Sleep Medicine Reviews (2005) **9**, 211–224

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SLEEP MEDICINE reviews

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THEORETICAL REVIEW

Sleep apnea is a manifestation of the metabolic syndrome

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KEYWORDS
Sleep apnea;
Visceral obesity;
Insulin resistance;
Interleukin-6;
Tumor necrosis factor-α;
Daytime sleepiness

Summary Obstructive sleep apnea (OSA) is a prevalent disorder particularly among middle-aged, obese men, although its existence in women as well as in lean individuals is increasingly recognized. Despite the early recognition of the strong association between OSA and obesity, and OSA and cardiovascular problems, sleep apnea has been treated as a 'local abnormality' of the respiratory track rather than as a 'systemic illness.' In 1997, we first reported that the pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNFα) were elevated in patients with disorders of excessive daytime sleepiness (EDS) and proposed that these cytokines were mediators of daytime sleepiness. Also, we reported a positive correlation between IL-6 or TNFα plasma levels and the body-mass-index (BMI). In subsequent studies, we showed that IL-6, TNFα, and insulin levels were elevated in sleep apnea independently of obesity and that visceral fat, was the primary parameter linked with sleep apnea. Furthermore, our findings that women with the polycystic ovary syndrome (PCOS) (a condition associated with hyperandrogenism and insulin resistance) were much more likely than controls to have sleep disordered breathing (SDB) and daytime sleepiness, suggests a pathogenetic role of insulin resistance in OSA. Other findings that support the view that sleep apnea and sleepiness in obese patients may be manifestations of the Metabolic Syndrome, include: obesity without sleep apnea is associated with daytime sleepiness; PCOS and diabetes type 2 are independently associated with EDS after controlling for SDB, obesity, and age; increased prevalence of sleep apnea in post-menopausal women, with hormonal replacement therapy associated with a significantly reduced risk for OSA; lack of effect of continuous positive airway pressure (CPAP) in obese patients with apnea on hypercytokinemia and insulin resistance indices; and that the prevalence of the metabolic syndrome in the US population from the Third National Health and Nutrition Examination Survey (1988–1994) parallels the prevalence of symptomatic sleep apnea in general random samples. Finally, the beneficial effect of a cytokine antagonist on EDS in obese, male apneics and that of exercise on SDB in a general random sample, supports the hypothesis that cytokines and insulin resistance are mediators of EDS and sleep apnea in humans.

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1087-0792/$ - see front matter
doi:10.1016/j.smrv.2005.01.006

In conclusion, accumulating evidence provides support to our model of the bi-directional, feed forward, pernicious association between sleep apnea, sleepiness, inflammation, and insulin resistance, all promoting atherosclerosis and cardiovascular disease.

Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder particularly among middle-aged, obese men, although its existence in women, as well as in lean individuals, is increasingly recognized.[1-5] Four percent of adult men and 2% of adult women in general population random samples meet the current clinical and polysomnographic criteria for the diagnosis of sleep apnea warranting immediate therapeutic intervention.[2-4] A much larger group, 17–24% of men and 5–9% of women, demonstrate an apnea/hypopnea index of more than five events per hour of sleep,[2-4] which was the originally proposed criterion for sleep apnea,[6] however, it is now clear that the majority of subjects do not experience excessive daytime sleepiness and/or cardiovascular problems.

As currently defined, OSA is associated with considerable morbidity and mortality, whereas the currently available treatments are associated either with limited efficacy and/or poor compliance.[1] An improvement in the understanding of the nature and pathophysiology of the disorder may lead to novel treatments.

In this review, we summarize the accumulating evidence that sleep apnea, to a large extent, is a manifestation of the (dys) metabolic syndrome or syndrome X.[7,8]

Sleep apnea: a manifestation of a metabolic syndrome

Despite the extensive literature on the role of anatomic abnormalities in the pathogenesis of sleep apnea,[9] the large majority of adult sleep apneics do not demonstrate structural abnormalities in their upper airways,[10,11] whereas inversely many patients with narrow upper airways due to clear-cut anatomic abnormalities do not have sleep apnea.[12] On physical examination, very few features have been helpful in defining the risk for OSA and the response to therapy. Several reports have emphasized that a thick neck or a large neck is an important variable.[13] However, neck size and BMI are highly correlated,[10,14] whereas gain in waist circumference over adult life has a stronger association than neck size with sleep disordered breathing (SDB) severity.[15] Furthermore, this association has not been carefully examined outside of the apnea literature.

A number of associated features of OSA suggest that sleep apnea is a manifestation of the metabolic syndrome. Indeed, there is a strong association of OSA with obesity,[1-4,6,10,11,16,17] male gender (android-central obesity), post-menopausal increase of its prevalence, systemic effects, e.g. hypertension and diabetes, and the natural course of symptoms,[1] all overlapping with the factors associated with the metabolic syndrome. It appears that in both conditions there is a vicious cycle of weight gain (particularly from young adulthood to middle age), snoring, development of breath cessation, daytime sleepiness, further weight gain, deterioration of breathing abnormalities, and more severe daytime sleepiness, all pointing towards a systematic illness rather than a local abnormality. The high rate of failure of surgical interventions in the oropharynx and the fact that even modest weight gain or loss respectively result in a significant worsening or improvement of sleep apnea in middle-aged individuals[18] suggest that anatomic abnormalities are not primary in adult sleep apnea.

Recently, it was publicly debated whether sleep apnea was an anatomic disorder or not.[19,20] Both pro and con views were based on the premise that obesity is a purely anatomic/mechanical factor. Although obesity may affect anatomy, including that of the upper airway, it appears that obesity's role in the genesis of sleep apnea is primarily through its metabolic activity and that the predominant fat in sleep apnea, just as in the metabolic syndrome, is the metabolically active visceral fat.

