

HIGHLIGHTED TOPIC | *Physiology and Pathophysiology of Sleep Apnea*

## Disorders of glucose metabolism in sleep apnea

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**Punjabi, Naresh M., and Vsevolod Y. Polotsky.** Disorders of glucose metabolism in sleep apnea. *J Appl Physiol* 99: 1998–2007, 2005; doi:10.1152/jappphysiol.00695.2005.—Sleep is a complex behavioral state that occupies one-third of the human life span. Although viewed as a passive condition, sleep is a highly active and dynamic process. The sleep-related decrease in muscle tone is associated with an increase in resistance to airflow through the upper airway. Partial or complete collapse of the airway during sleep can lead to the occurrence of apneas and hypopneas during sleep that define the syndrome of sleep apnea. Sleep apnea has become pervasive in Western society, affecting ~5% of adults in industrialized countries. Given the pandemic of obesity, the prevalence of Type 2 diabetes mellitus and metabolic syndrome has also increased dramatically over the last decade. Although the role of sleep apnea in cardiovascular disease is uncertain, there is a growing body of literature that implicates sleep apnea in the pathogenesis of altered glucose metabolism. Intermittent hypoxemia and sleep fragmentation in sleep apnea can trigger a cascade of pathophysiological events, including autonomic activation, alterations in neuroendocrine function, and release of potent proinflammatory mediators such as tumor necrosis factor- $\alpha$  and interleukin-6. Epidemiologic and experimental evidence linking sleep apnea and disorders of glucose metabolism is reviewed and discussed here. Although the cause-and-effect relationship remains to be determined, the available data suggest that sleep apnea is independently associated with altered glucose metabolism and may predispose to the eventual development of Type 2 diabetes mellitus.

sleep-disordered breathing; Type 2 diabetes mellitus; glucose tolerance; insulin resistance

THE PREVALENCE OF OVERWEIGHT and obesity in the United States and other industrialized nations is rapidly increasing. Over the last 40 yr, the average body mass index (BMI) in men and women aged 20–74 yr has increased from just over 25 kg/m<sup>2</sup> to almost 28 kg/m<sup>2</sup> (32, 34, 54). Current estimates indicate that the prevalence of obesity will continue to rise and impose an enormous burden on public health globally. Excess weight gain can increase the risk of several adverse health outcomes, notably hypertension, Type 2 diabetes mellitus, cardiovascular disease, and premature death (3, 33, 133). There is also overwhelming evidence that obesity is the most important determinant of sleep apnea, a chronic condition characterized by recurrent episodes of upper airway collapse during sleep. Epidemiologic research suggests that individuals with sleep apnea confront several long-term clinical sequelae, such as hypertension and cardiovascular disease, and may experience a reduction in life expectancy. Several studies have also identified that sleep apnea is associated with an increased prevalence of glucose intolerance, hyperinsulinemia, and Type 2 diabetes mellitus. Given that obesity is a common risk factor for disorders of glucose metabolism and sleep apnea, it remains to be determined whether the observed association is causal or

correlated because of the confounding effects of obesity. The major objectives of this review are to 1) amalgamate the recent literature that supports the notion of an independent, and perhaps causal, link between sleep apnea and disorders of glucose metabolism and 2) present the intermediate mechanisms that may underlie the association.

## DISEASE DEFINITION AND EPIDEMIOLOGY

*Disorders of glucose metabolism.* The natural history of Type 2 diabetes mellitus is marked by a gradual deterioration of glucose tolerance over time, progressing from normoglycemia to impaired fasting glucose or impaired glucose tolerance, to insulin resistance, and finally to Type 2 diabetes mellitus. According to the American Diabetes Association, impaired fasting glucose and impaired glucose tolerance are considered as prediabetic states, given the established high risk of future Type 2 diabetes mellitus as well as cardiovascular disease. On the basis of the most recent recommendations (2), impaired fasting glucose is defined as a fasting glucose of 100–125 mg/dl (5.6–6.9 mmol/l) and impaired glucose tolerance as a 2-h postchallenge glucose level of 140–199 mg/dl (7.8–11.2 mmol/l). Type 2 diabetes is diagnosed when the fasting glucose exceeds 125 mg/dl (6.9 mmol/l) or if the 2-h glucose level after a 75-g oral glucose load is at least 200 mg/dl (11.0 mmol/l).

