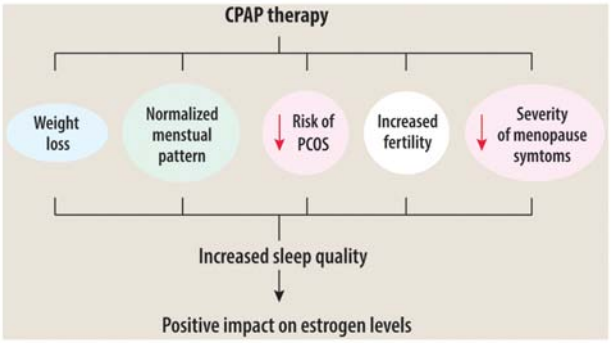

Figure 1. Effects of CPAP therapy on estrogen levels. CPAP therapy can improve sleep quality and potentially contribute to weight loss, which may increase estrogen levels. Patients with untreated OSAS may experience menstrual irregularities due to sleep disturbances and hormonal imbalances. Effective CPAP treatment can alleviate these symptoms and normalize menstrual patterns. Patients with OSAS may have a higher risk of developing conditions such as PCOS, which can decrease the estrogen levels. CPAP therapy may manage OSAS and mitigate the risk of PCOS-related hormonal disruption. CPAP therapy can improve fertility by addressing sleep-associated issues that may affect hormone production and reproductive health. CPAP therapy can improve sleep quality and decrease the severity of the menopausal symptoms, such as hot flushes and night sweats. CPAP-, continuous positive airway pressure; PCOS-, polycystic ovary syndrome.

4. OSAS and gonads

There are strong interrelationships between sex hormones and the respiratory function (39) however it is not clear which hormone serves a crucial role. Androgens, progesterone and E2 act directly through receptors in the nervous system. Sleep-disordered breathing, such as OSAS, can alter the hormonal homeostasis. The mechanisms may be different between sexes, as there are differences in terms of prevalent hormones and breathing control due to differences in lung size, hormonal fluctuations and body composition (40).

Numerous studies have shown a negative association between changes in sleep duration or architecture and the gonadal axis (41,42). There is a complex association between testosterone secretion, OSAS severity and obesity. Obesity is the leading cause of OSAS and low testosterone levels have been associated with increased body mass index (BMI) (43). Conversely, low testosterone levels facilitate weight gain. Certain authors have attributed the severity of OSAS to decreased testosterone concentration (44,45). Although most studies have investigated male subjects, similar effects have been observed in other sexes, with patients being more affected after than before menopause (1,2).

A study found that testosterone levels decrease with the increase in OSAS severity and are lower compared with those in control subjects (45). In another study that included obese men with associated metabolic syndrome and OSAS, the control group comprising male patients with similar clinical characteristics but without OSAS revealed that oxygen desaturation index correlated negatively with total and free testosterone levels (44). Therefore, hypoxia exerts independent effects on the pituitary-gonadal axis. A study comparing patients with OSAS with severe oxygen desaturation and those with less severe desaturation found a significant correlation between peak testosterone levels and total desaturation time, suggesting that hypoxia affects the circadian rhythm of testosterone (46). Similar findings were demonstrated in a study that compared testosterone levels with oxygen saturation of arterial blood (44). Loss of sleep quality, as assessed by altered normal sleep stage architecture, is also associated with reduced serum testosterone (47) and LH-testosterone profile (48). Although with advanced age there is a notable risk of developing sleep disorders, Luboshitzky *et al* (48) demonstrated that hypogonadism in patients with OSAS is age-independent.

Subnormal morning LH levels have been observed in 16 men with OSAS in whom testosterone levels were normal (49). Decreased LH and testosterone levels and their notable association with the Respiratory Disturbance Index suggest that pituitary-gonadal dysfunction is a consequence of OSAS rather than a primary independent disorder of the hypothalamic-pituitary-gonadal axis (48).

Gonadal hormones receptors are present in various types of tissues, including the lungs. The gonadal hormones have been found in epithelial cells that line the airways and alveoli of the lungs and can influence airway responsiveness and mucociliary clearance (50-52). Estrogen has been shown to affect the production of mucus in the airways and contributes to symptoms in conditions such as asthma and chronic obstructive pulmonary disease (53).

Activation of gonadal hormone receptors on smooth muscle cells can affect airway tone and reactivity, potentially contributing to bronchoconstriction or airway hyperresponsiveness. Gonadal hormone receptors on endothelial cell influence vascular function, including vasodilation, which may affect blood flow and oxygen exchange in the lung. Some immune cells within lung tissue, such as macrophages and lymphocytes, also express these receptors and modulate immune response in the lungs and may affect inflammation and immune cell function in respiratory disease.

The literature has revealed potential sites of gonadal hormone receptors in the lungs (Table I) (50-58). Research on gonadal hormones receptors in the lungs and their specific functions is ongoing.

Progesterone. Progesterone may help prevent premenopausal apnea (59). The bronchodilator effect of progesterone is caused by changes in smooth muscle tone of the airways (60). Progesterones, such as E2, prevent endothelial dysfunction and have a strong vasodilatory effect on the pulmonary circulation (61,62). Progesterone correlates with peak expiratory flow rate in humans during the luteal phase of the menstrual cycle (63). In classic interstitial pneumonia, progesterone receptors are expressed in the fibrotic regions (64). In the lung, progesterone results in upregulated IL-10, IL-1β, IL-5, IL-6, IL-22, tumor necrosis factor (TNF)-α, IL-4, steroid receptor coactivator/cyclin-dependent kinase inhibitor 1A, Erk, IL-9 and IL-13 as well downregulated or inhibited NF-κB, TGF-β1, connective tissue growth factor, transgelin, plasminogen activator inhibitor-1 and IFN-γ (65,66).

Progesterone is associated with hyperventilation during pregnancy. Animal studies have shown that lack of progesterone receptor correlates with loss of responsiveness to hypoxia, suggesting a beneficial role of progesterone on the airways (67,68,69).

Table I. Potential sites of gonadal hormone receptors in the lung.