Sleep apnea, cytokines, and EDS

Excessive daytime sleepiness (EDS) and fatigue are frequent symptoms in the general population and the chief complaint of the majority of patients referred for sleep apnea to Sleep Disorder Centers.

There is published evidence that the inflammatory cytokines tumor necrosis factor-α (TNFα), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are involved in physiological sleep regulation,[21,22] and that their increased secretion or exogenous administration to humans is associated with sleepiness and fatigue.[23]

In 1997, we published our first report on cytokines and disorders of EDS.[24] In that controlled study, we first demonstrated that TNFα was significantly elevated in sleep apneics and narcoleptics compared to that in normal controls ($P<0.001$). Also, IL-6 concentrations were markedly and significantly elevated in sleep apneics compared to normal controls (Fig. 1). Both TNFα and IL-6 plasma concentrations were positively correlated with the presence of EDS. Also in that study, we showed that IL-6 plasma levels were positively correlated with BMI.

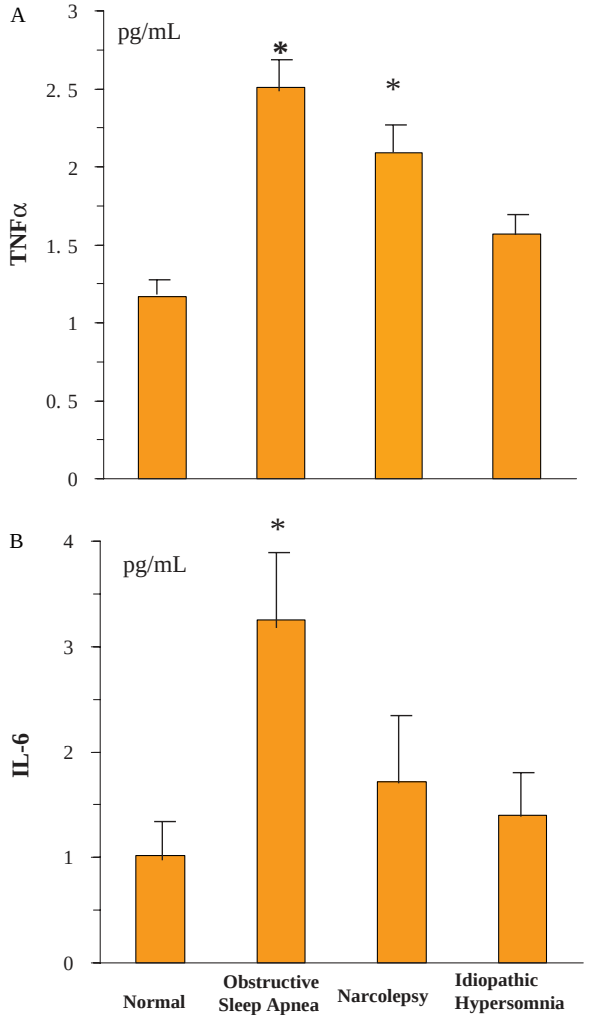

Figure 1 Plasma TNFα and IL-6 levels in normal subjects and patients with EDS. (A) *,$P<0.001$ vs. normal. (B) *,$P=0.028$ vs. normal. Reprinted with permission from Ref. 24.

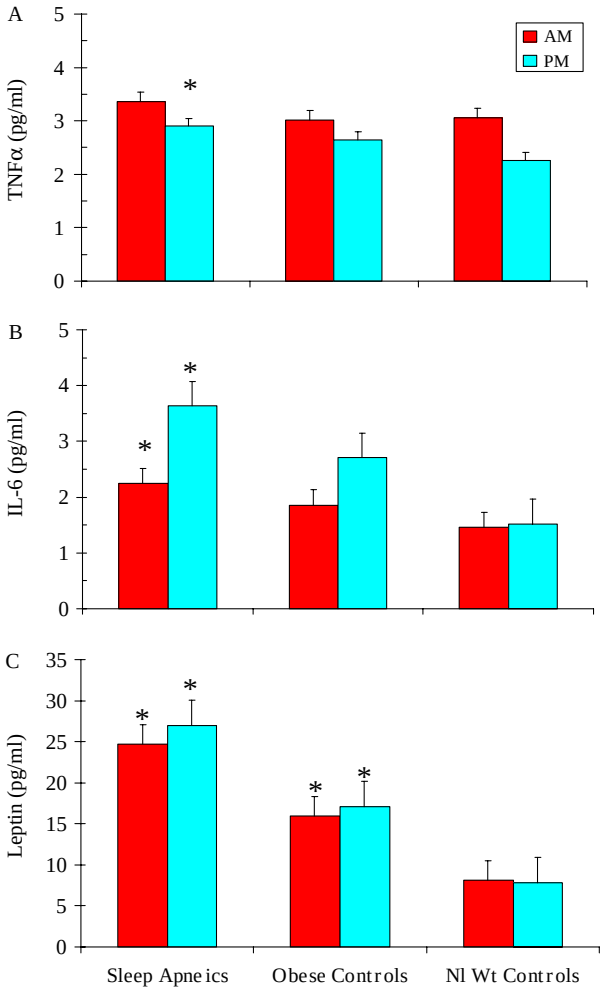

Figure 2 Plasma TNFα, IL-6, and leptin levels in sleep apneics and BMI-matched obese and normal weight controls. (A) *,$P<0.01$ vs. normal weight (nl wt) controls. (B) *,$P<0.05$ vs. nl wt controls. (C) *, <0.05 vs. obese and lean controls. Reprinted with permission from Ref. 25.

