Chapter 37
Diabetes and Sleep Disorders

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Introduction

The increasing incidence of both diabetes and sleep apnea coincides with the epidemic of obesity. An increasing body of evidence suggests that the connections between diabetes and obstructive sleep apnea-hypopnea syndrome (OSAH) are not simply due to the common risk factor of obesity. Physiologic derangements that result from OSAH appear to lead to impaired glucose metabolism, increasing the likelihood of diabetes and impairing the efficacy of its treatment.

OSAH is characterized by abnormal breathing patterns during sleep. These abnormal patterns include obstructive apneas, obstructive hypopneas, and respiratory effort related arousals (RERAs). Patients who have sleep apnea typically experience symptoms including excessive daytime sleepiness, fatigue, and neurocognitive dysfunction.

Considerable interest has been focused on the recognized associations between OSAH and organ system dysfunction like systemic hypertension,[1–6] pulmonary artery hypertension,[7–10] myocardial infarction,[11–14] cerebrovascular disease,[15,16] and cardiac arrhythmias.[17–22] Although considerable literature supports a true cause-effect relationship between OSAH and these diseases, the exact mechanisms remain controversial.

This chapter will focus on a brief overview of OSAH and the current literature regarding associations between OSAH and diabetes mellitus (see Fig. 37.1).

Obstructive Sleep Apnea–Hypopnea Syndrome

"Sleep disorders medicine is a clinical specialty which deals with the diagnosis and treatment of patients who complain about disturbed nocturnal sleep, excessive daytime sleepiness, or some other sleep-related problem."[23] Investigations at Stanford University in the 1970s pioneered research in sleep medicine and used respiratory and cardiac sensors combined with electroencephalography, electro-oculography and electromyography in all-night, polygraphic recordings. Holland and colleagues in 1974 named this continuous all-night array of data gathering polysmonography (see Fig. 37.2).[24]

Definitions

Sleep disordered breathing patterns (apnea, hypopnea, and RERA) are defined based on polysomnographic criteria.[25]

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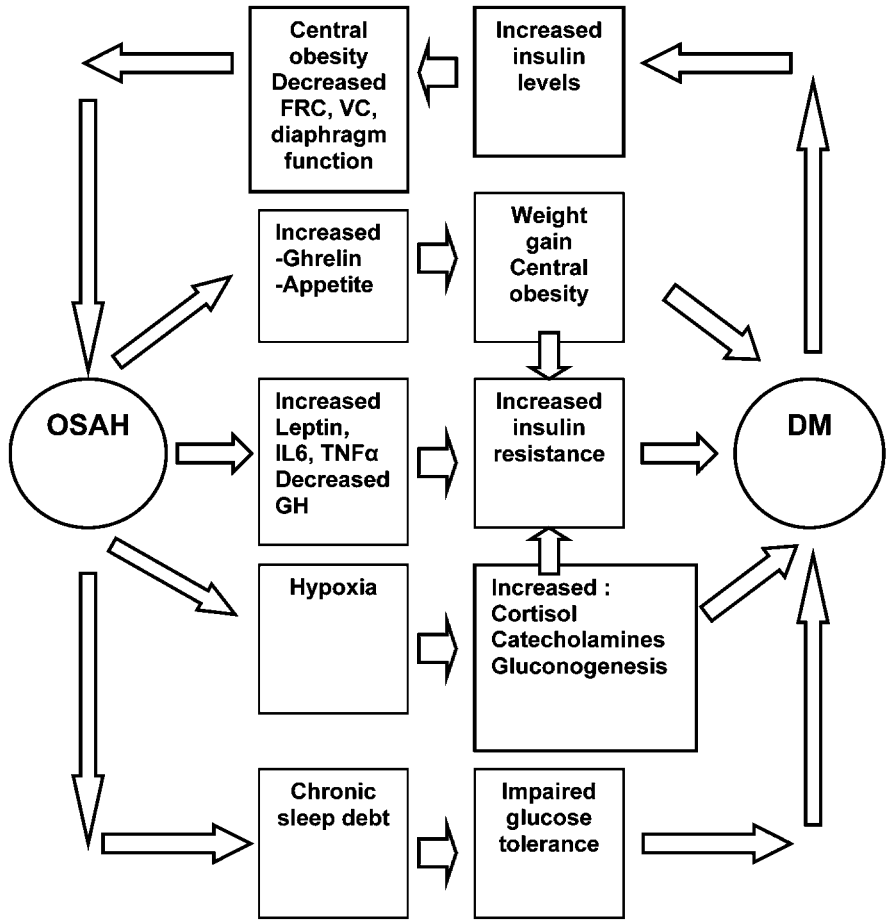

Fig. 37.1 Proven and putative interactions between obstructive sleep apnea–hypopnea syndrome (OSAH) and diabetes (DM). FRC = functional residual capacity, VC = vital capacity, IL6 = interleukin-6, TNFα = tumor necrosis factor alpha, GH = growth hormone

Apnea – A decrease in the airflow to less than 20% of the baseline, lasting at least 10 s, in adults.

Obstructive apnea – Absence of airflow but persistence of ventilatory effort defines obstructive apnea and is caused by the complete or near complete closure of the upper airway (see Fig. 37.2b).