The prevalence of clinically recognized diabetes mellitus has increased dramatically among men and women across ethnic

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groups and age groups. Currently, it is estimated that clinically diagnosed diabetes affects 5.9% of the adults (age  $\geq 20$  yr) in the United States, with an additional 2.4% with undiagnosed diabetes based on an elevated fasting glucose (4). Moreover,  $\sim 6.9\%$  of adults have impaired fasting glucose values and 15.6% have an abnormal glucose tolerance test (48). Epidemiologic projections for the year 2010 predict an increase by almost 50%, with the greatest increase occurring in developing nations (62). Type 2 diabetes mellitus is characterized by devastating micro- and macrovascular complications that impose an enormous strain on health care systems worldwide (140). Thus understanding the contribution of conditions such as sleep apnea in the pathogenesis of hyperglycemic states is of paramount significance if the population burden is to be reduced by early identification and intervention for the contributing cause.

**Sleep apnea.** Sleep apnea is clinically recognized as a heterogeneous group of disorders characterized by recurrent apneas (complete breathing cessation) and/or hypopneas (shallow breathing) during sleep. It is estimated this condition may affect at least 2–4% of the general population, with prevalence estimates that may be much higher based on demographic variables such as age, sex, and BMI (137). Obstructive sleep apnea is due to partial or complete collapse of the upper airway that occurs despite the presence of ongoing respiratory effort. In contrast, central sleep apnea is due to a decrease in respiratory effort that occurs in the absence of upper airway collapse. Although obstructive and central events can cooccur, obstructive sleep apnea is by far the most common condition in the general population and the focus of this review. The apnea-hypopnea index (AHI), the number of apneas and hypopneas per hour of sleep, is generally used as the disease-defining index for sleep apnea with a cut point of five events per hour of sleep as a threshold for diagnosis of sleep apnea.

Factors that increase the risk for sleep apnea include male sex (8, 95, 136), obesity (81, 138), age (9, 24), and race (24, 96). Most, if not all, cross-sectional surveys of clinic and population samples show that obesity and, in particular, central obesity are the strongest risk factors for sleep apnea (18, 19, 40, 55, 61, 69, 75, 107, 119). The clinical manifestations of sleep apnea are pervasive and include excessive daytime sleepiness (37), decrements in quality of life (6, 31), and increased predisposition toward driving-related accidents (36). Findings from epidemiologic studies indicate that sleep apnea is independently associated with hypertension (98) and cardiovascular disease (47). A growing body of literature suggests that sleep apnea is associated with fasting hyperglycemia, insulin resistance, and Type 2 diabetes mellitus (90). In the following sections, we discuss the possibility that sleep apnea exerts a causal and negative influence on glucose and insulin homeostasis and thereby predisposes to Type 2 diabetes mellitus.

#### SLEEP APNEA AND GLUCOSE METABOLISM: THE EVIDENCE

The question of whether sleep apnea is a precursor of vascular risk has stimulated intense research on its clinical consequences over the last two decades. Obstructive apneas and hypopneas lead to a number of acute pathophysiological consequences that include intermittent hypoxemia, severe sleep fragmentation, acute hypertension, activation of the sympathetic nervous system, alterations in intrathoracic pressure,

and decrease in stroke volume. Recurrent and chronic exposure to such pathophysiological events provides a number of plausible hypotheses on how this condition may lead to hypertension (98) and cardiovascular disease (47). An independent link between sleep apnea and altered glucose metabolism may represent yet another causal pathway toward cardiovascular disease. However, initial studies on sleep apnea and altered glucose metabolism were inundated with limitations often seen with pioneering work. A systematic review of the literature on sleep apnea and glucose metabolism in 2003 noted several concerns with the available literature, including the use of surrogate measures such as snoring and witnessed apneas to assess sleep apnea, relatively small sample sizes, use of highly select clinic-based populations, and inadequate adjustment for confounders (90). Thus inferences from these studies were often inconsistent, leading some to conclude that sleep apnea had no mechanistic role in pathogenesis of altered glucose metabolism (117). However, a number of observational and experimental studies conducted over the last several years confirm an independent association between sleep apnea and disorders of glucose metabolism. Observational studies can be classified into three different groups. These include cross-sectional and longitudinal studies that have related disorders of glucose metabolism to 1) surrogate markers of sleep apnea such as snoring and witnessed apneas, 2) polysomnography-defined sleep apnea, and 3) the effects of positive-pressure therapy. Complementing this repertoire of observational data, experimental interventions in humans and animal models have provided further insight on the pathophysiological link between sleep apnea and altered glucose metabolism.