Cell type	Gonadal hormone receptor	First author, year	(Refs.)
Epithelial	ERa, AR, PR	Tam *et al*, 2014; vom Steeg, 2020; Jain, 2012	(50-52)
Smooth muscle	ER, AR, PR	Bhallamudi, 2020; Kalidhindi, 2019; Matsui, 2000	(54-56)
Endothelial	ER	Bhallamudi, 2020	(54)
Immune	PR, ER, AR	vom Steeg, 2020; Azeez, 2021; Kovats, 2015	(51,57,58)

ER, estrogen receptor; AR, androgen receptor; PR, progesterone receptor.

Mouse responses to hypoxia and hypercapnia are suppressed after receiving small interfering RNA (siRNA) against membrane progesterone receptor-β but not receptor-αin the dorsal brainstem. Furthermore, the number of apnea episodes increases. The same study also revealed that membrane progesterone receptor β in the dorsal brainstem establishes sex-specific chemoreflex responses and reduces apnea frequency in adult mice, with females showing a higher ventilatory response to hypoxia and hypercapnia than males. Effects are eradicated by membrane progesterone receptor-β siRNA but not α (70).

Sleep duration can influence human reproduction by affecting hormonal regulation, menstrual regularity, fertility, stress levels and sexual function, all of which serve a role in reproductive health (32).

Some studies contend that the effect of progesterone on breathing is mediated by cells in the hypothalamus that contain progesterone receptors, either by modulating release of neuromodulators such as serotonin or by binding to and altering the function of γ-aminobutyric acid receptors (40,71,72).

Testosterone. Testosterone serves a protective role in the lung because it relaxes the bronchial lumen and decreases histamine response and airway inflammation (73-75). Furthermore, testosterone causes up-[IL-2, IFN-γ, haemoglobin subunit (Hbb)-β1, Hbb-γ and Hbb-θ1] and downregulation (IL-33, thymic stromal lymphopoietin, IL-4, IL-5, IL-13, angiopoietin-like 4 and cytochrome P450, family 1, subfamily A, polypeptide 1) of cytokines and inflammatory mediators in the lung (76-79).

A study suggested that the influence of testosterone on respiratory function is mediated by the action of estrogens (80). However, testosterone secretion is dependent on sleep cycle; its serum concentration increases during REM sleep. In addition, sleep of short duration (3 h) but with normal architecture is sufficient for normal levels of testosterone secretion (81). However, changes in serum testosterone levels have been demonstrated in sleep disorders in both animal models and human studies (82,83). A study of male rats found that sleep deprivation is followed by a reduction in serum testosterone levels and sperm quality compared with controls (82). Testosterone and prolactin levels are significantly lower in sleep-deficient individuals (83).

Although shorter sleep duration does not appear to alter testosterone levels, studies have shown that sleep duration of 5 h/night is associated with a 10-15% decrease in blood testosterone, decreased libido and vigour scores (assessed by measuring vitality, energy and general physical and mental well-being) (84,85).

In healthy young men, in the first part of sleep, dominated by periods of REM sleep, there is an increase in testosterone secretion (86). Sleep disturbance leads to decreased daily testosterone secretion (87). Following testosterone therapy, ventilatory sensitivity to carbon dioxide during sleep and wakefulness is enhanced in female patients (88).

Estrogen. The effect of estrogen on lung disease is not fully known. In the lung, estrogens induce cytokine and inflammatory mediator up-(IL-1β, IL-6, type I-IFN, TNF-α, NF-κB and toll-like receptor 8) and downregulation (TGF-β1 and IL-10) (58,89,90). The increased activity of thioredoxin, activation of the nuclear factor erythroid 2-related factor 2 (Nrf-2) and p38 mitogen-activated protein (p38 MAP) kinases, inhibition of vagal C-fibers and decrease expression of hypoxia-inducible factor (HIF)-1 have been linked to the positive effects of estrogen and phytoestrogens on obstructive sleep apnea and associated co-morbidities by decreasing OSAS severity, improving sleep quality, and mitigating hormonal and cardiovascular factors (91). The activation of p38 MAP kinase by estrogen may suppress HIF-1 to decrease lung inflammation, which may inhibit activation of vagal C-fibers to decrease bronchoconstriction to avoid obstruction when sleeping. In addition, estrogen-mediated thioredoxin and Nrf-2 upregulation enhances antioxidant defense and decreases inflammation (91). Another study reveals that the estrogen-related receptor-α/slow myosin heavy chain transcriptional regulatory cascade is a key factor in E2-mediated muscle protection, suggesting a potential novel therapeutic target for the treatment of postmenopausal OSAS (92).

OSAS is significantly more prevalent during and after the menopause. Decreased E2 may be associated with increased risk of OSAS in hormonally depressed patients during the peri- and postmenopause, in addition to greater BMI and age, supporting the hypothesis that decreased E2 associated with menopause affects upper airway patency (93). Patients are more likely to develop OSAS during pregnancy, polycystic ovary syndrome, during late menopause and post-menopause (94). There is an inverse link between E2 and OSAS based on reports that postmenopausal patients receiving hormone replacement therapy (HRT; estrogen or estrogen + progesterone) have a lower prevalence of OSAS than those without (32,91,92). Consequently, estrogen may provide protection during OSAS pathogenesis, but it is unclear if estrogen causes OSAS (93).

A previous study suggested that patients with an apnea-hypopnea index ≥25 require CPAP because they do not respond to HRT. HRT may be a good option for patients with less severe OSAS (94,95).

5. Fertility and OSAS

HIF-dependent and -independent pathways are two distinct mechanisms that can explain hypoxic effects on endocrine cells (96). Variations in protein phosphorylation and global transcription/translation efficiency are the key regulators of the HIF-independent process. Long-term control of the HIF-dependent pathway is triggered when HIF changes the expression of target genes.

As an effect of hypoxia, protein phosphorylation may change HIF activity (Fig. 2). Thus, protein phosphorylation serves an important role in mediating the activity of HIFs by regulating their stability, nuclear translocation and interaction with coactivators. This allows cells to adapt to hypoxic conditions by adjusting expression of specific genes involved in oxygen homeostasis and cell survival (e.g. erythropoietin, vascular endothelial growth factor, glucose transporter 1) (97,98).