In a new study that we controlled for obesity, the sleep apneic men had higher plasma concentrations of TNFα, IL-6, and leptin than nonapneic, obese men who had intermediate values or lean men who had the lowest values (Fig. 2).[25] Both cytokines and leptin correlated positively with BMI, whereas leptin and IL-6 levels correlated positively with plasma insulin levels. Several studies have shown inflammation or denervation changes within upper airway dilator muscles and have suggested that these local changes are a result of the mechanical vibrating effects of snoring and may contribute to the airway collapse.[26-28] However, these arguments have been weakened by the recent findings of Series et al. that the amount of inflammatory markers in uvula is linked primarily to obesity and only secondary to apneic activity and that obesity promotes inflammation in tissues subjected to

chronic mechanical damage.[28] Furthermore, these findings cannot explain why from those with apnea, only one-fifth develop symptomatic apnea and also why symptomatic apnea decreases with age while snoring increases with age.

Sleep apnea is associated with insulin resistance independently of obesity

The data, showing that sleep apnea is associated with hypercytokinemia, in connection with (a) the emerging literature linking cytokines to obesity and insulin resistance,[29-37] (b) the well-known relations between insulin resistance and cardiovascular disease risk,[7,38-42] and (c) the increased prevalence of cardiovascular disease in obstructive sleep apnea,[14,17] have prompted us to explore whether sleep apnea is associated with insulin resistance independently of obesity.

Earlier studies reported inconsistent results in terms of an association between sleep apnea and insulin resistance. A large study showed a modest relation ($r^2=0.10$) between the A/HI and fasting insulin levels, but not fasting blood glucose levels.[43] Two other studies showed an association between severity of sleep apnea and indices of insulin resistance[44] and that sleep apnea occurred commonly in obese patients with diabetes type II who had excessive daytime sleepiness or heavy snoring.[45] In contrast, two other controlled studies suggested that the relation between sleep apnea and plasma insulin levels[46] or insulin resistance[47] reflected the known effects of obesity. However, in one of these studies, the apneics were otherwise healthy normotensive individuals,[47] whereas in the second one, the apneics were lean and less symptomatic.[46] The weak correlations between sleep apnea and insulin levels in clinical samples and the absence of insulin resistance in otherwise asymptomatic apneics reported in some studies may be due to the possibility that sleep apnea is a heterogeneous disorder in terms of its association with insulin resistance and/or that sleep apnea without symptoms has a weak association with insulin resistance.

In our study, we included 14 obese men with symptomatic sleep apnea and 11 BMI- and age-matched, obese, non-apneic controls.[25] Mean fasting blood glucose levels were higher in the apneics than in obese controls (106.2 ± 4.1 vs. 85.4 ± 4.4; $P<0.01$). Mean plasma insulin levels were also higher in sleep apneics than in obese controls (25.7 ± 4.2 vs. 14.6 ± 2.5; $P<0.05$).

Similarly, two subsequent studies published in the *American Journal of Respiratory and Critical Care Medicine* in March of 2002 that employed larger samples reported an association between OSA and insulin resistance independently of obesity.[48,49] Importantly, Ip and associates observed that the association between OSA and insulin resistance was present even in nonobese subjects,[48] while Punjabi and co-workers reported insulin resistance even in mild forms of sleep apnea.[49] Taken together, these studies provide 'compelling evidence' in favor of an independent association between SDB and insulin resistance.[50]

Sleep apnea and hyperleptinemia

Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and energy expenditure.[51] Leptin levels correlate with BMI and insulin levels, and its secretion is further modulated by the stress system and cytokines.[51] Administration of leptin in animals is associated with increased blood pressure while it could prevent respiratory depression in obesity.[52]

Several studies have shown that sleep apnea is associated with hyperleptinemia that correlates to insulin levels.[25,53-55] In some of these studies, that included primarily obese patients, the higher levels of leptin have been accounted for by obesity and/or excessive visceral fat,[25,56] whereas in others that included primarily non-obese patients, elevated leptin levels were reported independently of obesity. In our study, apnea/hypopnea index did not make an additional contribution to leptin levels, and we suggested that the increase in leptin levels in sleep apnea may be related to the higher amount of visceral fat and/or cytokines. Also, there is evidence that evening leptin levels were relatively higher in sleep apneics compared to normal-weight controls. However, leptin levels were only measured at two time periods, and whether sleep apnea is associated with a change of the circadian secretion of leptin remains open for further investigation in studies that employ serial 24-h sampling.[25,55]

Visceral fat is the predominant fat problem in sleep apnea

Based on our finding that SDB is associated with insulin resistance independently of obesity, we proceeded to examine whether visceral fat, which is closely associated with insulin resistance,

correlates more strongly to sleep apnea than subcutaneous (SC) or total fat. We assessed body fat distribution using computed tomographic (CT) scanning. There were no significant differences between the two groups in terms of total body fat or SC fat. However, sleep apneics compared to obese controls had a significantly greater amount of visceral fat at L1, L3, L4, and L5 levels (all $P<0.05$). Interestingly, BMI correlated significantly with total body fat (measured at L3: $r_{xy}=0.83$; $P<0.01$) and SC fat ($r_{xy}=0.88$; $P<0.01$), but not with visceral fat. Importantly, visceral, but not SC fat, was significantly correlated with indices of sleep apnea ($r_{xy}=0.70$; $P<0.01$ for A/HI and $r_{xy}=-0.60$; $P<0.01$ for minimum SaO_2) (Fig. 3). These findings are consistent with reports that visceral fat accumulation is an important risk factor for OSA in obese subjects,[57] and the AHI is significantly correlated with intra-abdominal fat but not with subcutaneous fat in the neck region or parapharyngeal fat.[58]

