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Metabolic Dysfunction in PCOS: Relationship to Obstructive Sleep Apnea

Abstract

Polycystic ovary syndrome (PCOS) affects between 5 and 8% of women, making it one of the most common endocrinopathies in women. The disorder typically has its onset at puberty with evidence of excessive androgen production, obesity, and insulin resistance. Women with PCOS are more insulin resistant than weight-matched controls and have an exceptionally high prevalence of early-onset impaired glucose tolerance (30 - 40 percent), and type 2 diabetes (up to 10 percent). Over the past several years, chronic decreases in sleep duration and/or quality have been identified as a risk for the development of a number of metabolic derangements that are strikingly similar to those seen in PCOS. Specifically, decreased sleep quality due to obstructive sleep apnea (OSA) has been causally linked to insulin resistance, glucose intolerance, dyslipidemia and hypertension independent of body mass index (BMI). Until recently, however, it had not been recognized that OSA is present in a disproportionate number of women with PCOS: the risk for OSA is at least 5-10 fold higher compared to the risk in similarly obese women without PCOS. The causes and consequences of OSA in women with PCOS are addressed in this manuscript.

Keywords

Polycystic ovary syndrome; obstructive sleep apnea; metabolic syndrome; type 2 diabetes mellitus; impaired glucose tolerance; insulin resistance; obesity; cardiovascular; dyslipidemia

Introduction

It is now well established that the average duration of sleep has declined over the past several decades for most Americans. During the 1960's, the mean sleep duration was between 7 and 8 hours per night; current estimates place the average duration at less than 6 hours per night (1). Chronic sleep loss imposes a significant negative impact upon individual health as well as an enormous economic cost to society. Shortened sleep duration is associated with increased mortality (2, 3), even after adjusting for age, smoking, alcohol, exercise, depression, snoring, obesity, and history of cancer and cardiovascular disease (3). Reduced sleep time has also been reported as a risk factor for the development of obesity and for type 2 diabetes (4, 5) (11, 12). Results of the Sleep Heart Health Study showed that subjects sleeping 5 hours or less per night had an adjusted odds ratios for diabetes of 2.51 (95% CI, 1.57-4.02) when compared to those who slept 7 to 8 hours per night (5). This trend in shorter sleep duration mirrors the progressive rise in overweight and obesity in the United States (6) and evidence continues to emerge to support a causal link between these two

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conditions. Should either or both trends continue along their current trajectory, the metabolic and cardiovascular health consequences as well as economic costs will be staggering.

Obstructive sleep apnea (OSA) is a highly prevalent, chronic condition that is characterized by recurrent episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway leading to intermittent hypoxia, cortical microarousals, sleep fragmentation and chronic sleep loss (7-9). The severity of OSA is defined by the number of obstructive events per hour of sleep [apnea-hypopnea index or AHI], and is usually characterized as mild, moderate, or severe. Obstructive sleep apnea is now well-documented to be an important contributor to both metabolic disturbances (insulin resistance, type 2 diabetes) and adverse cardiovascular events (10-27) even in milder forms of OSA (25, 28-30).

Obstructive respiratory events can occur throughout the sleep cycle and can also cluster in REM sleep or NREM sleep (31). Studies have consistently demonstrated that REM-related OSA occurs more commonly in younger individuals, women, children, and in patients with mild or moderate OSA rather than severe OSA (32-35). Although gender is known to impact upon the distribution (REM vs. NREM) of obstructive events, the physiologic basis for this gender-based difference has not been established. Likewise, whether the cardiometabolic consequences of OSA differ in frequency or severity as a consequence of the distribution of obstructive events (REM vs. NREM) has not been established.