The association between hypoxia caused by lung disease, such as chronic obstructive pulmonary disease, and decreased serum testosterone in men has been described (99,100). It has also been shown that erectile dysfunction is frequently present in these patients (99). Other factors that may contribute to infertility include increased oxidative stress, insulin resistance, systemic inflammation and aberrant secretion of reproductive hormones (100).

Sexual dysfunction has been reported in people with from sleep disorders and is a pathology of interest (101).

Oxidative stress is considered the link between OSAS and infertility. Increased oxidative stress may be an etiological factor for decreased sperm fertility and studies on mice and human male subjects have revealed that intermittent hypoxia correlates with increased testicular oxidative stress and decreased sperm motility (102,103). Chronic inflammation is associated with impairments in spermatogenesis, sperm quality and, consequently, fertility (104). In chronic inflammation, IL-6, TNF and C-reactive protein are the primary markers increased in patients with OSAS but are decreased by CPAP (105).

The risk of infertility is significantly increased with duration of OSAS. In addition, patients with untreated OSAS have an increased risk of infertility (22).

6. CPAP therapy

CPAP therapy has not been unequivocally shown to normalize the pituitary-gonadal axis in male patients (36,37,48). Studies published so far show controversial effects, as is the case with testosterone therapy (31,88). Although studies have shown that CPAP therapy contributes to increased testosterone levels, meta-analyses have not confirmed significant changes in this hormone after initiation of therapy (106-109). Conflicting results may be generated by suboptimal studies or therapeutic methodologies, such as insufficient duration of CPAP therapy (Table II).

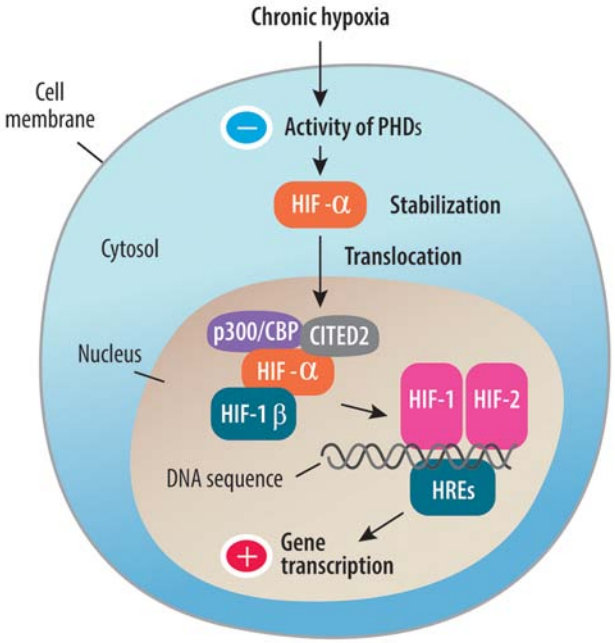

Figure 2. HIF pathway in chronic hypoxia. HIFs are heterodimeric proteins composed of α (HIF-1α, HIF-2α or HIF-3α) and β subunits. Under normoxic conditions, HIF-α subunits are rapidly degraded by the proteasome. However, under hypoxic conditions, PHDs that target HIF-α for degradation become less active due to decreased oxygen availability. This leads to the stabilization of HIF-α subunits. Once stabilized, HIF-α subunits translocate into the cell nucleus, where they form a complex with HIF-1β. This complex is required to form either transcription factor HIF-1 or HIF-2. Phosphorylation of HIF-α subunits enhances their interaction with coactivator proteins, such as p300/CBP and CITED2. These coactivators recruit RNA polymerase and other transcriptional machinery to the target genes, promoting gene expression. Phosphorylation regulates the stability of HIF-α subunits. Phosphorylation of HIF-α subunits occurs as a result of signaling pathways activated by growth factors, cytokines or other stimuli. Phosphorylation modulates HIF activity in response to cellular signals. DNA sequences influence HREs by containing specific binding sites that allow HIF proteins to attach to them, regulating the expression of target genes under hypoxic conditions. HIF, hypoxia-inducible factor; PHD, prolyl hydroxylases; p300-a transcriptional coactivator; CBP CREB-binding protein; CITED2p300, CBP-interacting transactivator with Glu/Asp-rich C-terminal domain 2; HRE, hypoxia response element.

The independent effect of OSAS on blood testosterone concentration has been demonstrated in certain studies (44,110-114) but not in all cross-sectional studies (33,47).

Following 3 months of CPAP treatment, serum testosterone concentration is normalized (115,116). CPAP therapy (long- or short-term) does not affect hormonal status in female patients (117). Compared with female patients, higher long-term CPAP is required for male patients with minimally symptomatic OSAS (118).

Serum levels of FSH, LH, progesterone and testosterone are significantly lower in 153 patients with OSAS patients than in controls (8). CPAP therapy has no effect on prolactin, E2 and progesterone levels and increases serum levels of FSH, LH and testosterone (119). The hypothalamic-pituitary-gonadal axis is primarily influenced by nocturnal hypoxemia and sleep disturbances in OSAS, which lowers blood levels of sex hormones. The decrease in testosterone is likely caused by a decrease in Leydig cell population, according to a study on brown Norway rats (120). Long-term exposure to hypoxia can lead to low sperm count

Table II. Effect of continuous positive airway pressure therapy on plasma testosterone in patients with obstructive sleep apnea syndrome.

First author, year	Number of patients	Duration of study, months	Timing of measurement	Testosterone levels	(Refs.)
Meston *et al*, 2003	101	1	Mid-morning	Decreased	(109)
Zhang *et al*, 2016	207	3	Morning	No change	(107)
Celec *et al*, 2014	67	6	Morning	No change	(33)

and infertility as testosterone is a key paracrine factor for spermatogenesis (121).

Weight loss may be a key factor in reversing gonadal dysfunction; massive weight loss (20% weight loss) normalizes testosterone levels (34,48,122).

7. Discussion

According to studies, sleep-disordered breathing is underdiagnosed and may underlie several multisystem disorders (6,12,13,19). Hypoxia, frequent nighttime awakening and stress influence hormonal secretion, which affects physical and cognitive development, obesity and infertility, which pose public health problems (92,100,102,103).