Based on these results, we proposed that visceral obesity/insulin resistance is determined by both genetic/constitutional and environmental factors,

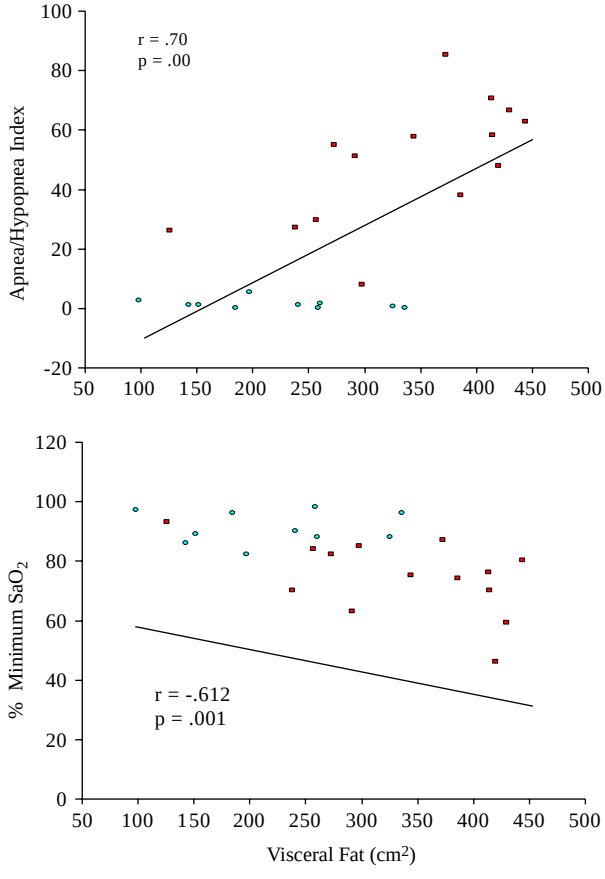

Figure 3 Visceral fat significantly correlates with indices of sleep apnea. ■, sleep apneics; ○, obese controls. Reprinted with permission from Ref. 25.

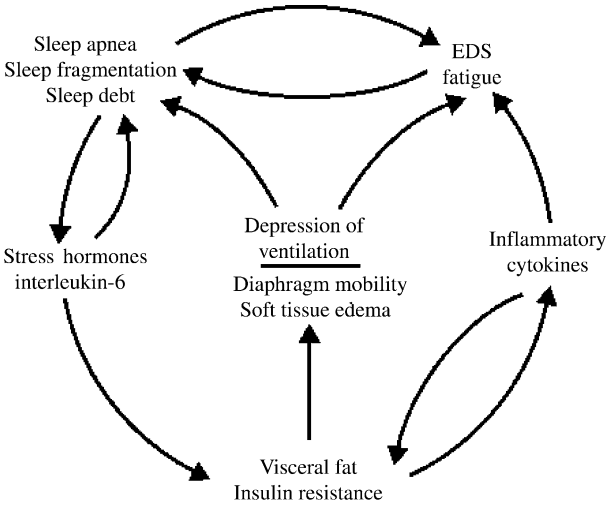

Figure 4 A heuristic model of the complex feed forward associations between visceral fat/insulin resistance, inflammatory cytokines, stress hormones, excessive daytime sleepiness and fatigue, and sleep apnea.

which progressively lead to worsening metabolic syndrome manifestations and sleep apnea. Sleep apnea may lead to a worsening of visceral obesity and the metabolic syndrome by providing a stress stimulus and causing nocturnal elevations of hormones, such as cortisol and insulin, that promote visceral adiposity, metabolic abnormalities, and cardiovascular complications (Fig. 4).[25,59]

Effects of continuous positive airway pressure on metabolic measures

Most studies on the effects of continuous positive airway pressure (CPAP) on insulin resistance have failed to demonstrate an improvement of insulin resistance indices.[60] In contrast, most studies have reported that CPAP decreases leptin levels after a short-term (2–4 days) or a long-term (3–6 months) use[53] with the exception of a recent study and our own unpublished data that showed no effect of CPAP on leptin levels in obese apneics.[56] The lack of effect of CPAP on insulin resistance may be secondary to several factors, i.e. noncompliance, irreversible changes due to chronic effects, small sample size, or a pathogenetic role of the metabolic abnormality. We and other investigators, after reviewing these studies, have suggested that glucose intolerance and insulin resistance may be involved in the pathogenesis of sleep apnea and refractory to the effects of CPAP, whereas hyperleptinemia is a marker of metabolic abnormalities, such as sympathetic activation, associated with sleep apnea and not a causative factor.[53]

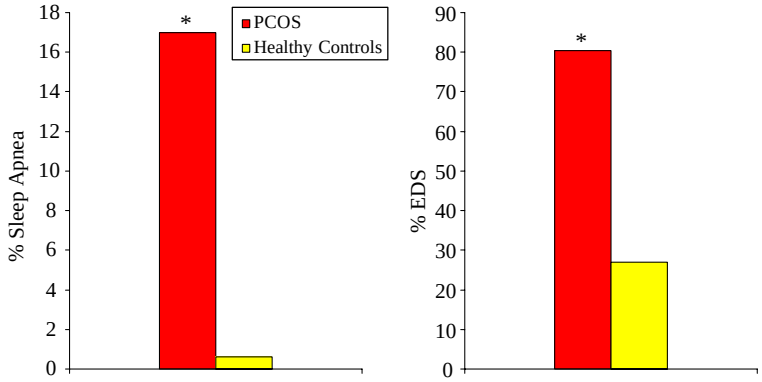

Figure 5 Prevalence of obstructive sleep apnea and excessive daytime sleepiness (EDS) in women with the polycystic ovary syndrome is markedly higher than in healthy controls. *, $P<0.05$. Reprinted with permission from Ref. 8.