The majority of patients (approximately 80%) with OSA have either mild (AHI<15) or moderate (AHI<30) disease (36, 37). Among these individuals, obstructive events often cluster in REM sleep (32) (so-called “REM-related OSA”) leading to selective fragmentation of REM sleep (32). While the precise prevalence of REM-related OSA has not been established, based upon data from a number of clinical studies in which polysomnography has been utilized, it appears to be between 10% and 36% of those having OSA (32, 33). Recently, it has been reported that among the 14% of individuals studied as part of the Sleep Heart Health Study (SHHS) who had an overall AHI • 5.5, the AHI in REM sleep was • 13, while the AHI in non-REM sleep was < 8 (17).

REM sleep is associated with greater sympathetic activity and cardiovascular instability in healthy human subjects and patients with OSA when compared to NREM sleep (38, 39). These acute hemodynamic changes of REM sleep could play a part in triggering ischemic events in patients with cardiovascular disease (39-42). Indeed, obstructive apneas and hypopneas during REM sleep tend to be longer in duration, lead to greater degrees of hypoxemia (43, 44) and higher levels of sympathetic activity compared to events in NREM sleep (38). Despite the more significant degrees of hypoxemia and sympathetic activity, patients with REM-related OSA generally have overall milder OSA due to REM sleep occupying only 15-25% of sleep time in adults. Moreover, the majority of studies thus far have failed to demonstrate an association between AHI in REM and subjective or objective measures of sleepiness (16, 17, 20, 45).

Sex differences in prevalence of OSA

In a recent study conducted by Mokhlesi et al (46) out of 1,019 consecutive adults referred for their first in-laboratory clinical PSG for suspicion of OSA over a 10 month period, 931 patients (91.4%) had OSA (AHI ≥ 5). Obstructive sleep apnea was mild to moderate (AHI < 30) in 61% of women in contrast to 37% of men ($p<0.0001$). The prevalence of REM-related OSA was 13.5% (47). These data confirmed previous reports that REM-related OSA was more prevalent in women (78% vs. 48%; $p<0.001$) and among younger individuals (45±15 years vs. 52±14 years; $p<0.001$). We also found a higher prevalence of REM-related OSA in African-Americans compared to Caucasians (65% vs. 55%, $p=0.008$). The higher prevalence of OSA in African-Americans had not been previously reported and it remains

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unclear why African-American patients with OSA have a higher prevalence of REM-related OSA. It is important to note that our cohort consisted of 58% African Americans.

Although clinic-based studies had previously reported a significant gender gap in the prevalence of OSA, more recent large population-based studies have demonstrated that the prevalence of OSA is only 1.5-3 times higher in men than in women and this gender gap narrows even further after menopause. This discrepancy between clinic and population-based prevalence suggests a strong referral bias for evaluating OSA favoring men and it has been hypothesized to be partly attributed to different clinical presentations of OSA in women. Women may not present with the "classic" symptoms of OSA (loud snoring, EDS, nocturnal choking episodes, or witnessed apneas), and therefore may less likely be referred for a formal evaluation. In two clinic-based studies comparing men and women with similar degrees of obesity and OSA, women were more likely to present with "atypical complaints" such as insomnia or depression, and less likely to have observed apneas (48, 49). However, two population-based studies have reported similar symptoms of OSA in men and women (50, 51). As a result, there may be other reasons for the gender disparity in diagnosing OSA such as the possibility that health care providers disregard typical symptoms in women or alternatively, women are less likely to seek medical attention because of loud snoring. The lack of recognition of OSA in women may impact mortality, as one study found that women with OSA had a higher 5 year mortality rate when compared to men with OSA (37). Additionally, women have a higher prevalence of REM-related OSA and several studies have reported a lack of association between AHI in REM and subjective or objective measures of sleepiness. This suggests that women may not present with the classic symptom of excessive daytime sleepiness. Taken together, the evidence suggests that women are under-diagnosed and consequently undertreated for OSA compared to men.