**Surrogate markers of sleep apnea and glucose metabolism.** Given the relative ease by which self-reports of habitual snoring or witnessed apneas can be assessed, it is not surprising to find that initial research efforts correlated these surrogate markers of sleep apnea to indexes of altered glucose metabolism or Type 2 diabetes mellitus. Epidemiologic studies on large samples recruited from Denmark (60), Sweden (42), and the United States (28) show that, irrespective of the source population, habitual snoring was independently associated with abnormalities in glucose tolerance or serum insulin levels or overt diabetes mellitus. More recent analyses from other study samples continue to confirm a high prevalence of habitual snoring in individuals with Type 2 diabetes mellitus (66) or a higher prevalence of metabolic syndrome in habitual snorers (97). However, a major problem with these studies is their inability to differentiate cause and effect from simple association. It is certainly possible that alterations in glucose metabolism represent an upstream event that eventually predisposes to upper airway collapse during sleep and manifests as habitual snoring or sleep apnea. In fact, laboratory-based investigations show that diabetic patients with autonomic neuropathy are more likely to have obstructive and central sleep apnea than diabetic patients without autonomic neuropathy (30, 80). Fortunately, some of these concerns have been addressed by two prospective studies on habitual snoring and Type 2 diabetes mellitus. Prospective cohort studies rate highest in terms of epidemiologic evidence as they fulfill an important criterion for causality, i.e., establishing a temporal relationship between the exposure variable and the outcome. Establishing temporality is particularly important for chronic diseases such as Type 2 diabetes mellitus that develop many years subsequent to earlier

exposure (e.g., obesity, sleep apnea). The first of two such cohort studies was conducted in Sweden on a sample of 2,668 men aged 30–69 yr (26). In this group, habitual snoring was found to be a risk factor for self-reported diabetes independent of age, weight, physical activity, and other confounders. Obesity and habitual snoring were additive in the overall risk for developing diabetes. Despite the large sample size and 10-yr follow-up, a major weakness of that study was the use of self-report to assess sleep apnea and diabetes status. The potential bias of self-reports was subsequently addressed by prospective data from the Nurses' Health Study, in which Type 2 diabetes mellitus was based on composite criteria using clinical and laboratory findings (1). In a sample of 69,852 women with data over a 10-yr period, the relative risk for diabetes mellitus, comparing regular snorers with nonsnorers, was 2.03 (95% confidence interval: 1.71–2.40). The increase in risk for diabetes in snoring women was independent of various confounders such as BMI, physical activity, and family history of diabetes. Nevertheless, the misclassification error resulting from the use of snoring as a marker of sleep apnea precludes any inferences regarding its impact on glucose metabolism. Furthermore, the lack of objective sleep-related data limits our understanding of the pathophysiological processes through which sleep apnea might lead to altered glucose metabolism. Specifically, without objective sleep data, it is just not possible to characterize the links between the nocturnal changes in sleep apnea and glucose metabolism. For example, is it the degree of sleep-related hypoxia or the frequency of arousals that best predicts the development of metabolic dysfunction? What candidate mechanisms (e.g., sympathetic activation, inflammation) triggered by intermittent hypoxemia and sleep fragmentation produce the long-term changes in glucose metabolism? Despite the ongoing debate about the merits of specific indexes of sleep apnea severity, polysomnography provides the best means currently available to resolve such questions.