Notably, CPAP is effective in reducing increased sympathetic activity and hypercortisolemia in sleep apnea probably by reducing the stress of intermittent hypoxia and sleep fragmentation.[61] Whereas two studies reported that CPAP decreases IL-6 levels and visceral fat in non-obese apneics,[62,63] preliminary findings from our center indicate no effect of CPAP on these variables in obese male apneics.[61] Besides that the groups of apneics in these studies are different in terms of BMI, no other reason is apparent to explain these opposite results.

Sleep apnea is very frequent in disorders in which insulin resistance is a primary pathophysiologic abnormality

Our finding that sleep apnea is associated with insulin resistance independently of obesity prompted us to explore the other side of this bi-directional association. In other words, if insulin resistance is underlying sleep apnea's pathogenetic mechanisms, then the latter should be more prevalent in disorders in which insulin resistance is a primary abnormality, such as the polycystic ovary syndrome (PCOS).[64,65]

PCOS is associated with OSA and EDS independent of obesity

Fifty-three pre-menopausal women with PCOS [age range, 16–45 year; body mass index (BMI) range, 24.3–67.7] were prospectively studied in the sleep laboratory. The diagnosis of PCOS was made by the presence of chronic anovulation (six or fewer menstrual periods per year) in association with elevated circulating androgen levels.[64]

Control women were 452 pre-menopausal women (age range, 20–42 year; BMI range, 16.1–59.9) selected from a general random sample.[4] Obstructive sleep apnea was diagnosed using Sleep Disorders Clinic criteria, which employed sleep laboratory (A/HI $\geq$ 10) plus clinical findings.[3,4]

In this study, PCOS women were 30 times more likely to suffer from sleep disordered breathing (SDB) than controls [OR = 30.6, 95% CI (7.2, 139.4), $P<0.0001$]. Specifically, nine of the PCOS women (17.0%) were given treatment for OSA or upper airway resistance syndrome in contrast to only three (0.6%) controls (two for OSA and one for upper airway resistance syndrome) (Fig. 5). Even when we controlled for BMI, the difference between the two groups remained significant.

Insulin resistance is the strongest predictor of sleep apnea in PCOS

In order to understand further the relation between the presence of SDB in PCOS patients and potential predictive factors, age, BMI, free and total testosterone, fasting insulin levels and glucose to insulin ratio were included in a logistic regression analysis. The backward conditional analysis eliminated all variables but insulin and glucose to insulin ratio, suggesting that insulin resistance was a stronger predictor for sleep apnea than age, BMI, or testosterone.

Our findings on the association of PCOS and OSA were confirmed in two other studies,[66,67] suggesting that visceral obesity/insulin resistance, which is frequently associated with PCOS,[64] is at the basis of the pathogenetic mechanisms leading to sleep apnea.[68]

Sleep loss and sleep apnea are associated with impaired glucose metabolism and diabetes

Sleep deprivation of 60 h is associated with decreased peripheral insulin sensitivity.[69] More recently, Van Cauter and colleagues demonstrated that restricting sleep to four hours per night for six nights in young, healthy individuals lowers glucose tolerance.[70]

Several studies have shown an increased prevalence of sleep apnea and sleep disordered breathing in patients with diabetes mellitus type II.[45,71] Two large prospective studies, the one from Sweden and the other from the US (Nurses' Health Study Cohort) showed that regular snoring is associated with a 2- to 7-fold risk for type II diabetes over a 10-year period.[72,73] These studies collectively suggest that diabetes is strongly associated with OSA and, along with hypertension, should be added to the signs and symptoms of this prevalent sleep disorder.

From a mechanistic standpoint, it has been reported that in humans and animals, insulin-dependent diabetes mellitus can lead to an overall depression in ventilatory control mechanisms.[74]

Effects of menopause and hormone replacement therapy on sleep apnea

In a recent large epidemiologic study, Bixler and colleagues demonstrated that the prevalence of sleep apnea is quite low in pre-menopausal women (0.6%) as well as post-menopausal women on hormone therapy (HT).[4] Further, in these women, the presence of sleep apnea appeared to be associated exclusively with obesity (BMI $>$ 32.3%). Post-menopausal women without HT had a prevalence of sleep apnea that was close, although still lower, to the prevalence in men. Loss of estrogen after menopause is associated with elevated IL-6, increasing obesity (primarily central) and an increase of cardiovascular disease.[75] It is possible that elevation of inflammatory cytokines, central obesity and/or insulin resistance are risk factors for increased prevalence of OSA and cardiovascular disease in post-menopausal women. Furthermore, a recent study from the Women's Health Initiative Hormone Trial reported that estrogen plus progestin decreased diabetes and insulin resistance in post-menopausal women, which might be a mechanism through which HT protects women from sleep apnea.[76] The adverse effect of menopause and the protective role of gonadal hormones in sleep apnea in women was confirmed in the Sleep Heart Health Study as well as in a Wisconsin cohort.[77,78]

The age distribution of symptomatic sleep apnea and metabolic syndrome are similar

Efforts to characterize apnea based on the number of apneic events during sleep have provided inconsistent results. The apnea/hypopnea index as a summary measure cannot predict the clinical impact of the disorder, i.e. degree of sleepiness or presence of cardiovascular problems.[1,3,4,10,11,14,17] Both clinical experience and findings from large epidemiologic studies point to at least two types of adult OSA; one type associated with significant morbidity, e.g. daytime sleepiness and/or cardiovascular events such as coronary artery or cerebrovascular accidents, and the other type which is associated with less clinical consequences. The factors that influence the clinical impact of the disorder in patients with similar degree of apneic activity are not known but may be part of the genetic and/or constitutional background of these patients.