Central apnea – Absence of both airflow and ventilatory effort defines central sleep apnea (see Fig. 37.2a).

Mixed apnea – A combination of both obstructive and central apnea defines a mixed apnea.

Hypopnea – Hypopnea is defined as a decrease in the airflow (to less than 70% of baseline airflow), but not to the extent that is seen with apnea (less than 20% of the baseline), lasting for at least 10 s, and associated with at least a 3% oxyhemoglobin desaturation.

Respiratory effort related arousals (RERAs) – RERAs are defined as a sequence of breaths lasting at least 10 s and characterized by increasing respiratory effort or flattening of the nasal pressure waveform (indicating increased upper airway resistance), leading to arousal from sleep but not meeting the criteria for apnea or hypopnea.

Apnea-hypopnea index (AHI) – the total number of apneas and hypopneas per hour of sleep constitutes the AHI.

Respiratory disturbance index (RDI) – the total number of apneas, hypopneas, and RERAs per hour of sleep constitutes the RDI.

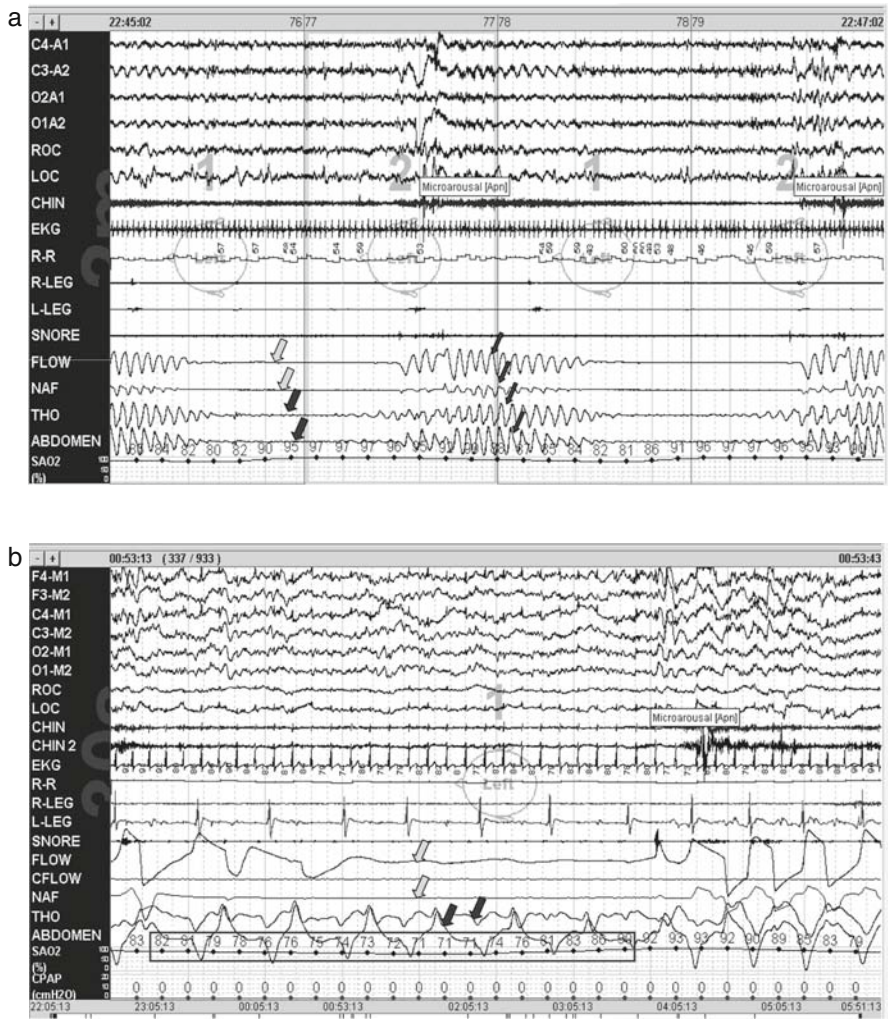

Fig. 37.2a (**a**) Central Sleep Apnea. The figure shows a 2-min segment (four 30-s epochs) of an overnight polysomnogram in a patient with central sleep apnea. The epoch reveals absence of airflow during period of apnea (*light gray wide arrows*) associated with absence of any thoracic or abdominal movement (*dark gray wide arrows*). This combination of absent airflow and absent ventilatory effort (manifested by lack of abdominal/thoracic movement) defines central sleep apnea. The periods of apnea can be seen to alternate with periods of respiration (*narrow dark gray arrows*) and each period of apnea is followed by a microarousal (C4, C3, O2, O1: EEG leads; ROC, LOC: Eye leads; NAF: Nasal air flow; THO: Thorax). The authors acknowledge Mangala Narasimhan, DO, for providing this clinical example. (**b**) Obstructive sleep apnea. The figure shows a 30-s epoch from an overnight polysomnogram of a patient with obstructive sleep apnea. The epoch reveals absence of airflow (*light gray arrows*) with persistence of abdominal and thoracic movements (*dark gray arrows*). This combination of absent airflow with persistent ventilatory effort is characteristic of obstructive sleep apnea. Also noticeable is the oxygen desaturation that is associated with the apnea boxed area in the oxygen saturation channel (SaO2) (F4, F3, C4, C3, O2, O1: EEG leads; ROC, LOC: Eye leads; NAF: Nasal air flow; THO: Thorax). The authors acknowledge Mangala Narasimhan, DO, for providing this clinical example

Obstructive sleep apnea-hypopnea syndrome (OSAH) – OSAH is defined as the presence of an AHI or a RDI >5 events/h in a symptomatic patient or an AHI or a RDI >15 events/h in an asymptomatic patient.[26] The severity of OSAH is defined based on the AHI or the RDI (mild OSAH 5–15 events/h; moderate OSAH 15–40 events/h; severe OSAH > 40 events/h).