*Polysomnography-defined sleep apnea and glucose metabolism.* In addition to the indirect evidence relating habitual snoring and glucose metabolism, there are now several studies correlating adverse metabolic outcomes to indexes of sleep apnea severity derived from overnight polysomnography. Early attempts at describing the associations between disorders of glucose metabolism and sleep apnea measures such as the AHI and degree of oxyhemoglobin desaturation suffered to some extent from a number of methodological flaws. Limited sample size, inadequate correction for confounding covariates, and inconsistencies in exposure and outcome assessment inevitably led to a lack of consensus on the metabolic implications of sleep apnea (20, 27, 69, 117, 120, 123, 130). It was not until 2002 that two independent groups simultaneously published convergent findings associating sleep apnea with altered glucose metabolism and generated further research interest on this topic. The first study utilized a clinic sample of 270 patients from Hong Kong and reported that the AHI and minimum oxygen saturation during sleep were independent correlates of insulin resistance (57). The second study utilized a community sample of 150 healthy men from the United States and reported that the AHI and the degree of nocturnal desaturation were associated with glucose intolerance and insulin resistance independent of obesity (92). Although the conclusion from both of these studies was that sleep apnea may promote adverse metabolic outcomes, the lack of central obesity measures and

the exclusion of women in the latter study represent major weaknesses. Perhaps the best evidence for the association between sleep apnea and glucose metabolism comes from the large multicenter Sleep Heart Health Study (91). In a community sample of 2,656 subjects, the AHI and average oxygen saturation during sleep were associated with elevated fasting and 2-h glucose levels during an oral glucose tolerance test. Sleep apnea severity was also associated with the degree of insulin resistance independent of BMI and waist circumference, among other confounders. Similar findings continue to be reproduced in a number of other smaller clinic-based studies (17, 21, 71, 74, 122). Although these recent findings implicate intermittent hypoxemia and sleep fragmentation in the pathogenesis of metabolic dysfunction, correlation is insufficient to prove causation. Therefore, conclusions on the significance of sleep apnea in disorders of glucose metabolism will require sustained longitudinal research efforts in which overnight polysomnography is implemented to characterize the physiological abnormalities in sleep and breathing.

*Effects of sleep apnea treatment on glucose metabolism.* If cross-sectional and longitudinal surveys of clinic- or population-based samples are unsatisfactory in establishing an etiologic link, an alternative approach would be to mitigate sleep apnea with continuous positive airway pressure (CPAP) treatment and explore changes in glucose metabolism. There are now 12 studies (5, 12, 15, 16, 20, 50, 51, 58, 99, 100, 109, 118) examining the metabolic profiles in sleep apnea before and after CPAP treatment. On the basis of the available data summarized in Table 1, it is apparent that there is substantial variation, with major differences in treatment duration and primary outcomes across these studies. Most could be criticized for lack of a control group, insufficient statistical power, and absence of data on CPAP compliance. Thus the failure to detect changes in glucose metabolism with CPAP in all but 3 of the 12 studies is not surprising. In the largest study (51) documenting a beneficial effect of CPAP to date, improvement in insulin sensitivity, as assessed by the hyperinsulemic euglycemic clamp, was observed over a 3-mo period after the initiation of CPAP. Interestingly, insulin sensitivity increased within 2 days of therapy, with further improvements occurring at the 3-mo follow-up. As expected, obesity was an important modifier of the treatment effect, with nonobese patients experiencing a rapid improvement in insulin sensitivity compared with obese patients. An implication of this finding is that obesity might have masked the ability to detect changes in glucose metabolism in a number of the negative studies listed in Table 1. We interpret these data together to indicate that, as with other sleep apnea-related outcomes, specific patient subsets are more CPAP responsive than others, and this may well be true for the observed improvements in glucose metabolism. In the absence of controlled clinical trials on the metabolic effects of CPAP, intervention studies cannot close the scientific gap on whether sleep apnea and disorders of glucose metabolism are causally associated or merely correlated.

*Experimental evidence on sleep apnea and glucose metabolism.* In light of the methodological issues that are inherent with observational and interventional data, several investigators have used an experimental approach to ascertain whether sleep apnea and its concomitants, intermittent hypoxemia and recurrent arousals, alter glucose metabolism. Using a mouse model of intermittent hypoxia to simulate the hypoxic stress of

Table 1. *Studies on continuous positive airway pressure treatment in sleep apnea and glucose metabolism*