Large epidemiologic studies have shown that the prevalence of significant apneic activity as measured in the sleep laboratory largely not associated with clinical symptoms (non-symptomatic apnea) is much higher than that of sleep apnea based on the presence of both sleep laboratory and clinical findings (symptomatic apnea). In 1993, Young and colleagues reported that the prevalence of OSA, defined categorically as an apnea/hypopnea index (A/HI) $>$5, was 9% in women and 24% in men.[2] In contrast, adults with both an A/HI $>$5 and symptoms of sleepiness represented only about 2% of women and 4% of men in their middle-aged sample. Similarly, Bixler et al. in a random sample of the general population ranging from 20 to 100 years reported that the prevalence of sleep apnea using sleep disorders clinic criteria (A/HI $>$ 10 and daytime symptoms) was about 4% in men and 1.2% in women. In the same study, the prevalence of sleep apnea using only sleep laboratory criteria (A/HI $>$ 5) increased significantly in both men and women (17.5% for men and 4.8% for women).[3,4] These data clearly suggest that the prevalence of symptomatic apnea is much lower compared to that of non-symptomatic apnea and that factors other than apneic activity determine the clinical impact of the disorder.

Also, the age distribution of the prevalence and severity of sleep apnea support the distinction in

two types of apnea, i.e. symptomatic vs. non-symptomatic. The typical profile of a sleep apneic in a sleep disorders clinic is that of a middle-aged, obese man.[1,6,10,11,16] In contrast, studies using sleep laboratory criteria alone observed a high prevalence of sleep apnea ranging from 24 to 62% in elderly populations.[79] These findings appeared to establish the existence of a monotonic relation between age and sleep apnea. These seemingly discrepant results, in terms of the age that the prevalence of apnea peaks, were understood from the findings of large epidemiologic studies that used both clinical and laboratory criteria. Using sleep disorders clinic criteria, the prevalence of sleep apnea changed with age in a quadratic fashion, increasing from over 1% in the youngest group to almost 5% in the middle-aged group, and then returning to less than 2% in the older subjects. In contrast, the prevalence of sleep apnea based on obstructive A/HI > 10 increased monotonically with age from 3.8 to 17.7% in men and from 0.7 to 9.2% in women.[3,4] These apparently competing age distributions have led the researchers to propose that there are at least two types of apnea.[3,80] The first type of apnea would have an age-related distribution with a peak around age 55 years for men and 65 years for women and would account for the symptomatic apnea (Fig. 6), and the second type would occur primarily in the elderly and would not have the clinical consequences of the first type.

The view that the effects of sleep apnea cannot be accounted for by a simple count of the number of apneic events is supported by the fact that apnea is more severe after controlling for A/HI in the young. For example, the degree of hypoxia after controlling for number of apneas and BMI is more severe in the young than in the old.[3] Also, the association between A/HI and hypertension is stronger in the young than in the old.[41,81] Finally, daytime sleepiness is more strongly associated with the young than with the old apneics.[82] These findings are consistent with several studies that have shown stronger relations among hypertension, vascular disease, and mortality in younger subjects with sleep apnea than in older subjects.[10,17]

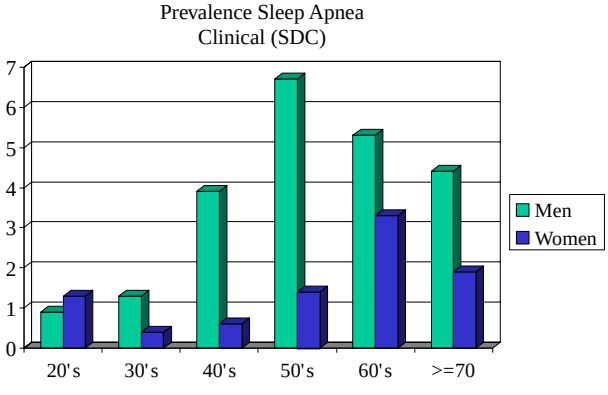

Figure 6 The age distribution of sleep apnoea by decade (apnoea/hypopnoea index ≥10 and presence of daytime symptoms), peaks in the sixth decade for men (■) and the seventh for women (■). Data from Refs. 3 and 4.

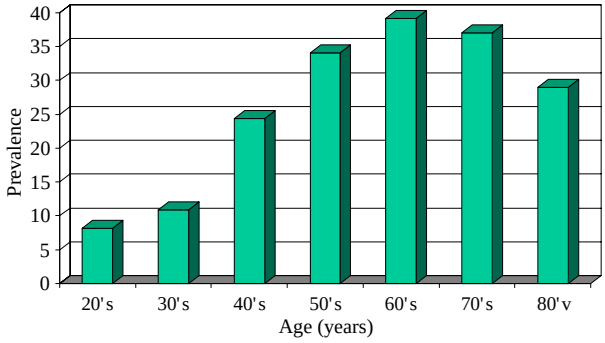

Figure 7 Prevalence of metabolic syndrome in men in the U.S. population based on data from the Third National Health and Nutrition Examination Survey, 1988–1994 (adapted from reference 74).