Epidemiology

It has become evident that OSAH is a common medical condition and that it remains undiagnosed in many adults. The National Sleep Foundation conducted the Sleep in America 2005 Poll utilizing the Berlin Questionnaire (a validated tool to identify OSAH) via telephone interviews.[27] Of the 1506 respondents, 26% met the Berlin Questionnaire criteria for high risk for OSAH. The poll concluded that as many as one in four American adults could benefit from an evaluation for the presence of sleep disordered breathing.

The prevalence of OSAH is between 3 and 9% using the criteria of an AHI >5 events/h accompanied by at least one symptom, according to one study.[28] However, the reported prevalence of OSAH in the literature is highly variable, due to heterogeneity in the populations studied and the definitions of disease. Prevalence increases with age (two- to threefold by the age of 65 years).[28] Among adults, men have a higher prevalence than women. Among younger adults (under 35 years), African-Americans have a higher prevalence than Caucasians.[29] Asians have a similar prevalence compared to Americans, despite a lower mean body weight.[29]

Pathophysiology of OSAH

Loss of patency of the upper airway during sleep is the primary physiologic change that gives rise to the signs and symptoms of OSAH. In normal subjects, and those with OSAH, during inspiration the intrathoracic pressure becomes subatmospheric, leading to inflow of air. This negative intrathoracic pressure is transmitted to the upper airway, exerting a suction effect on the soft tissues. Before the onset of inspiration, reflexes that stimulate pharyngeal dilator muscles are activated and these dilator muscles keep the upper airway from collapsing in response to the suction effect.

During sleep, the pharyngeal dilator muscles are less active due to diminished neural output from the brainstem nuclei.[30] The caliber of the upper airway is smaller in patients with OSAH, either due to an excess of soft tissue or due to an excessively compliant airway. The combination of these two factors results in either complete or near complete closure of the upper airway in patients with OSAH during sleep. This closure of the upper airway results in obstructive or mixed apnea. With the onset of apnea, the carbon dioxide level in the blood increases, leading to an escalation of the respiratory drive. The patient starts to make progressively stronger inspiratory efforts against a closed upper airway, ultimately leading to arousal from sleep which results in opening of the upper airway. Opening of the airway leads to normalization of the carbon dioxide level, the respiratory drive decreases and the patient resumes sleep. With the onset of sleep, the stage is set for the evolution of the same sequence of events again. This repetitive cycle of sleep, apnea, and arousals from sleep results in fragmentation of sleep and gives rise to the symptoms of sleep apnea. This is a simplified model for the mechanism of OSAH. The true mechanism involves a more complex interplay between cortical, neuromuscular, endocrine, and mechanical components.

Clinical Features

History

Snoring, excessive daytime sleepiness, and fatigue are common symptoms of OSAH. The chronicity and insidious onset of symptoms often leads to unawareness or underestimation of the true severity and significance of these symptoms. The Epworth Sleepiness Scale (ESS) is a simple and quick screening questionnaire which allows the assessment of the severity of subjective sleepiness (Table 37.1).[31] The presence of the patient's bed partner or family member when obtaining the history is very helpful, as the patient's abnormal sleeping patterns are often most reliably reported by them. Some of the other clinical features of OSAH are the following:

- Choking, gasping, or sensation of being smothered, causing arousal from sleep
- Restlessness during sleep

Table 37.1 Epworth sleepiness scale[31]

How likely are you to fall asleep while
- Sitting and reading
- Watching television
- Sitting quietly in a public place
- Riding as a passenger in a car for 1 hour without a break
- Lying down to rest in the afternoon when circumstances permit
- Sitting and talking with someone
- Sitting quietly after lunch without alcohol
- Sitting in a car as the driver, while stopped for a few minutes in traffic

Score:
- 0 = Would never doze
- 1 = Slight chance of dozing
- 2 = Moderate chance of dozing
- 3 = High chance of dozing

A score greater than 10 is consistent with excessive sleepiness

Source: Johns.[31]

- Periods of "stopped breathing" (witnessed apneas) terminated by loud snorting or snoring
- Morning headaches, dry mouth
- Daytime cognitive deficits, lack of concentration, changes in mood
- Impaired libido and impotence
- History of gastroesophageal reflux, menstrual irregularities, type 2 diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease, renal disease

Physical Exam

The physical exam may be normal but often shows an obese body habitus, large neck circumference (collar size greater than 17), crowded upper airway, and hypertension.