Obstructive Sleep Apnea in Women with PCOS

Women with PCOS have been documented to develop OSA at rates that equal and may even exceed those in men. The high prevalence of OSA has been thought to be a function of both elevated levels of testosterone (a defining feature of PCOS) as well as the obesity that commonly accompanies the disorder. Howeve r, it appears that the high prevalence of OSA in PCOS cannot be fully accounted for on the basis of these two factors alone. In two studies (52, 53), the severity of sleep apnea did not correlate with BMI and in a third (54), even after controlling for BMI, PCOS women were as much as 30 times more likely to have sleep disordered breathing and 9 times more likely than controls to have daytime sleepiness. Insulin resistance was found to be a stronger predictor of sleep disordered breathing than was age, BMI, or circulating testosterone concentrations (53). It also appeared that women with PCOS taking oral contraceptives were less likely to have sleep disordered breathing (53), consistent with recent results from the Sleep Heart Health Study Research Group in which hormone replacement therapy was associated with a lower likelihood of sleep disordered breathing among postmenopausal women (55). Finally, women with PCOS had a significantly higher mean AHI compared to weight-matched controls (22.5 ± 6.0 vs. 6.7 ± 1.7; $P<0.01$), with the difference being most pronounced in REM sleep (41.3 ± 7.5 vs. 13.5 ± 3.3; $P<0.01$) (54). We have prospectively tested 52 women with PCOS and 21 control women with an overnight polysomnogram (PSG) and a 75gm oral glucose tolerance test (OGTT). Women were similar in age (PCOS: 29.7 ± 0.7 yr, controls: 30.7 ± 1.1 yr; $p=0.42$). The majority of women in both groups were obese: mean BMI among controls was 36.0 ± 1.5 kg/m2 (range: 27.7 – 48.8 kg/m2); mean BMI in the PCOS group was 39.2 ± 1.0 kg/m2 (range 23.2 – 58.8 kg/m2). Twenty-nine women (56%) with PCOS women had OSA compared with four controls (19%). Thus, the adjusted odds ratio for OSA in PCOS was 7.1; 95% confidence interval, 1.7-45.7; $P = 0.01$ after controlling for age, BMI, and ethnicity. PCOS women with OSA were more insulin resistant than women without OSA: (HOMA

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index 5.7 ± 0.4 vs. 3.5 ± 0.4; P = 0.006) after controlling for age, BMI, and ethnicity. Impaired glucose tolerance was found in 16 of 29 (55%) PCOS women with OSA and only six of 23 (26%) of those without OSA (unadjusted P = 0.049). Insulin resistance and glucose intolerance were highly correlated with the presence and severity of OSA. Among PCOS women with normal glucose tolerance, the presence of OSA was associated with a nearly 2-fold higher fasting insulin level and HOMA index. The severity of OSA was a highly significant predictor of the fasting concentrations of glucose and insulin as well as the 2-h glucose concentration and HOMA index. Because the risk imparted by obesity does not appear to be sufficient to fully account for the high prevalence of sleep disordered breathing in PCOS, additional factors have been invoked including the hyperandrogenemia (7, 35, 56, 57) that is characteristic of PCOS.

Sex differences in PSG findings in OSA

There are a limited number of well-controlled studies comparing PSG findings in women versus men. Generally, women have a higher BMI for a given AHI level than men and weight changes have a lesser impact on AHI in women than in men. REM-related OSA is disproportionately more common in women than in men and, for the same BMI, OSA is less severe in women because of milder OSA during NREM sleep. Because REM sleep is a state of elevated sympathetic nervous activity, it is possible that REM-related OSA may have more severe metabolic and cardiovascular implications than OSA during NREM sleep. Positional OSA, i.e. where obstructive events occur much more in the supine position than in the lateral position, is more common in men than in women. These sex differences do not appear to be age- or weight-dependent.(33, 35) In one study of morbidly obese patients with OSA, women had lower sleep efficiency compared to men (70% vs. 80%) with greater disturbance of sleep architecture and sleep disruption despite a milder OSA (AHI 42 vs. 57). However, in community based studies such as the Wisconsin Sleep Cohort (9), women with OSA had a higher sleep efficiency with more SWS than men. Differences in concentrations of circulating sex steroids – estrogens, progestins, and androgens – appear to play an important role in the differences between men and women, both in normal sleep as well as OSA. However, women tend to be underrepresented in most studies of OSA.