Studies have reported associations between sexual dysfunction, hormonal disorder and severity of apnea-hypopnea index (123,124). These studies have shown lower levels of progesterone and estrogen in patients with OSAS associated with development of sexual disorder. OSAS can have a negative impact on sexual function, either through direct effects or by causing hormonal imbalances (95,125).

Although most studies (43-46) have reported an association between sleep disorders and plasma testosterone levels, estrogens and progesterone impact on upper airway stability and respiratory control during the menstrual cycle. These hormones have been characterized as protective and are hypothesized to results in lower rates of OSAS in female patients. Levels of progesterone, E2 and 17-OH progesterone are lower in female patients with OSAS (123). In addition, previous polysomnographic investigations have shown that, regardless of body weight, OSAS is more common and severe in postmenopausal compared with premenopausal patients (2,124).

Breathing disorders during sleep affect secretion of gonadal hormones through various mechanisms (32-34). Sleep apnea often leads to disrupted sleep patterns characterized by repeated awakening due to breathing interruptions (14,41,42). These awakenings affect the normal circadian rhythm of gonadal hormone secretion (123). Prolactin secretion typically follows a diurnal pattern, with higher levels during the night and lower levels during the day. Sleep disruption can alter this pattern, leading to irregular prolactin secretion (123). These interruptions affect the normal circadian rhythm of hormone secretion, including progesterone (9). Progesterone levels typically vary throughout the menstrual cycle and are influenced by sleep quality and duration. Sleep apnea can be a source of chronic stress for the body, as it continually activates the stress response system, including the release of stress hormones such as cortisol (29,30). Elevated stress hormones can decrease the secretion of gonadal hormones. Prolonged stress leads to changes in the balance of gonadal hormones (32). Sleep apnea is characterized by episodes of hypoxia during breathing interruptions. Hypoxia can affect the function of the hypothalamus and pituitary gland, which are involved in regulating gonadal hormone secretion and changes in ovarian function (36,37). Thus, hypoxia can lead to dysregulation of hormone secretion pathways, potentially altering hormones levels. Sleep apnea is often associated with obesity and metabolic changes, such as insulin resistance (100). These factors contribute to alterations in gonadal hormone regulation. Sleep apnea leads to increased activity of the sympathetic nervous system (12). This heightened sympathetic activity influences hormone secretion, including prolactin. The exact mechanisms by which sympathetic activation affects prolactin are complex and not fully understood (12).

CPAP therapy is currently the gold standard of treatment for patients with sleep apnoea syndrome (13). Although this therapy allows effective control of breathing during sleep, a notable number of patients stop using it or use it inconsistently 12 months after initiation (118). Studies on the effect of CPAP therapy suggest that conflicting results may also be due to suboptimal studies or therapeutic methodologies, such as insufficient duration of CPAP therapy (36,37,107,118). On the other hand, although respiratory events are resolved by CPAP treatment, obesity may be an important risk factor for hypogonadism (38,48).

To the best of our knowledge, there is relatively limited data on the link between hypoxia induced by sleep-disordered breathing and gonadal hormonal imbalance (99,100,121). Moreover, data are often inconsistent, potentially due to the presence of factors such as obesity, stress and the long time required for the onset of sleep-disordered breathing disease. Social factors including obesity, socio-economic disparities, lifestyle choices, environmental conditions, urban noise pollution and sleep schedules influenced by workplace demands may also contribute to sleep-disordered breathing.

CPAP therapy does not have a clear positive impact on restoring gonadal hormonal balance (107). Long-term therapy may be more likely to normalize gonadal function, but, to the best of our knowledge, long-term studies have not been performed.

Although there is an association between sleep-disordered breathing and gonadal dysfunction via direct effects of hypoxia and hypothalamic-pituitary-gonadal axis dysfunction, CPAP therapy does not normalize this dysfunction (36,37). Patients

suffering from sleep-disordered breathing diseases might experience a prolonged period before their serum gonadal hormone levels return to normal due to these dysfunctions (32). Hormonal dysfunctions secondary to sleep apnea syndrome affect quality of life and hormonal homeostasis.