Study	No. of Subjects	Study Cohort	Control Group	Outcome	Treatment Duration	Conclusions
Babu et al. (5)	25	Type 2 diabetic patients with sleep apnea	None	Hemoglobin A1c and postprandial	3 mo	Decrease in HbA1c and postprandial glucose values in the morning
Brooks et al. (12)	10	Diabetic patients with sleep apnea	None	Hyperinsulinemic euglycemic clamp Fasting glucose and insulin	4 mo	Improvement in insulin responsiveness No change in fasting glucose or insulin
Chin et al. (15)	31	Sleep apnea patients	Sleep apnea patients	Oral glucose tolerance test with insulin measurements	6 mo	No change in glucose and insulin levels except in patients with accompanying weight loss
Cooper et al. (16)	6	Sleep apnea patients	None	Glucose samples every 30 min during sleep and insulin and C-peptide samples every hour	1 night	No change in glucose, insulin, and C-peptide profiles during sleep
Davies et al. (20)	10	Sleep apnea patients	Matched controls	Fasting insulin	3 mo	No change in insulin levels with treatment
Harsch et al. (50)	9	Type 2 diabetic patients with sleep apnea	None	Hyperinsulinemic euglycemic clamp	3 mo	Improvement in insulin sensitivity at 3 mo
Harsch et al. (51)	40	Sleep apnea patients	None	Hyperinsulinemic euglycemic clamp	3 mo	Improvement in insulin sensitivity at 2 days and 3 months
Ip et al. (58)	9	Sleep apnea patients	None	Fasting glucose and insulin	6 mo	No change in fasting glucose and insulin
Saarclainen et al. (99)	7	Sleep apnea patients	None	Hyperinsulinemic euglycemic clamp	3 mo	No change in insulin responsiveness
Saini et al. (100)	8	Sleep apnea patients	None	Glucose-insulin samples every 10 min during sleep	1 night	No change in glucose and insulin profiles
Smurra et al. (109)	16	Endocrine clinic patients with sleep apnea ( <i>n</i> = 10) Sleep apnea patients ( <i>n</i> = 6)	None	Oral glucose tolerance test in 10 patients Hyperinsulinemic euglycemic clamp in 6 patients	2 mo	No difference in glucose tolerance and insulin sensitivity
Stoohs et al. (118)	5	Sleep apnea patients	None	Fasting glucose and insulin Glucose-insulin samples every 30 min during sleep	2 mo	Increase in fasting and nocturnal glucose No change in fasting or nocturnal insulin levels

HbA1c, glycosylated hemoglobin.

sleep apnea, Polotsky and colleagues (86) have shown that long-term (~12 wk) exposure to intermittent hypoxia is associated with time-dependent increase in fasting serum insulin levels and worsening glucose tolerance. The response to hypoxia, however, was only evident in the obese leptin-deficient *ob/ob* mice, suggesting that disruption of leptin pathways may be important for hypoxia-mediated alterations in glucose metabolism. Elevations in fasting insulin levels have also been demonstrated in other animal models including newborn calves (14) after 2 h of hypoxic exposure and in rats (93, 94) with a more sustained exposure (~7 days). Finally, humans acutely exposed to hypoxia either in the setting of higher altitude (11, 65) or in the context of an experimental paradigm (83) demonstrate worsening of glucose tolerance with a concomitant increase in circulating levels of epinephrine. It is important, however, to recognize that exposure to sustained hypoxia such as with high altitude is not associated with persistent abnormalities in glucose homeostasis, as changes in counterregulatory hormones occur with sustained exposure (65). Although our knowledge of the long-term effects of intermittent hypoxia is fairly limited, the available data suggest that, for a given level and duration of exposure, the systemic and cellular responses are more potent with intermittent than with sustained hypoxia (88). The repetitive cycles of hypoxia-reoxygenation with intermittent hypoxemia increase oxidative stress and in-

duce a number of reactive mechanisms that are regulated, in part, by hypoxia-inducible factor 1 (HIF-1) (102). HIF-1 induces the expression of several genes that encode numerous glycolytic enzymes (59, 76–78) and glucose transporters. Thus intermittent hypoxemia in sleep apnea may influence glucose homeostasis by modulating glucose transport and utilization through effects on HIF-1.