Laboratory

Routine laboratory data are of no value in either establishing or excluding the diagnosis of OSAH.

Diagnosis

Polysomnography

Polysomnography (PSG) is the gold standard for the diagnosis of OSAH. It is an expensive and time-consuming test; therefore, patient selection is important. During the test multiple physiologic variables are measured including sleep stages, respiratory effort and airflow, arterial oxygen saturation, cardiac rate and rhythm, body position, and limb movements (Fig. 37.2). By monitoring these variables, an assessment is made of the total sleep time, sleep efficiency, the different sleep stages, snoring, oxygen desaturation, cardiac rhythm disturbances, abnormal limb movements, and abnormal breathing patterns.

More recently, portable monitors for home sleep studies have become available. However, the information obtained from these devices is more limited as compared to PSG. Overnight pulse oximetry alone is also not a recommended method for the diagnosis or exclusion of OSAH. It can have a high sensitivity or specificity based on the criteria used, but not both.

Treatment

Treatment of OSAH comprises behavioral modification, continuous positive airway pressure (CPAP) by nasal or face mask, oral appliances, medications, and in select cases ENT evaluation for correctable anatomic abnormalities that may be contributing to the OSAH.

Behavioral modifications – Weight loss,[32,33] avoidance of alcohol[34] and drugs that depress the central nervous system and worsen apneas and hypopneas, and education about the risks of driving and using dangerous equipment associated with excessive daytime sleepiness are therapeutic measures that are of benefit and should be recommended to all patients with OSAH.

Continuous Positive Airway Pressure – The cornerstone of treatment for OSAH is CPAP therapy. The positive airway pressure delivered by the CPAP machine functions as a pneumatic splint that keeps the upper airway open while the patient is sleeping. The effectiveness of CPAP is limited by patient compliance, as the device has to be worn nightly, optimally for the entire night. Compliance has been shown to improve with simple interventions like patient education about OSAH and the benefits of CPAP therapy, in-hospital and home care support, and follow-up telephone calls.[35–37]

CPAP when used correctly has been shown to reduce mortality, morbidity, and healthcare costs.[38–41] Therapy also improves subjective and objective sleepiness, quality of life, and cognitive function.[42,43]

Oral Appliances (OA) – A variety of oral appliances are currently in use that have been shown to benefit OSAH patients.[44,45] Some advance the mandible forward while others hold the tongue anteriorly and away from the posterior pharyngeal wall. CPAP is more effective than OA in reducing respiratory disturbances but the subjective outcomes show little difference.[46]

Surgery – Uvulopalatopharyngoplasty is the most common surgery performed for OSAH. Others include genioglossus advancement, maxillary-mandibular advancement, and radiofrequency ablation, alone or in combination. So far, trials have failed to consistently show benefits of surgery. It should be reserved for patients who fail or are not candidates for nonsurgical therapy.

Pharmacologic therapy – Modafinil is the only FDA-approved drug for the treatment of residual hypersomnolence due to OSAH.[47,48] Its role is solely as adjunctive therapy for patients inadequately controlled by CPAP or OA alone and it cannot replace primary therapy. Although several mechanisms appear to be operative, investigation continues as to their relative importance. However, its mechanism of action appears to differ from the traditional adrenergic agents, which probably relates to its low abuse potential. Several mechanisms seem to contribute to its enhancement of wakefulness. There is inhibition of GABA release in the cerebral cortex via serotenergic pathways and augmented dopaminergic effect by blocking its reuptake. In addition, modafinil inhibits the norepinephrine reuptake transporter in the ventrolateral preoptic nucleus.

Sleep Disordered Breathing and Diabetes Mellitus

Obesity has reached epidemic proportions in the United States. It is estimated that more than half of the adult population in this country is overweight or obese. The striking increase in the prevalence of obesity over the last two decades has affected men and women across all ages and in various racial and ethnic groups. Coincident with the increase in obesity has been a dramatic increase in the incidence of cardiovascular disease, cerebrovascular disease, hypertension, and type 2 diabetes mellitus.

The Center for Disease Control and Prevention has noted that the prevalence of diabetes among Americans has risen from 1.5 million to 15.8 million cases per year, from 1980 to 2005. This represents an enormous disease burden and one that is likely to rise further in the years ahead.

As mentioned previously, the reported prevalence of OSAH in the US has varied, depending on the definitions and the population studied. Most experts in the field accept that it remains an underdiagnosed and often untreated malady. As the “epidemic of obesity” worsens, these numbers are likely to increase in the coming years as well.

Phenotypically, the patients with diabetes commonly are hypertensive, overweight or obese, have poor metabolic control, suffer from cardiac disease, and list fatigue and lethargy as common complaints. The typical patient with OSAH has a remarkably similar clinical profile, apart from the hyperglycemia seen in diabetes. The relationship between diabetes and OSAH is controversial because a true causal association has still not been proven. The question of whether diabetes may be a cause or a consequence of sleep disordered breathing, or whether these are just comorbid conditions, still needs to be definitively answered. Obesity as a cause of both insulin resistance and diabetes mellitus is often a confounding factor. Similarly, whether treatment of obstructive sleep apnea with CPAP results in clinical improvement of insulin resistance remains an area of some dispute.

