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Obstructive sleep apnea and metabolic dysfunction in polycystic ovary syndrome

Katie Nitsche, BA, Research Assistant, David A. Ehrmann, MD, Professor of Medicine *

Section of Endocrinology, Diabetes, and Metabolism, The University of Chicago, 5841 S. Maryland Ave., Mail Code 1027, Chicago, IL, USA

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Obstructive sleep apnea (OSA) is an underrecognized, yet significant factor in the pathogenesis of metabolic derangements in polycystic ovary syndrome (PCOS). Recent findings suggest that there may be two "subtypes" of PCOS, i.e. PCOS with or without OSA, and these two subtypes may be associated with distinct metabolic and endocrine alterations. PCOS women with OSA may be at much higher risk for diabetes and cardiovascular disease than PCOS women without OSA and may benefit from therapeutic interventions targeted to decrease the severity of OSA. The present chapter will review what is currently known about the roles of sex steroids and adiposity in the pathogenesis of OSA, briefly review the metabolic consequences of OSA as well as the metabolic abnormalities associated with PCOS, review the prevalence of OSA in PCOS and finally present early findings regarding the impact of treatment of OSA on metabolic measures in PCOS.

Background

Polycystic ovary syndrome (PCOS) affects approximately 5–8% of women in the United States and typically manifests at the time of puberty with menstrual irregularity, hirsutism, and obesity.[1] The ability to diagnose PCOS at an early age has important implications, since those affected have a substantial risk for subsequent development of a number of metabolic[2,3] and cardiovascular[4–6] disorders. Specifically, women with PCOS have among the highest reported rates of early-onset

* Corresponding author. Tel.: +1 773 702 5770; Fax: +1 773 834 0486.
E-mail address: dehrmann@medicine.bsd.uchicago.edu (D.A. Ehrmann).

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impaired glucose tolerance and type 2 diabetes[7,8] as well as an increase in risk for hypertension[9], dyslipidemia[10,11], coronary[10] and other vascular disorders.[12–14] An important addition to this list of health risks is obstructive sleep apnea (OSA), which now appears to be present in a disproportionate number of women with PCOS. Indeed, the risk for OSA is at least 5-fold higher, and perhaps as much as thirty-fold higher in PCOS[15], than in similarly obese women. Results of our recent studies suggest that there may in fact be two "subtypes" of women with PCOS – those with OSA and those without OSA – and that these two subtypes may be associated with distinct metabolic and endocrine alterations. Because nearly all published studies characterizing metabolic and cardiovascular abnormalities in PCOS have not controlled for the potential impact of OSA and chronic sleep loss, the precise role of OSA as a cause of these derangements is not yet known.

PCOS women with OSA may have a much greater predisposition for development of diabetes and cardiovascular disease than PCOS women without OSA. Further, data are beginning to emerge to indicate that metabolic alterations may improve from therapeutic interventions targeted to decrease the severity of OSA.

Chronic sleep loss and obstructive sleep apnea: role of sex steroids and adiposity

As reviewed elsewhere in this volume (Chapter 3), it is clear that the past several decades have witnessed a significant decline in the average duration of sleep for most Americans. During the 1960s, the mean sleep duration was between 7 and 8 h per night; today, the percentage of both men and women who sleep less than 6 h per night has increased dramatically.[16] Chronic sleep loss imposes a significant negative impact upon individual health as well as an enormous economic cost to society. A number of studies have reported that shortened sleep duration is associated with increased mortality.[17,18] In the Nurses Health Study, it was found that sleeping less than 6 h per night was associated with an increased risk of death, even after adjusting for age, smoking, alcohol, exercise, depression, snoring, obesity, and history of cancer and cardiovascular disease.[18] Reduced sleep time has also been reported as a risk factor for the development of obesity as well as for type 2 diabetes.[19–23] Results of the Sleep Heart Health Study showed that subjects sleeping 5 h 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 7–8 h per night.[20] This trend in shorter sleep duration mirrors the progressive rise in overweight and obesity in the United States[24] and evidence continues to emerge to support a causal link between these two 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 is one of the major causes of chronic sleep disruption. It is characterized by episodic partial or complete upper airway obstruction during sleep leading to intermittent hypoxia, sleep fragmentation and a reduction in the quantity of deep non-rapid eye movement (NREM) sleep (stages 3 and 4, commonly referred to as slow wave sleep [SWS]). Sleep disruption resulting in reduced SWS has been associated with a rise in plasma cortisol levels and interpreted to indicate that SWS has a "restraining" effect on the hypothalamic-pituitary-adrenal axis.[25] Consistent with this is the finding that pharmacologic augmentation of SWS leads to a significant decline in salivary-free cortisol levels.[26]

Current estimates of OSA prevalence in the United States[27,28] are likely to underestimate the true prevalence of the disorder since 82% of men, and an even greater (93%) proportion of women with moderate to severe OSA have not been clinically diagnosed.[29] It has been consistently noted that men have a higher prevalence of OSA compared to women.[29] In community-based studies, the male:female ratio is usually between 2:1 and 3:1[30] in contrast to a ratio of 8:1 in clinic-based studies.[31]

OSA has been independently associated with glucose intolerance and insulin resistance even after adjustments for obesity and age.[32–36] Treatment of OSA with continuous positive airway pressure (CPAP) can improve insulin sensitivity[37] and is associated with a reduction in postprandial glucose and glycohemoglobin levels in individuals with type 2 diabetes.[38]

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 (Table 1).