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Authors' contributions

CC and EC conceptualized the study. CC, EC, LP, CP and SDR designed the methodology and wrote the manuscript. CC, EC, LP, CP and SDR performed the literature review. SDR constructed tables. LP and CP edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin JL, *et al*: Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 7: 687-698, 2009.
2. Matsumoto T and Chin K: Prevalence of sleep disturbances: Sleep disordered breathing, short sleep duration, and non-restorative sleep. Respir Investig 57: 227-237, 2019.
3. Bixler EO, Papaliaga MN, Vgontzas AN, Lin HM, Pejovic S, Karataraki M, Vela-Bueno A and Chrousos GP: Women sleep objectively better than men and the sleep of young women is more resilient to external stressors: effects of age and menopause. J Sleep Res 18: 221-228, 2009.
4. Gaillard JM and Blois R: Spindle density in sleep of normal subjects. Sleep 4: 385-391, 1981.
5. Casper-Gallup State of Sleep in America 2022 Report. https://www.gallup.com/analytics/390536/sleep-in-america-2022.aspx.
6. Song Z, Jiang R, Li C, Jin F and Tao M: Menopausal Symptoms and sleep quality in women aged 40-65 years. Biomed Res Int 2022: 2560053, 2022.
7. Franklin KA, Sahlin C, Stenlund H and Lindberg E: Sleep apnoea is a common occurrence in females. Eur Respir J 41: 610-615, 2013.
8. Farias JG, Bustos-Obregón E, Orellana R, Bucarey JL, Quiroz E and Reyes JG: Effects of chronic hypobaric hypoxia on testis histology and round spermatid oxidative metabolism. Andrologia 37: 47-52, 2005.
9. Martins FO and Conde SV: Gender differences in the context of obstructive sleep apnea and metabolic diseases. Front Physiol 12: 792633, 2021.
10. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE and Somers VK: Obstructive sleep apnea and cardiovascular disease: A scientific statement from the american heart association. Circulation 144: e56-e67, 2021.
11. Mehra R, Chung MK, Olshansky B, Dobrev D, Jackson CL, Kundel V, Linz D, Redeker NS, Redline S, Sanders P, *et al*: Sleep-disordered breathing and cardiac arrhythmias in adults: Mechanistic insights and clinical implications: A scientific statement from the American heart association. Circulation 146: e119-e136, 2022.
12. Young T, Palta M, Dempsey J, Skatrud J, Weber S and Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328: 1230-1235, 1993.
13. Franklin KA and Lindberg E: Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis 7: 1311-1322, 2015.
14. Benkirane O, Delwiche B, Mairesse O and Peigneux P: Impact of sleep fragmentation on cognition and fatigue. Int J Environ Res Public Health 19: 15485, 2022.
15. Cowie MR, Linz D, Redline S, Somers VK and Simonds AK: Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 78: 608-624, 2021.
16. Douglas NJ, White DP, Pickett CK, Weil JV and Zwillich CW: Respiration during sleep in normal man. Thorax 37: 840-844, 1982.
17. Sunwoo BY and Owens RL: Sleep deficiency, sleep apnea, and chronic lung disease. Clin Chest Med 43: 337-352, 2022.
18. Francis ME, Kusek JW, Nyberg LM and Eggers PW: The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. J Urol 178: 591-596, 2007.
19. Jennum P and Sjøl A: Epidemiology of snoring and obstructive sleep apnoea in a Danish population, age 30-60. J Sleep Res 1: 240-244, 1992.
20. Chen L, Pivetta B, Nagappa M, Saripella A, Islam S, Englesakis M and Chung F: Validation of the STOP-Bang questionnaire for screening of obstructive sleep apnea in the general population and commercial drivers: A systematic review and meta-analysis. Sleep Breath 25: 1741-1751, 2021.
21. World Health Organisation: Infertility. [(accessed on 10 August 2022)]. Available online: https://www.who.int/health-topics/infertility#tab=tab_1.
22. Jhuang YH, Chung CH, Wang ID, Peng CK, Meng E, Chien WC and Chang PY: Association of obstructive sleep apnea with the risk of male infertility in Taiwan. JAMA Netw Open 4: e2031846, 2021.
23. Lim ZW, Wang ID, Wang P, Chung CH, Huang SS, Huang CC, Tsai PY, Wu GJ, Wu KH and Chien WC: Obstructive sleep apnea increases risk of female infertility: A 14-year nationwide population-based study. PLoS One 16: e0260842, 2021.
24. Espinoza-Cuadros F, Fernández-Pozo R, Toledano DT, Alcázar-Ramírez JD, López-Gonzalo E and Hernández-Gómez LA: Speech signal and facial image processing for obstructive sleep apnea assessment. Comput Math Methods Med 2015: 489761, 2015.
25. Kumagai H, Sawatari H, Kiyohara Y, Kanoh A, Asada K, Kawaguchi K, Arita A, Murase Y, Konishi N, Hoshino T, *et al*: Nocturnal hypoxemia is related to morning negative affectivity in untreated patients with severe obstructive sleep apnea. Sci Rep 12: 21262, 2022.
26. Bianchi MT, Cash SS, Mietus J, Peng CK and Thomas R: Obstructive sleep apnea alters sleep stage transition dynamics. PLoS One 5: e11356, 2010.
27. Alvarez-Martins I, Remédio L, Matias I, Diogo LN, Monteiro EC and Dias S: The impact of chronic intermittent hypoxia on hematopoiesis and the bone marrow microenvironment. Pflugers Arch 468: 919-932, 2016.
28. Nieminen P, Löppönen T, Tolonen U, Lanning P, Knip M and Löppönen H: Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. Pediatrics 109: e55, 2002.
29. Chapotot F, Buguet A, Gronfier C and Brandenberger G: Hypothalamo-pituitary-adrenal axis activity is related to the level of central arousal: Effect of sleep deprivation on the association of high-frequency waking electroencephalogram with cortisol release. Neuroendocrinology 73: 312-321, 2001.