Impact of Sex-Steroids and Body fat Distribution on Risk for OSA

Role of Progesterone

Progestins have been generally characterized as protective against the development of OSA in women. Much of the evidence to support this view is derived from studies in which sleep was evaluated in relation to pregnancy status (58, 59), age and phase of the menstrual cycle (60, 61), menopausal status (62), or in response to hormone replacement therapy (62). Progesterone is the key hormone thought to underlie the differences in sleep measures that exist across the normal menstrual cycle. Progesterone levels are low during the follicular (pre-ovulatory) phase; post ovulation (luteal phase), when progesterone is synthesized by the corpus luteum, plasma levels rise by up to two log orders. When sleep measures are obtained and compared between follicular (low progesterone) and luteal (high progesterone) phases, it is apparent that upper airway resistance is lower during the luteal phase (60).

The expected rise in progesterone with pregnancy is thought to attenuate the severity of preexisting OSA as well as to “protect” from its development in women without OSA pre-conception (59). These effects have been ascribed to levels of progesterone that would normally counterbalance the increase in OSA risk imparted by pregnancy-associated weight gain. Progesterone is thought to promote its effects through direct stimulation of respiratory drive via an increased ventilatory response to both hypercapnea and hypoxia (63, 64).

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Progesterone may also act to enhance upper airway dilator muscle activity (65) and reduce airway resistance.

Role of Androgens

Androgens are thought to play a significant role in the sexual dimorphism in sleep architecture and in the pathogenesis of OSA (56, 57). O'Connor, et al (35) analyzed records of 830 patients with OSA to determine whether there were differences in polysomnographic features between men and women, particularly with respect to the distribution of respiratory events during REM and non-REM sleep. Although the AHI during total sleep time was significantly higher in men compared to women (31.8 ± 1.0 vs 20.2 ± 1.5; $P<0.001$), the number of respiratory events occurring in REM sleep was greater in women as reflected by the so-called REM difference (i.e., the difference in the AHI in REM and AHI in non-REM sleep) in women and men. The REM difference was greater in women than men (28.1 ± 1.5 vs. 10.3 ± 1.1; $P<0.001$) at all levels of severity of sleep apnea. These findings were consistent and remained significant even after adjustment for the effects of covariates including weight, age, and duration of apnea. Thus, women with obstructive sleep apnea appear to have a higher proportion of respiratory events in REM compared to men, and to have a higher prevalence of apnea occurring mostly during REM.

Several studies have also shown that testosterone influences both neural control of breathing (66) and upper airway mechanics (67). Zhou et al (68) examined the effect of testosterone on apneic threshold in women during sleep. Eight normal, healthy, pre-menopausal women were studied before and after treatment with transdermal testostosterone (5 mg/day) administered in the follicular phase of the menstrual cycle. The authors concluded that testosterone increases apneic threshold in premenopausal women, thus leading to breathing instability during sleep.

Role of Body Fat and its Distribution

The risk of OSA is increased as a function of both total body fat mass as well as body fat distribution. Visceral fat appears to be more metabolically active and the quantity of visceral fat has been shown to highly correlate with OSA risk (69-71). The relative proportion of visceral fat to total body fat is higher in obese men compared to obese women. This difference is thought to contribute to the higher prevalence of OSA in men than women. Factors responsible for gender differences in body fat distribution include sex steroid concentrations, especially androgens. These factors are particularly relevant to the pathogenesis of OSA in women with PCOS.