Pathophysiology

Sleep disordered breathing has widespread systemic effects, many of which are underappreciated by those outside of the sleep specialist community. Activation of a multitude of adaptive physiological responses, including endocrine alterations, occurs when cellular gas exchange and acid–base balance are perturbed during apneas, hypopneas, and RERAs. Conversely, manifestation of sleep apnea is critically linked to inputs to the control of breathing. A body of research has established that the control of breathing incorporates both voluntary and involuntary (emotional, metabolic, neural, and endocrine) mechanisms.

Sleep disordered breathing may interact with the endocrine system in several ways (Fig. 37.1). OSAH with recurrent episodes of apnea and hypopnea causes sleep fragmentation and disturbance of the sleep cycle and stages. Frequent arousals from sleep induce stress responses resulting in increased levels of stress hormones.[49] Hypoxia results in alterations in the hypothalamo-pituitary axis and disordered secretion from several endocrine glands.[50] Animal studies using rats and dogs have shown that the levels of ACTH, renin, aldosterone, vasopressin, and corticosteroids increase with acute hypercapnia and hypoxia.[51,52]

Over time, multiple studies have shown an independent association between sleep apnea and insulin resistance.[53–59] Vgontzas et al.[56] showed that the circulating levels of insulin, the adipostatic hormone leptin, and the inflammatory cytokines tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are increased in patients with sleep apnea, independent of obesity. Both leptin and the two cytokines are released into the interstitial fluid of the adipose tissue and are known to cause marked insulin resistance.[60,61]

A recent study postulated that a possible mechanism for the development of diabetes in patients with sleep disordered breathing is that OSAH contributes to weight gain and obesity, especially central obesity.[62] It is established that central obesity leads to insulin resistance via increased lipolysis and fatty acid availability.[63] Sleep curtailment, as occurs in OSAH, has been shown to increase appetite and ghrelin levels, and to decrease leptin levels, all possibly leading to weight gain.[64]

Studies in animals and humans have shown perturbation in glucose homeostasis as a direct consequence of hypoxia.[65–69] A study by Strohl et al.[53] found that insulin levels increase with the level of apneic activity in patients with a BMI greater than 29. The authors postulated that once a "critical mass" was reached, low oxygen values could trigger release of hormones (catecholamines and cortisol) that would result in gluconeogenesis and/or interfere with insulin action.

A small study of 18 patients with sleep disordered breathing found that the frequency of oxygen desaturations with sleep apnea was associated with abnormalities in glucose tolerance tests and indices of insulin resistance.[70]

In a larger study by Ip et al.,[54] the minimum oxygen saturation in patients with sleep disordered breathing was found to be an independent predictor of fasting insulin levels and insulin resistance.

Punjabi et al.[57] looked at the association of insulin sensitivity and glucose tolerance with hypoxemia secondary to sleep disordered breathing. The investigators included the average drop in oxygen saturation associated with respiratory events as a continuous variable in a multivariable logistic regression model. They found that for every 4% decrease in oxygen saturation, the associated odds ratio for worsening glucose tolerance was 1.99 (95% confidence interval, 1.11–3.56) after adjusting for percent body fat, BMI, and AHI. As with glucose intolerance, insulin resistance also was related to the severity of hypoxemia associated with apneas and hypopneas. The study reported an independent relationship between the minimum oxygen saturation at night and the indices

for insulin sensitivity after adjusting for percent body fat. The investigators noted that for a two-point increase in the minimum oxygen saturation during sleep, there was an improvement in the insulin sensitivity suggesting a less insulin-resistant state with less hypoxemia during sleep.

Sleep apnea patients have low growth hormone levels.[58] Growth hormone secretion is decreased in OSAH not only due to obesity but also due to fragmented sleep causing a reduction in the amount of slow wave sleep. Repetitive hypoxemia may, in addition, affect growth hormone secretion. Growth hormone deficiency in adults is associated with impaired psychological well-being, insulin resistance, endothelial dysfunction, increased visceral fat, increased cardiovascular mortality, and accelerated aging.[71]

Spiegel et al.[72] examined the effect of chronic sleep debt on metabolic and endocrine functions. In 11 healthy young men aged between 18 and 27 years, who were restricted to 4 h in bed for 6 nights, there was clear impairment of carbohydrate tolerance. The rate of glucose clearance after injection of an intravenous bolus of glucose (300 mg/kg body weight) was nearly 40% slower compared to when the subjects spent 12 h in bed. Glucose effectiveness (a measure of the ability of glucose to mediate its own disposal independent of insulin) was 30% lower, which is about the same amount of difference observed between normoglycemic white men and patients with non-insulin-dependent diabetes. The acute insulin response to glucose, which has been identified as an early marker for diabetes, was 30% lower, a magnitude similar to that seen in gestational diabetes.

To complete the circle, Strohl et al.[53] hypothesized that hyperinsulinemia causes central fat deposition. Increasing central obesity would result in decreased functional residual capacity (FRC), decreased vital capacity, impaired diaphragm muscle action and, through a coupling of FRC to upper airway size, reduced pharyngeal size. These factors would propagate apneic activity and increase the susceptibility for sleep apnea.