Interestingly, a recent study showed that the age distribution of the metabolic syndrome is similar to the age distribution of symptomatic sleep apnea.[83] Specifically, in a study on the prevalence of the metabolic syndrome in the US population from the Third National Health and Nutrition Examination Survey 1988–1994, it was demonstrated that the prevalence of the metabolic syndrome that is closely linked to insulin resistance rose with age, reached peak levels between ages 50 and 70, and then declined (Fig. 7). Also, menopause increased the risk for metabolic syndrome in women. The similarities in age distribution between symptomatic sleep apnea and metabolic syndrome support our proposal that insulin resistance/visceral adiposity is more strongly linked to symptomatic apnea.

Metabolic abnormalities are associated with excessive daytime sleepiness

Daytime sleepiness is a critical symptom of sleep apnea but is not pathognomonic. A number of sleep, medical, and mental diseases and disorders include this symptom. We here review evidence that obesity and diabetes may be key mediators of this symptom.

EDS and BMI are positively related

EDS and obesity in non-apneic obese

Based on the fact that daytime sleepiness and fatigue are frequent complaints of obese people, we examined in a sleep laboratory study whether obesity without sleep apnea is associated with daytime sleepiness.[84]

Our sample consisted of 73 obese patients, without sleep apnea, upper airway resistance syndrome or hypoventilation syndrome, who were consecutively referred for treatment of their obesity and 45 controls matched for age. All patients and normal controls were monitored in the sleep laboratory for eight hours at night and two daytime naps, each for one hour the following day. Obese patients compared to controls were sleepier during the day whereas their nighttime sleep was disturbed. Forty-two (57%) of the 73 obese patients reported daytime sleepiness that was on average moderately severe. One (2%) of 45 controls reported daytime sleepiness (mild). During both naps, sleep latency, wake time after sleep onset and total wake time were significantly lower, whereas percentage of sleep time was significantly higher in obese patients compared to controls. Based on these data, we concluded that daytime sleepiness is a morbid characteristic of obese patients and might be related to a metabolic/circadian abnormality of the disorder.

EDS and obesity in an apneic population

The effect of BMI on the association of EDS with SDB was examined in a general random sample of 1741 men and women.[82] Variables that were controlled for included age, BMI, gender, menopausal status, race, alcohol, and smoking. In the multiple logistic regression analysis, EDS had a strong association with BMI (OR = 10.3 (3.3,33.3) for every increase of log BMI). Also, in terms of the relative contribution to the complaint of EDS, the strongest risk factor was BMI, then age, and then SDB (standardized effect sizes were 3.9, −3.1, 2.3, respectively). These results suggest that EDS is strongly associated with BMI. Although SDB makes an independent contribution to the complaint of EDS, its effect is weaker than that of BMI. This association may in part account for the difference in the proportion of those with SDB who are obese in a sleep disorders clinic population and epidemiologic samples, because EDS is a major complaint leading to a sleep disorders clinic evaluation. Similar findings in regard to the independent contribution of obesity in sleepiness associated with OSA was reported in several studies of patients with and without sleep apnea.[85,86] Combined, these data suggest that obesity is a strong independent factor contributing to EDS, both in the general population as well as in those with a diagnosis of sleep apnea.

Diabetes, and insulin resistance contribute to EDS independently of obesity, sleep apnea, and age

Fatigue is a frequent complaint of patients with diabetes. The underlying mechanisms are unknown. In 1993, Feinberg alerted sleep specialists to the possibility that untreated diabetes should be considered in patients with severe sleepiness for which other causes had been ruled out.[87]

Bixler and his colleagues assessed the association of EDS with a history of diabetes or fasting hyperglycemia (fasting blood glucose >126) in a large sample of 1741 subjects.[88] EDS was reported by 15.1% of those with diabetes compared to 7.5% of those without. In the multiple logistic regression analysis, EDS was shown to have a significant association with diabetes when controlling for sleep apnea, obesity, and age.[88] The authors concluded that diabetes should be considered in the differential diagnosis whenever excessive daytime sleepiness is present.

Daytime sleepiness is reported very frequently by women with PCOS in whom insulin resistance is a common metabolic abnormality.[64] In our sample of 53 pre-menopausal women with PCOS, sleep apnea was diagnosed in 17%, whereas 4 out of 5 patients complained of EDS. Even in the non-obese category (BMI <32.3), 75.0% of PCOS women complained of EDS in contrast to only 22.5% of non-obese controls.[65] This suggests that in this syndrome of glucose dysregulation, EDS is prevalent and independent of sleep apnea or obesity.[59,67]

These data taken together suggest that diabetes/insulin resistance makes an independent contribution to the complaint of EDS after controlling for OSA, age, and BMI and provide preliminary evidence that diabetes/insulin resistance is a significant predictor for sleepiness independent of sleep apnea and obesity.

In conclusion, primary disorders of metabolism, such as obesity and diabetes, appear to be causally associated with EDS, a cardinal symptom of OSA that is frequently thought to be solely or primarily related to hypoxia and/or sleep fragmentation secondary to intermittent breathing cessation.

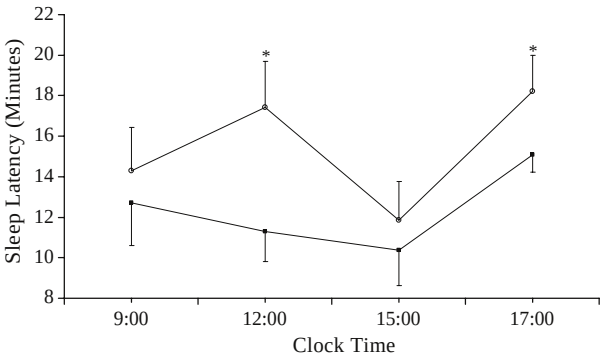

Figure 8 Sleep latencies during daytime testing with MSLT in the placebo (■) and etanercept (○) conditions. Each data point represents the mean ± SE. *, $P < 0.05$, adjusted change between placebo and etanercept. Reprinted with permission from Ref. 89.