30. Nicolaides NC, Vgontzas AN, Kritikou I and Chrousos G: HPA axis and sleep. Endotext [Internet]. Feingold KR, Anawalt B, Blackman MR, *et al* (eds). South Dartmouth (MA): MDText.com, Inc., 2020. https://www.ncbi.nlm.nih.gov/books/NBK279071/. Accessed May 2, 2023.
31. Grech A, Breck J and Heidelbaugh J: Adverse effects of testosterone replacement therapy: An update on the evidence and controversy. Ther Adv Drug Saf 5: 190-200, 2014.
32. Kalmbach DA, Arnedt JT, Pillai V and Ciesla JA: The impact of sleep on female sexual response and behavior: A pilot study. J Sex Med 12: 1221-1232, 2015.
33. Celec P, Mucska I, Ostatníková D and Hodosy J: Testosterone and estradiol are not affected in male and female patients with obstructive sleep apnea treated with continuous positive airway pressure. J Endocrinol Invest 37: 9-12, 2014.
34. Petersen M, Kristensen E, Berg S, Giraldi A and Midgren B: Sexual function in female patients with obstructive sleep apnea. J Sex Med 8: 2560-2568, 2011.
35. Clifton DK and Steiner RA: Neuroendocrinology of reproduction. Yen & Jaffe's Reproductive Endocrinology, pp3-33, 2009.
36. Hsueh AJW, Kawamura K, Cheng Y and Fauser BCJM: Intraovarian control of early folliculogenesis. Endocr Rev 36: 1-24, 2015.
37. Thibault C and Levasseur MC: Ovulation. Hum Reprod 3: 513-523, 1988.
38. Richard-Eaglin A: Male and female hypogonadism. Nurs Clin North Am 53: 395-405, 2018.
39. Fuentes N and Silveyra P: Endocrine regulation of lung disease and inflammation. Exp Biol Med (Maywood) 243: 1313-1322, 2018.
40. Behan M and Wenninger JM: Sex steroidal hormones and respiratory control. Respir Physiol Neurobiol 164: 213-221, 2008.
41. Schmid SM, Hallschmid M, Jauch-Chara K, Lehnert H and Schultes B: Sleep timing may modulate the effect of sleep loss on testosterone. Clin Endocrinol (Oxf) 77: 749-754, 2012.
42. Touzet S, Rabilloud M, Boehringer H, Barranco E and Ecochard R: Relationship between sleep and secretion of gonadotropin and ovarian hormones in women with normal cycles. Fertil Steril 77: 738-744, 2002.
43. Kim SD and Cho KS: Obstructive sleep apnea and testosterone deficiency. World J Mens Health 37: 12-18, 2019.
44. Gambineri A, Pelusi C and Pasquali R: Testosterone levels in obese male patients with obstructive sleep apnea syndrome: Relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. J Endocrinol Investig 26: 493-498, 2003.
45. Bercea RM, Patacchioli FR, Ghiciuc CM, Cojocaru E and Mihaescu T: Serum testosterone and depressive symptoms in severe OSA patients. Andrologia 45: 345-350, 2013.
46. Kouchiyama S, Honda Y and Kuriyama T: Influence of nocturnal oxygen desaturation on circadian rhythm of testosterone secretion. Respiration 57: 359-363, 1990.
47. Barrett-Connor E, Dam TT, Stone K, Harrison SL, Redline S and Orwoll E; Osteoporotic Fractures in Men Study Group: The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. J Clin Endocrinol Metab 93: 2602-2609, 2008.
48. Luboshitzky R, Aviv A, Hefetz A, Herer P, Shen-Orr Z, Lavie L and Lavie P: Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. J Clin Endocrinol Metab 87: 3394-3398, 2002.
49. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, O'Connor GT, Rapoport DM and Robbins JA: Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med 167: 1186-1192, 2003.
50. Tam A, Wadsworth S, Dorscheid D, Man SFP and Sin DD: Estradiol increases mucus synthesis in bronchial epithelial cells. PLoS One 9: e100633, 2014.
51. vom Steeg LG, Dhakal S, Woldetsadik YA, Park HS, Mulka KR, Reilly EC, Topham DJ and Klein SL: Androgen receptor signaling in the lungs mitigates inflammation and improves the outcome of influenza in mice. PLoS Pathog 16: e1008506, 2020.
52. Jain R, Ray JM, Pan JH and Brody SL: Sex hormone-dependent regulation of cilia beat frequency in airway epithelium. Am J Respir Cell Mol Biol 46: 446-453, 2012.
53. Siegfried JM: Sex and gender differences in lung cancer and chronic obstructive lung disease. Endocrinology 163: bqab254, 2022.
54. Bhallamudi S, Connell J, Pabelick CM, Prakash YS and Sathish V: Estrogen receptors differentially regulate intracellular calcium handling in human nonasthmatic and asthmatic airway smooth muscle cells. Am J Physiol Lung Cell Mol Physiol 318: L112-L124, 2020.
55. Kalidhindi RSR, Katragadda R, Beauchamp KL, Pabelick CM, Prakash YS and Sathish V: Androgen receptor-mediated regulation of intracellular calcium in human airway smooth muscle cells. Cell Physiol Biochem 53: 215-228, 2019.
56. Matsui K, Takeda K, Yu ZX, Valencia J, Travis WD, Moss J and Ferrans VJ: Downregulation of estrogen and progesterone receptors in the abnormal smooth muscle cells in pulmonary lymphangioleiomyomatosis following therapy. An immunohistochemical study. Am J Respir Crit Care Med 161: 1002-1009, 2000.
57. Azeez JM, Susmi TR, Remadevi V, Ravindran V, Sasikumar Sujatha A, Ayswarya RNS and Sreeja S: New insights into the functions of progesterone receptor (PR) isoforms and progesterone signaling. Am J Cancer Res 11: 5214-5232, 2021.
58. Kovats S: Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol 294: 63-69, 2015.
59. Martin SE, Mathur R, Marshall I and Douglas NJ: The effect of age, sex, obesity and posture on upper airway size. Eur Respir J 10: 2087-2090,1997.
60. LoMauro A and Aliverti A: Respiratory physiology of pregnancy: Physiology masterclass. Breathe (Sheff) 11: 297-301, 2015.
61. Artem'eva MM, Kovaleva YO, Medvedev OS and Medvedeva NA: Effect of chronic administration of estradiol on responsiveness of isolated systemic and pulmonary blood vessels from ovariectomized wistar rats with hypoxic pulmonary hypertension. Bull Exp Biol Med 159: 427-430, 2015.
62. English KM, Jones RD, Jones TH, Morice AH and Channer KS: Gender differences in the vasomotor effects of different steroid hormones in rat pulmonary and coronary arteries. Horm Metab Res 33: 645-652, 2001.
63. de Zambotti M, Nicholas CL, Colrain IM, Trinder JA and Baker FC: Autonomic regulation across phases of the menstrual cycle and sleep stages in women with premenstrual syndrome and healthy controls. Psychoneuroendocrinology 38: 2618-2627, 2013.
64. Vafashoar F, Mousavizadeh K, Poormoghim H, Haghighi A, Pashangzadeh S and Mojtabavi N: Progesterone aggravates lung fibrosis in a mouse model of systemic sclerosis. Front Immunol 12: 742227, 2021.
65. Migliaccio A, Piccolo D, Castoria G, Di Domenico M, Bilancio A, Lombardi M, Gong W, Beato M and Auricchio F: Activation of the Src/p21ras/Erk pathway by progesterone receptor via cross-talk with estrogen receptor. EMBO J 17: 2008-1018, 1998.
66. Kunzmann S, Ottensmeier B, Speer CP and Fehrholz M: Effect of progesterone on Smad signaling and TGF-β/Smad-regulated genes in lung epithelial cells. PLoS One 13: e0200661, 2018.
67. Potvin C, Rossignol O, Uppari N, Dallongeville A, Bairam A and Joseph V: Reduced hypoxic ventilatory response in newborn mice knocked-out for the progesterone receptor. Exp Physiol 99: 1523-1537, 2014.
68. Saaresranta T and Polo O: Hormones and breathing. Chest 122: 2165-2182, 2002.
69. Chiarella SE, Cardet JC and Prakash YS: Sex, cells, and asthma. Mayo Clin Proc 96: 1955-1969, 2021.
70. Boukari R, Rossignol O, Baldy C, Marcouiller F, Bairam A and Joseph V: Membrane progesterone receptor-β, but not-α, in dorsal brain stem establishes sex-specific chemoreflex responses and reduces apnea frequency in adult mice. J Appl Physiol (1985) 121: 781-791, 2016.
71. Robinson JE and Kendrick KM: Inhibition of luteinizing hormone secretion in the ewe by progesterone: Associated changes in the release of gamma-aminobutyric Acid and noradrenaline in the preoptic area as measured by intracranial microdialysis. J Neuroendocrinol 4: 231-236, 1992.
72. Rupprecht R: Neuroactive steroids: Mechanisms of action and neuropsychopharmacological properties. Psychoneuroendocrinology 28: 139-168, 2003.
73. Verma MK, Miki Y and Sasano H: Sex steroid receptors in human lung diseases. J Steroid Biochem Mol Biol 127: 216-222, 2011.
74. Hoffman EA, Ahmed FS, Baumhauer H, Budoff M, Carr JJ, Kronmal R, Reddy S and Barr RG: Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample. The MESA lung study. Ann Am Thorac Soc 11: 898-907, 2014.