In summary, while there are several putative mechanisms by which OSAH is thought to cause impaired glucose metabolism and insulin sensitivity, a clear and definite answer is still lacking (Fig. 37.1).

Insulin Levels and OSAH

The reported prevalence of OSAH in the United States has varied from 1 to 25%.[57] While many studies that have reported prevalence of OSAH have included patients with moderate to severe obesity (often with BMI in excess of 40 kg/m^2) the prevalence of OSAH in the mildly obese was unknown, until recently. A study conducted by Punjabi et al.[57] examined the prevalence of sleep disordered breathing in 150 otherwise healthy males, who had an average BMI of 30.5 kg/m^2. Using an AHI cutpoint of $\geq$5, $\geq$10, and $\geq$15 events/h as the disease defining cutpoint for sleep disordered breathing, the overall prevalence was 62, 45, and 41%, respectively. The prevalence of sleep disordered breathing with hypersomnolence (defined using the Multiple Sleep Latency Test, which measures the duration in minutes to sleep onset in a darkened room) at the described AHI cutpoints was 27, 24, and 23%, respectively. The Wisconsin Sleep Cohort Study[73] reported a prevalence of 24% in the general adult male population with only 4% self-reported daytime sleepiness. The differences in age of the population studied and methodology may account for some of the differences in the reported prevalence in these two studies.

There were several early studies that reported the association between sleep disordered breathing and insulin resistance. Mondini and Guilleminault[74] reported six cases of sleep apnea syndrome among 19 diabetic patients. Katsumata et al.[75] observed a high prevalence of comorbid sleep apnea with non-insulin-dependent diabetes mellitus in a male hospital-based population. Grunstein et al.[76] reported a strong association between sleep apnea and acromegaly, an insulin-resistant state without an increase in BMI. However, Catterall et al.[77] found no evidence of clinically significant sleep apnea among 16 diabetic patients with severe autonomic neuropathy.

Strohl et al.[53] studied 261 males who were referred to a sleep laboratory for symptoms of sleep disordered breathing. The majority of the patients (>98%) were of Caucasian, non-Hispanic origin. The investigators examined the relationship of levels of apneic activity and BMI to fasting serum insulin and fasting blood glucose concentrations, which were measured the morning after the polysomnography. They found that if BMI remained relatively low (BMI < 29), there is no increase in the fasting insulin levels, regardless of AHI. In patients with BMI >29, an escalation in fasting insulin levels is seen with increasing AHI. The highest levels of insulin were seen in morbidly obese patients (BMI > 33) with an AHI >25. They concluded that fasting insulin levels are

directly, significantly, and independently associated with AHI in obese males. There was no statistically significant association between fasting blood glucose and the level of apneic activity in this study. Both fasting insulin levels and fasting blood glucose were independently associated with increase in BMI.

In an effort to find a relationship between sleep apnea, pattern of obesity (central versus generalized), and insulin resistance, Vgontzas et al.[56] conducted a study involving patients with OSAH ($n = 14$), BMI-matched obese control patients without OSAH ($n = 11$), and normal weight control patients ($n = 12$). All the study subjects were male. All the patients with OSAH had an AHI of more than 20. All potential participants in the study underwent PSG for one night and those who met inclusion criteria underwent additional PSG for another three nights. Levels of leptin, interleukin-6, and tumor necrosis factor-α (as markers of insulin resistance) were measured. Computed tomographic (CT) scanning was used to assess and compare the distribution of abdominal fat (intra-abdominal versus subcutaneous) in the sleep apneic individuals and in obese controls. The levels of leptin, tumor necrosis factor-α, and interleukin-6 were highest in the patients with OSAH, lowest in the controls with normal weight, and intermediate in the obese controls without OSAH. The sleep apneic patients had a significantly greater amount of visceral fat compared to obese controls. Visceral but not subcutaneous fat was significantly correlated with AHI and minimum oxygen saturation. In this study, mean fasting blood glucose levels and mean plasma insulin levels were significantly higher in apneics than in obese controls.

In the study by Punjabi et al.[57] the investigators examined the relationship between insulin sensitivity and sleep disordered breathing in mildly obese, otherwise healthy males. They used the oral glucose tolerance test and insulin sensitivity indices derived from the glucose tolerance test to examine this relationship. They found that there was a significant association between the severity of sleep disordered breathing and the 2-h glucose level, the insulin levels and the insulin sensitivity. They did not find a significant association between fasting blood glucose and the AHI.

Ip et al.[54] also looked at a cross-sectional cohort of patients with sleep apnea of varying degrees of intensity. They enrolled 270 subjects in their study and while they had both men and women in the cohort, the majority were male. They used the homeostasis model assessment method for estimation of insulin resistance (HOMA-IR) in their patients. The euglycemic clamp method is considered the gold standard technique for estimation of insulin resistance but the technique is invasive and labor-intensive, hindering its use as a research tool when investigating large numbers of subjects. Many researchers use validated alternatives such as the HOMA-IR and other indices of insulin sensitivity (or insulin resistance). This study also found a significant association between the severity of sleep apnea and fasting insulin levels as well as insulin resistance. Additionally, they also found a significant association between the minimum oxygen saturation and insulin levels and insulin resistance. There was no difference between men and women in terms of these associations.