In addition to the adverse effects of intermittent hypoxemia, there is increasing support for the notion that abnormalities in sleep itself can alter glucose metabolism. Short-term sleep restriction (4 h/night for 6 nights) in normal subjects has been shown to worsen glucose tolerance, increase levels of evening cortisol, and heighten sympathetic activity (115). Acute sleep deprivation can also dampen growth hormone secretion (127, 128), modulate neuroendocrine control of appetite (114, 116, 121), and elicit an inflammatory response (73) and may thus unfavorably influence glucose and insulin homeostasis. Collectively, the above evidence suggests that hypoxia and sleep loss can independently contribute to disorders of glucose metabolism and thus may be vital in the putative causal pathway between sleep apnea and altered glucose metabolism. However, research efforts into the metabolic implications of sleep fragmentation and subsequent sleep loss are limited. Abrupt nocturnal awakenings can promote pulsatile cortisol release (113). Clinical studies show that frequency of nocturnal arous-

als is positively correlated with morning levels of serum and salivary cortisol (25). Thus activation of the hypothalamic-pituitary-adrenal (HPA) axis due to sleep fragmentation may be an important event mediating alterations in glucose metabolism. Obviously, additional studies are warranted to delineate the additive and interactive effects of sympathetic and HPA axis activation due to recurrent sleep fragmentation in sleep apnea.

**SLEEP APNEA AND GLUCOSE METABOLISM: INTERMEDIATE MECHANISMS**

Several potential mechanisms have been purported to explain how sleep apnea may alter glucose metabolism. As shown in Fig. 1, we speculate that intermittent hypoxemia and sleep fragmentation alter the autonomic, HPA, and somatotrophic axes, increase circulating levels of inflammatory cytokines, and induce certain adipokines and thus alter glucose metabolism. In the discussion that follows, we briefly review each of these possible intermediate mechanisms that may play a role in altering glucose metabolism in sleep apnea.

*Alterations in autonomic and neuroendocrine function.* Intermediate pathways through which sleep apnea may alter glucose metabolism include the sympathetic nervous system and the HPA axis. Numerous studies have shown that patients with sleep apnea exhibit elevated levels of sympathetic neural traffic. Each episode of obstructive apnea is accompanied by transient periods of sympathoexcitation that resolve after termination of the event. Hypoxemia is an important stimulus for altering autonomic activity, with larger desaturations causing greater increases in sympathetic activity (68, 108). However, other factors, including hypercarbia and recurrent arousals from sleep, can also increase autonomic output (110–112).

Sympathetic hyperactivity can influence glucose homeostasis by increasing glycogen breakdown and gluconeogenesis. Further predisposition toward metabolic dysfunction in sleep apnea may also occur through its effects on the HPA axis. Experimental partial or total sleep deprivation has been shown to increase levels of plasma cortisol by 37% and 45%, respectively (67). The resulting increase in evening cortisol can have marked effects on serum glucose and insulin levels and insulin secretion rate. Although the paradigm of sleep deprivation is different from apnea-related sleep fragmentation, autonomic activation in sleep apnea may also increase corticotropin-releasing hormone and cortisol production. In fact, a small clinic-based study has documented an increase in serum cortisol levels in patients with sleep apnea (10). Although such findings are supportive of HPA hyperactivity in sleep apnea, studies on CPAP effects on cortisol levels have produced mixed results (10, 41, 43). Controlled clinical studies are needed to further address whether HPA abnormalities in sleep apnea are reversible with treatment.

In addition to the deleterious effects of sleep apnea on the sympathetic and HPA axes, several investigators have also shown that sleep apnea exerts a negative influence on somatotrophic function (16, 100). The resulting decrease in hepatic production of insulin-like growth factor I (IGF-I) may represent yet another factor linking sleep apnea to impaired glucose metabolism. Prospective observational data from the United Kingdom have shown that lower circulating IGF-I levels predict the subsequent risk of developing impaired glucose tolerance or Type 2 diabetes even after consideration of other risk factors in middle-aged adults (101). Nevertheless, the current state of the art regarding the independent contribution of sympathetic activity and abnormalities in HPA and somato-