Cardiovascular disease in PCOS

Women with PCOS have multiple risk factors for cardiovascular disease, including dyslipidemia, hypertension, impaired glucose tolerance/type 2 diabetes, subclinical vascular disease, and even significant reductions in maximal oxygen consumption and lower maximal workload (72). It now appears that OSA can be added to the list of cardiovascular risk factors in PCOS and the treatment of OSA appears to ameliorate some of the cardiovascular dysfunction seen in these women (73).

Women with PCOS appear to have an increased burden of subclinical atherosclerosis in a number of key arterial locations: the carotid artery (74-76), femoral artery, and coronary arteries (77). The mechanisms leading to this increased burden of atherosclerosis are not fully elucidated but have been ascribed to androgen excess, insulin resistance, inflammation (78), and the presence of a pro-thrombotic state.

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Although numerous studies have suggested that women with PCOS have an increased prevalence of coronary atherosclerosis, data from other large cohorts have suggested that this may not be the case. While the reasons for such discrepancies are not well understood, most investigators have concluded that subclinical atherosclerosis is not only present in women with PCOS, it is also likely associated with abnormal function of the endothelium and ultimately the microvasculature. Whether abnormalities in microvascular function are independent of factors including insulin resistance, glucose intolerance and even OSA remains to be determined. Similarly, whether macrovascular function (i.e. aortic stiffness) is independently affected by PCOS is not fully understood (79). Thus, the bulk of data favor an association between PCOS and atherosclerosis, yet little is known about whether there are significant structural and/or functional myocardial defects in PCOS. In one study (72) women with PCOS had an enlarged left atrium, increased left ventricular mass, lower left ventricular ejection fraction, and diastolic dysfunction. Evidence of diastolic dysfunction and left ventricular stiffness has also been detected as has subclinical impairment of left ventricular systolic function as determined by abnormalities in myocardial strain and diastolic dysfunction were present in women with PCOS and suggested that these findings may be linked to insulin resistance. In yet another study, abnormal echocardiography indices were detected in 14 of 30 PCOS subjects (but none of the controls), including valvular heart disease in nine, diastolic dysfunction in two, right ventricular enlargement in one, right atrial enlargement in one and pulmonary hypertension in one. PCOS subjects also showed an increased left ventricular mass (LVM) ($P < 0.001$). Contrary to the above 4 studies, 2 other studies respectively involving 48 and 26 PCOS subjects found no echocardiographic differences when compared to control subjects. Although a significant amount is known about the relationship between obstructive sleep apnea and heart disease, our review of the literature suggests that only three studies have taken advantage of the numerous strengths of cardiac magnetic resonance to study the effects of obstructive sleep apnea on cardiac structure and function. Furthermore, none have actually investigated the effects of OSA on the tissue characteristics of the myocardium. Magalang et al. studied 13 patients with OSA and found no improvement in right ventricular function and myocardial perfusion reserve despite an improvement in right ventricular volumes following treatment with 3 months of CPAP therapy; however, the study was potentially underpowered. In another larger study with more patients, Colish et al. were able to demonstrate an improvement in left ventricular remodeling, right ventricular volumes, and biatrial volumes in 47 OSA patients after 12 months of CPAP therapy. In yet another study, Nguyen et al. (80) randomized 20 patients with moderate to severe OSA to receive either active vs. sham CPAP therapy. They found that patients with OSA had decreased myocardial perfusion reserve that improved after 3 months of CPAP therapy. Surprisingly, none of these studies demonstrated an improvement in left or right ventricular function following CPAP therapy despite the accurate and reproducible measurements made using cardiac magnetic resonance, potentially due to small sample sizes or inadequate treatment duration.

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HIGHLIGHTS

- PCOS is among the most common endocrine disorders in women.
- Women with PCOS are highly predisposed to develop impaired glucose tolerance and type 2 diabetes.
- Obstructive sleep apnea (OSA) contributes to the metabolic disturbances associated with PCOS.
- Correction of OSA is associated with amelioration of metabolic dysfunction in PCOS.