The effects of cytokine antagonists and exercise on excessive daytime sleepiness and sleep apnea

In order to test our hypothesis that the pro-inflammatory cytokines TNFα and IL-6 are mediators of excessive daytime sleepiness in humans, we proceeded with a pilot study during which we administered etanercept, a medication that neutralizes TNFα, or placebo, in eight male, obese apneics.[89] There was a significant and marked decrease of sleepiness by etanercept, which increased sleep latency during the multiple sleep latency test (MSLT) by about 3.1 min compared to placebo (Fig. 8). Also, the number of apneas/hypopneas per hour was reduced significantly by the drug compared to placebo (52.8 ± 9.1 vs 44.3 ± 10.3; adjusted difference − 8.4 ± 2.3; $P < 0.05$). We concluded that neutralizing TNFα activity is associated with a significant reduction of objective sleepiness in obese patients with OSA and that this effect suggests that pro-inflammatory cytokines contribute to the pathogenesis of OSA/sleepiness.

Finally, a recent study showed that in 1104 men and women enrolled in the Wisconsin Sleep Cohort Study, ≥7 h of exercise per week compared to 0 h of exercise per week was associated with a significant reduction of A/HI (5.3 vs. 2.8) independent of BMI, age, gender, and other covariates.[90] Given the well-known effects of exercise on insulin resistance and visceral adiposity, even when controlling for weight changes, we speculate that this favorable effect of exercise on sleep apnea is through correction of metabolic abnormalities, such as insulin resistance and body fat distribution.

Metabolic abnormalities and collapse of the upper airway during sleep

Sleep apnea is broadly thought of as a disorder that is characterized by recurrent collapse of the upper airway during sleep, leading to periods of intermittent hypoxia and sleep fragmentation. It is not known how the metabolic abnormalities associated with sleep apnea and reviewed in this paper lead to a collapse of the upper airway during sleep. However, some emerging data provide hints for the link between systemic metabolic aberrations and upper airway collapse. First, it has been reported that in humans and animals, insulin-dependent diabetes mellitus can lead to an overall depression in ventilatory control mechanisms,[91] whereas both leptin deficiency and leptin resistance may lead to respiratory depression in obesity, especially during sleep.[92] Second, the reported inflammation of upper airway tissues may be related primarily to obesity, a condition of systemic inflammation. Third, obesity/insulin resistance, by releasing growth factors, may lead to soft tissue edema in the neck. Finally, male type of obesity (central) may impact more severely on upper airway function than female type of obesity (peripheral).[93] Thus, the observed hypercytokinemia, hyperleptinemia, and hyperinsulinemia/visceral adiposity, through central and peripheral effects, may lead to a collapse of the upper airway during sleep. It should be kept in mind that since the number of apneas (collapses) only partially explains the symptoms associated with sleep apnea, such as sleepiness and cardiovascular problems, the metabolic abnormalities present in symptomatic sleep apnea may lead to these symptoms through pathways independent of the airway collapse.

Conclusions

The studies reviewed in this article provide support to our model of the bi-directional, feed forward, pernicious association between sleep apnea and insulin resistance primarily in obese patients. Indeed, visceral obesity/insulin resistance, determined by both genetic/constitutional and environmental factors, may be the principal culprit leading to sleep apnea, which, in turn, may accelerate these metabolic abnormalities, possibly through progressive elevation of stress hormones and cytokines such as cortisol, IL-6, and TNFα. Furthermore, daytime sleepiness is frequently associated with obesity, diabetes type 2, and insulin resistance independently of SDB. Understanding the complex

interaction between sleep, sleepiness, SDB, inflammation, insulin resistance, and obesity may lead to more effective, better tolerated treatments for SDB and sleepiness, thereby lowering the adverse cardiovascular complications detrimental in these populations. In the meantime, weight management, healthy eating habits, and regular exercise and sleep—all of which appear to improve insulin sensitivity independently of the effects on body weight—should be recommended to any subject that suffers from SDB and sleepiness.

Practice points

- Symptomatic sleep apnea is more frequent in patients with metabolic syndrome.
- Sleep apnea and sleepiness are more prevalent in patients in which insulin resistance is a primary pathogenetic mechanism, such as women with PCOS.
- Metabolic syndrome, insulin resistance, and obesity are stronger determinants of sleepiness compared to apnea/hypopnea index.
- Weight loss and exercise should be routinely recommended in obese apneics because (a) of their beneficial effects on metabolic syndrome/insulin resistance, which are not improved even by the successful use of CPAP and (b) their effects on SDB and sleepiness.

Research agenda

In the future we need to:

- Study further the nature of the association of inflammation process, insulin resistance/metabolic syndrome, and sleep apnea, especially in nonobese patients.
- Explore the mechanisms of sleepiness by including metabolic aberrations in the model of sleep apnea—sleepiness.
- Use agents that neutralize cytokines or improve insulin sensitivity as a means to reduce sleepiness and sleep apnea.
- Study the effects as well as the mechanism of life-style changes, such as weight loss and exercise, on sleep apnea and sleepiness
- Study in animal models the linkage between respiratory control, obesity, insulin resistance, and sleep.

Acknowledgements

Supported by the National Institutes of Health Grants: HL40916, HL51931, and HL64415.

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