75. Kouloumenta V, Hatziefthimiou A, Paraskeva E, Gourgoulianis K and Molyvdas PA: Non-genomic effect of testosterone on airway smooth muscle. Br J Pharmacol 149: 1083-1091, 2006.
76. Laffont S, Blanquart E, Savignac M, Cénac C, Laverny G, Metzger D, Girard JP, Belz GT, Pelletier L, Seillet C and Guéry JC: Androgen signaling negatively controls group 2 innate lymphoid cells. J Exp Med 214: 1581-1592, 2017.
77. Lamont KR and Tindall DJ: Androgen regulation of gene expression. Adv Cancer Res 107: 137-162, 2010.
78. Cephus JY, Stier MT, Fuseini H, Yung JA, Toki S, Bloodworth MH, Zhou W, Goleniewska K, Zhang J, Garon SL, *et al*: Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. Cell Rep 21: 2487-2499, 2017.
79. Mikkonen L, Pihlajamaa P, Sahu B, Zhang FP and Jänne OA: Androgen receptor and androgen-dependent gene expression in lung. Mol Cell Endocrinol 317: 14-24, 2010.
80. Zabka AG, Mitchell GS and Behan M: Conversion from testosterone to oestradiol is required to modulate respiratory long-term facilitation in male rats. J Physiol 576: 903-912, 2006.
81. Wittert G: The relationship between sleep disorders and testosterone in men. Asian J Androl 16: 262-265, 2014.
82. Alvarenga TA, Hirotsu C, Mazaro-Costa R, Tufik S and Andersen ML: Impairment of male reproductive function after sleep deprivation. Fertil Steril 103: 1355-1362.e1, 2015.
83. Jauch-Chara K, Schmid SM, Hallschmid M, Oltmanns KM and Schultes B: Pituitary-gonadal and pituitary-thyroid axis hormone concentrations before and during a hypoglycemic clamp after sleep deprivation in healthy men. PLoS One 8: e54209, 2013.
84. Leproult R and Van Cauter E: Effect of 1 week of sleep restriction on testosterone levels in young healthy men. JAMA 305: 2173-2174, 2011.
85. Su L, Zhang SZ, Zhu J, Wu J and Jiao YZ: Effect of partial and total sleep deprivation on serum testosterone in healthy males: A systematic review and meta-analysis. Sleep Med 88: 267-273, 2021.
86. Luboshitzky R, Herer P, Levi M, Shen-Orr Z and Lavie P: Relationship between rapid eye movement sleep and testosterone secretion in normal men. J Androl 20: 731-737, 1999.
87. Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P and Lavie P: Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. J Clin Endocrinol Metab 86: 1134-1139, 2001.
88. Ahuja D, Mateika JH, Diamond MP and Badr MS: Ventilatory sensitivity to carbon dioxide before and after episodic hypoxia in women treated with testosterone. J Appl Physiol (1985) 102: 1832-1838, 2007.
89. Smith LC, Moreno S, Robertson L, Robinson S, Gant K, Bryant AJ and Sabo-Attwood T: Transforming growth factor beta1 targets estrogen receptor signaling in bronchial epithelial cells. Respir Res 19: 160, 2018.
90. Shim B, Pacheco-Rodriguez G, Kato J, Darling TN, Vaughan M and Moss J: Sex-specific lung diseases: Effect of oestrogen on cultured cells and in animal models. Eur Respir Rev 22: 302-311, 2013.
91. Zhang L, Ou X, Zhu T and Lv X: Beneficial effects of estrogens in obstructive sleep apnea hypopnea syndrome. Sleep Breath 24: 7-13, 2020.
92. Chen HH, Lu J, Guan YF, Li SJ, Hu TT, Xie ZS, Wang F, Peng XH, Liu X, Xu X, *et al*: Estrogen/ERR-α signaling axis is associated with fiber-type conversion of upper airway muscles in patients with obstructive sleep apnea hypopnea syndrome. Sci Rep 6: 27088, 2016.
93. Galvan T, Camuso J, Sullivan K, Kim S, White D, Redline S and Joffeet H: Association of estradiol with sleep apnea in depressed perimenopausal and postmenopausal women: A preliminary study. Menopause 24: 112-117, 2017.
94. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A and White DP: Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 86: 1175-1180, 2001.
95. White DP: The hormone replacement dilemma for the pulmonologist. Am J Respir Crit Care Med 167: 1165-1166, 2003.
96. Lee HC and Tsai SJ: Endocrine targets of hypoxia-inducible factors. J Endocrinol 234: R53-R65, 2017.
97. Gleadle JM and Ratcliffe PJ: Induction of hypoxia-inducible factor-1, erythropoietin, vascular endothelial growth factor, and glucose transporter-1 by hypoxia: Evidence against a regulatory role for Src kinase. Blood 89: 503-509, 1997.
98. Déry MAC, Michaud MD and Richard DE: Hypoxia-inducible factor 1: Regulation by hypoxic and non-hypoxic activators. Int J Biochem Cell Biol 37: 535-540, 2005.
99. Cojocaru C, Turcanu A, Mihaescu T, Ciobica A, Timofte D, Alexinschi O, Anton E and Cojocaru E: A biological perspective for the management of chronic obstructive pulmonary disease by testosterone. Arch Biol Sci 67: 257-259, 2015.
100. Palnitkar G, Phillips CL, Hoyos CM, Marren AJ, Bowman MC and Yee BJ: Linking sleep disturbance to idiopathic male infertility. Sleep Med Rev 42: 149-159, 2018.
101. Hammoud AO, Carrell DT, Gibson M, Peterson CM and Meikle AW: Updates on the relation of weight excess and reproductive function in men: Sleep apnea as a new area of interest. Asian J Androl 14: 77-81, 2012.
102. Torres M, Laguna-Barraza R, Dalmases M, Calle A, Pericuesta E, Montserrat JM, Navajas D, Gutierrez-Adan A and Farréet R: Male fertility is reduced by chronic intermittent hypoxia mimicking sleep apnea in mice. Sleep 37: 1757-1765, 2014.
103. Alahmar AT: Role of oxidative stress in male infertility: An updated review. J Hum Reprod Sci 12: 4-18, 2019.
104. Seshadri S, Bates M, Vince G and Jones DIL: The role of cytokine expression in different subgroups of subfertile men. Am J Reprod Immunol 62: 275-282, 2009.
105. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, Hirano T and Adachi M: Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 107: 1129-1134, 2003.
106. Zhang XB, Jiang XT, Du YP, Yuan YT and Chen B. Efficacy of continuous positive airway pressure on testosterone in men with obstructive sleep apnea: A meta-analysis. PLoS One 9: e115033, 2014.
107. Zhang XB, Lin QC, Zeng HQ, Jiang XT, Chen B and Chen X: Erectile dysfunction and sexual hormone levels in men with obstructive sleep apnea: Efficacy of continuous positive airway pressure. Arch Sex Behav 45: 235-240, 2016.
108. Cignarelli A, Castellana M, Castellana G, Perrini S, Brescia F, Natalicchio A, Garruti G, Laviola L, Resta O and Giorgino F: Effects of CPAP on testosterone levels in patients with obstructive sleep apnea: A meta-analysis study. Front Endocrinol (Lausanne) 10: 551, 2019.
109. Meston N, Davies RJO, Mullins R, Jenkinson C, Wass JAH and Stradling J:. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. J Intern Med 254: 447-454, 2003.
110. Canguven O, Selepci B, Albayrak S, Selimoglu A, Balaban M and Bulbul M: Is there a correlation between testosterone levels and the severity of the disease in male patients with obstructive sleep apnea? Arch Ital Urol Androl 82: 143-147, 2010.
111. Kirbas G, Abakay A, Topcu F, Kaplan A, Ünlü M and Peker Y: Obstructive sleep apnoea, cigarette smoking and serum testosterone levels in a male sleep clinic cohort. J Int Med Res 35: 38-45, 2007.
112. Hammoud AO, Walker JM, Gibson M, Cloward TV, Hunt SC, Kolotkin RL, Adams TD and Meikle W: Sleep apnea, reproductive hormones and quality of sexual life in severely obese men. Obesity (Silver Spring) 19: 1118-1123, 2011.
113. Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID and Sullivan CE: Neuroendocrine dysfunction in sleep apnea: Reversal by continuous positive airways pressure therapy. J Clin Endocrinol Metab 68: 352-358, 1989.
114. Clarke BM, Vincent AD, Martin S, Adams R, Appleton S, Vakulin A, Jesudason D and Wittert GA: Obstructive sleep apnea is not an independent determinant of testosterone in men. Eur J Endocrinol 183: 31-39, 2020.
115. Santamaria JD, Prior JC and Fleetham JA: Reversible reproductive dysfunction in men with obstructive sleep apnoea. Clin Endocrinol (Oxf) 28: 461-470, 1988.
116. Jayaraman G, Majid H, Surani S, Kao C and Subramanian S: Influence of gender on continuous positive airway pressure requirements in patients with obstructive sleep apnea syndrome. Sleep Breath 15: 781-784, 2011.
117. Li Z, Tang T, Wu W, Gu L, Du J, Zhao T, Zhou X, Wu H and Qin G: Efficacy of nasal continuous positive airway pressure on patients with OSA with erectile dysfunction and low sex hormone levels. Respir Med 119: 130-134, 2016.