The prevalence of OSAH in women is reported to be much lower than in men, especially in premenopausal women. In premenopausal women, the prevalence of OSAH has been directly linked to BMI. However, in a study of premenopausal women with polycystic ovary syndrome, OSAH was seen independent of BMI but was significantly associated with indices of insulin resistance.[55] This supported a close independent link between insulin resistance and OSAH in this population.

A hypothesis that was tested recently proposed that diabetes mellitus was associated with central sleep apnea rather than obstructive sleep apnea.[70–78] Participants in this study were part of the Sleep Heart Health Study cohort. The Sleep Heart Health Study was a longitudinal multicenter study designed to determine the cardiovascular and other consequences of sleep disordered breathing. The subjects were an ethnically diverse cohort of men and women aged 40 years and above, who were members of existing parent cohorts. The parent cohorts included the Framingham Heart study, Strong Heart Study, Atherosclerosis Risk in Communities Study and Cardiovascular Health Study among others. Data from 6441 participants constitute the Sleep Heart Health Study cohort. Of these, 4872 participants were without cardiovascular disease at baseline and among these, diabetes was present in 470 individuals. Sleep data in the diabetic individuals ($n = 470$) was compared to the sleep data in the nondiabetic controls ($n = 4402$). Descriptive analyses indicated differences between diabetic and nondiabetic participants in RDI, sleep stages, sleep time with saturation <90%, central sleep apnea index, and periodic breathing (Cheyne–Stokes pattern of respiration). However, multivariable regression analyses eliminated all associations except that between diabetes and periodic breathing as well as diabetes and percentage of sleep time spent in rapid-eye-movement (REM) sleep. There was a nonstatistically significant elevation in the

odds of an increased central apnea index. Noteworthy in this report was the lack of association between obstructive sleep apnea and diabetes, once adjustment for BMI was made in the analyses. Based on these results, the study proposed an additional pathway for the development of sleep disordered breathing in diabetes. Instability of breathing during sleep, particularly associated with central breathing abnormalities, may result in part from dysfunction of the autonomic nervous system, a common complication of diabetes.

Although this is one of the largest population studies conducted to date, sleep data were collected by in-home PSG as opposed to the gold standard data collected in a sleep laboratory. As a second counterpoint, the definition of obstructive sleep apnea used in the study is different than the current accepted definition. However, the report adds to the growing body of literature linking abnormalities of glucose metabolism to sleep disordered breathing. It also highlights the fact that obesity is a major confounding factor in such studies. Even more important is the fact that an increased occurrence of sleep disordered breathing in patients with diabetes, even if caused by obesity, may represent a modifiable risk factor for cardiovascular disease.

Similar to the results of the above study, Stoohs and colleagues[79] found that the relationship between worsening insulin sensitivity and sleep disordered breathing in a group of 50 "healthy, normotensive individuals" was completely accounted for by increased BMI.

All the studies involving sleep disordered breathing and diabetes mellitus have been cross-sectional in design and while the preponderance of these show an association between OSAH and indices of insulin sensitivity, a true causal relationship can only be inferred and has never been definitively established. The first longitudinal study of the relationship between sleep disordered breathing and diabetes mellitus was published in 2005.[63] The objective of the study was to determine the prevalence and incidence of diabetes in patients with sleep disordered breathing. The study had 1387 subjects in the cross-sectional analysis. Of this cohort, 978 subjects reported no diagnosis of diabetes on the first visit and these patients were included in the longitudinal analysis. These 978 subjects were followed for 4 years to determine the incidence of diabetes. In the cross-sectional analysis, it was found that self-reported diabetes was three to four times more prevalent in subjects with an AHI of 15 or greater than in those with an AHI of less than 5. An independent relationship existed even after controlling for shared risk factors such as age, gender, and body habitus. A significant independent association was also found when a more inclusive definition for diabetes was used, that included either physician diagnosis or elevated fasting blood glucose. However, the study did not find a statistically significant independent causal effect in the development of type 2 diabetes in the longitudinal analysis. The incidence of diabetes over a 4-year follow-up period was not significantly related to the severity of sleep disordered breathing at the time of initial enrollment in the cohort when shared risk factors were taken into account.

Prospective studies prior to this had used snoring as a surrogate for sleep disordered breathing without the benefit of nocturnal PSG.[80,81] These studies had concluded that snoring is an independent risk factor for the development of diabetes. However, the specificity of snoring for severe sleep disordered breathing is not high.

How does one reconcile the finding of an independent association between sleep disordered breathing and diabetes in multiple cross-sectional studies with the lack of an independent causal effect in the only prospective, longitudinal study to date? Reichmuth et al.,[62] who conducted the longitudinal study, postulate that diabetes is often preceded by a "prediabetic" state including insulin resistance, impaired glucose tolerance, and possibly impaired fasting glucose, but the progression from one of these conditions to diabetes is variable and not well defined. It is possible that sleep disordered breathing impairs glucose metabolism without progression to overt diabetes. A widely accepted theory is that insulin resistance precedes diabetes and in individuals with a genetic predisposition, insulin secretion falters and diabetes ensues. Sleep disordered breathing may not affect this last step independent of other factors such as obesity, age, or genetic predisposition. Other factors that may have affected the results of the longitudinal study are patient selection (selection of a subpopulation of patients who were more resistant to the adverse metabolic effects of sleep apnea, older patients, only 4% of patients with an AHI of more than 30), the type of sleep disordered breathing (pure OSAH versus central apnea or mixed apnea) and the length of follow-up may have been insufficient (the latent period to development of diabetes may extend beyond the duration of the study).

Effect of CPAP Therapy on Insulin Resistance

It is a reasonable hypothesis that if sleep disordered breathing is a cause of diabetes (or insulin resistance), then treatment of the former should result in improvement of the latter. Unfortunately, the data until now have neither definitely supported nor refuted this hypothesis. The effectiveness of any therapy is modified by the compliance with the therapy and use of CPAP, even with the newest, most user-friendly models, is especially beset with noncompliance. There is also the question of the duration of therapy with CPAP required before there is any evidence of improvement in the metabolic profile of the patients with sleep disordered breathing.

Facchini et al.,[82] in a study looking at the effect of 8 weeks of CPAP treatment, did not show any improvement of overnight glucose tolerance in obese patients with OSAH. On the contrary, they found that there was an increase in the levels of plasma glucose and insulin after CPAP treatment. However, this was a small study of four patients. Similarly, in a later study, Smurra et al.[83] found lack of improvement in insulin responsiveness in ten patients (non-obese or moderately overweight with a BMI < 37) after 2 months of CPAP treatment.

Brooks et al.[84] studied insulin responsiveness in ten patients with non-insulin-dependent diabetes mellitus and severe OSAH (mean AHI of 47), both before and after 4 months of CPAP treatment. Insulin responsiveness was measured by the euglycemic clamp method. There was a statistically significant improvement in insulin responsiveness after 4 months of CPAP treatment. However, there was no change in the fasting insulin level, fasting blood glucose level and HbA_{1c}. The authors of the study postulated that this lack of effect may have been due to the fact that the increase in insulin responsiveness was relatively modest, especially in the context of severe insulin resistance in the severely obese patients (mean BMI of 42.7 kg/m^2) in this study. Another possibility was that the patients were at the plateau of the dose-response curve between glycemia and insulin resistance, where improvement in one would not necessarily be paralleled by improvement in the other. Lastly, all three of the above studies (Facchini et al., Smurra et al., and Brooks et al.) may have lacked statistical power due to the small number of patients.

Harsch et al.[85] investigated insulin resistance after CPAP treatment in 40 patients with OSAH (AHI > 20). None of the patients had a diagnosis of diabetes mellitus. The investigators performed studies with the hyperinsulinemic euglycemic clamp method before CPAP treatment was initiated, and then 2 days after, and 3 months after CPAP treatment was initiated. They found that insulin sensitivity improved significantly after 2 days of CPAP treatment and this improvement remained stable after 3 months of treatment. They also noted that the magnitude of improvement was smaller in obese patients as compared to non-obese (BMI < 30) patients, suggesting that in obese individuals insulin sensitivity is mainly determined by obesity and to a smaller extent by sleep apnea. The rapid improvement in insulin sensitivity lends credence to the hypothesis that insulin resistance is mainly induced by increased nocturnal sympathetic drive, mediated by adrenal hormones with short half-lives.

The same group of investigators later published the results of a similar study involving nine patients with overt type 2 diabetes mellitus and OSAH (mean AHI of 43.1).[86] In this study, there was no improvement in insulin sensitivity after 2 days of CPAP treatment but a statistically significant improvement was seen after 3 months of CPAP treatment. The investigators regarded the lack of a quick improvement in insulin sensitivity in the diabetic group as the consequence of a more fixed and genetically determined degree of insulin resistance, which is thus more difficult to reverse in diabetic than in nondiabetic patients. Similar to the study by Brooks et al. this study also did not demonstrate an improvement in HbA_{1c} with CPAP treatment.

Finally, Babu et al.[87] in a study of 25 patients with type 2 diabetes mellitus and OSAH (mean AHI of 56) measured changes in interstitial glucose levels and hemoglobin A_{1c} levels before and after a mean of 83 ± 50 days of CPAP treatment. They observed that mean postprandial glucose values were significantly reduced and that there was a statistically significant reduction in hemoglobin A_{1c} levels after CPAP treatment. Furthermore, in patients who used CPAP for more than 4 h/day, the reduction in HbA1c level was significantly correlated with days of CPAP use.

Summary

In conclusion, sleep disordered breathing is now recognized as being much more prevalent than was originally suspected. The preponderance of cross-sectional studies points toward an independent association between sleep disordered breathing and diabetes mellitus or a "prediabetic" state of insulin resistance. This relationship has not been conclusively shown to be due to a direct causal effect. The data from studies examining the improvement of diabetes with CPAP treatment span the spectrum from no effect, to improvement in insulin sensitivity but not glycemic control, to significant improvement in glycemic control.

Although there is a growing body of literature on this subject, it is clear that the understanding of the complex interactions between diabetes and sleep disordered breathing is still in its infancy. The field remains wide open for further research, especially for the longitudinal analyses and the effects of CPAP treatment.

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