118. Turnbull CD, Bratton DJ, Craig SE, Kohler M and Stradling JR: In patients with minimally symptomatic OSA can baseline characteristics and early patterns of CPAP usage predict those who are likely to be longer-term users of CPAP. J Thorac Dis 8: 276-281, 2016.
119. Lima N, Cavaliere H, Knobel M, Halpern A and Medeiros-Neto G: Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat. Int J Obes Relat Metab Disord 24: 1433-1437, 2000.
120. Chen H, Hardy MP, Huhtaniemi I and Zirkin BR: Age-related decreased Leydig cell testosterone production in the brown Norway rat. J Androl 15: 551-557, 1994
121. Li Z, Wang S, Gong C, Hu Y, Liu J, Wang W, Chen Y, Liao Q, He B, Huang Y, *et al*: Effects of environmental and pathological hypoxia on male fertility. Front Cell Dev Biol 9: 725933, 2021.
122. Saad F, Doros G, Haider KS and Haider A: Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: Real-world data from a controlled registry study. Int J Obes (Lond) 44: 1264-1278, 2020.
123. Netzer NC, Eliasson AH and Strohl KP: Women with sleep apnea have lower levels of sex hormones. Sleep Breath 7: 25-29, 2003.
124. Dancey DR, Hanly PJ, Soong C, Lee B and Hoffstein V: Impact of menopause on the prevalence and severity of sleep apnea. Chest 120: 151-155, 2001.
125. Köseoğlu N, Köseoğlu H, Itil O, Oztura I, Baklan B, Ikiz AO and Esen AA: Sexual function status in women with obstructive sleep apnea syndrome. J Sex Med 4: 1352-1357, 2007.