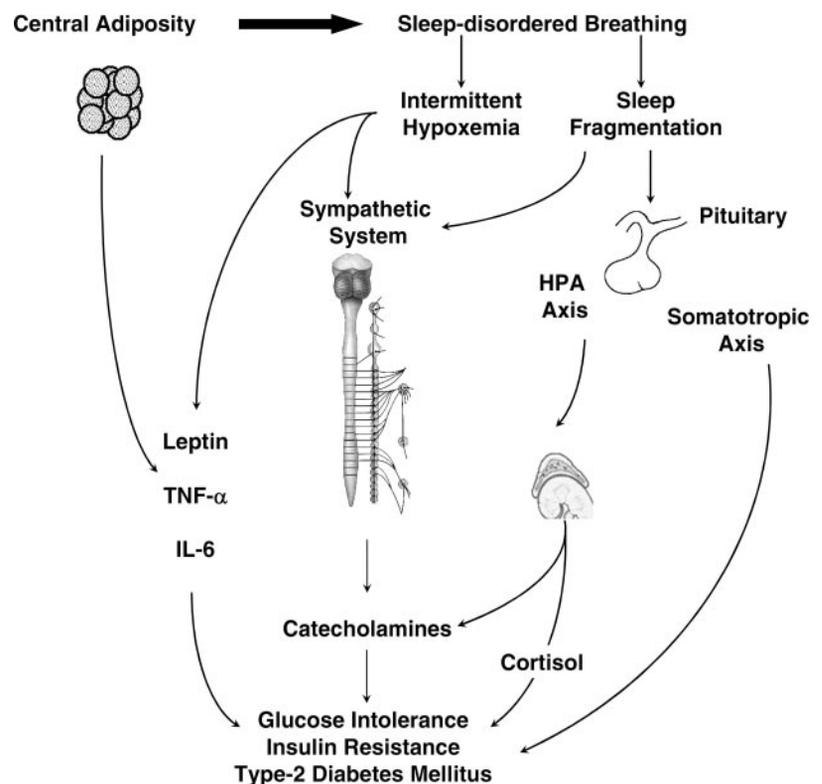


Fig. 1. Intermediate pathways linking sleep apnea, glucose intolerance, insulin resistance, and Type 2 diabetes mellitus. HPA, hypothalamic-pituitary-adrenal; IL, interleukin; TNF, tumor necrosis factor.

tropic function to impaired glucose metabolism in sleep apnea is relatively limited.

**Inflammatory cytokines.** Sleep apnea-related hypoxia may alter glucose metabolism by promoting the release of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)- $\alpha$ . Indeed, two clinic-based studies have shown that plasma levels of IL-6 and TNF- $\alpha$  are higher in patients with sleep apnea compared with normal subjects (70, 130). TNF- $\alpha$  is a key intermediate in the development of insulin resistance and metabolic syndrome, as shown by several different but convergent lines of empirical evidence (56). For example, although obese mice with homozygous null mutations at the TNF- $\alpha$  or TNF receptor loci remain obese, they appear to be protected from developing obesity-related insulin resistance (126, 129). Additionally, *in vitro* and *in vivo* (135) studies have shown that TNF- $\alpha$  can impair insulin signaling and lead to derangements in insulin-mediated glucose uptake and storage. *In vivo* data also show that TNF- $\alpha$  inhibition can improve insulin sensitivity. Finally, insulin-sensitizing thiazolidinediones appear to decrease TNF- $\alpha$  release and antagonize TNF- $\alpha$ -induced inhibition of insulin signaling (53). In addition to TNF- $\alpha$ , IL-6 is another cytokine that has been implicated in the pathogenesis of insulin resistance and Type 2 diabetes mellitus. High levels of IL-6 are found in patients with Type 2 diabetes mellitus (85), and higher levels correlate with insulin resistance and with an increased risk for Type 2 diabetes mellitus (29, 45, 89). However, the role of IL-6 in disorders of glucose metabolism remains controversial. Experimental data from knockout animal models suggest that IL-6 may actually improve glucose tolerance (132). Thus, despite the increasing acceptance that glucose intolerance, insulin resistance, and Type 2 diabetes mellitus are mediated, in part, by an inflammatory response, further basic and clinical research is clearly still required to further clarify the role of these cytokines in altered glucose metabolism.

**Role of adipokines.** Our understanding of adipocyte biology has dramatically changed in the last decade. The adipocyte is influenced by afferent messages from several different sources, including the autonomic nervous system and the HPA axis. The adipocyte is also a source of several efferent messages, including leptin, TNF- $\alpha$ , IL-6, adiponectin, and resistin. Leptin is an adipocyte-derived cytokine that regulates satiety and food intake via the HPA axis. In addition to central effects in the hypothalamus, leptin has a wide range of peripheral effects on the physiological processes that regulate glucose homeostasis (13). *In vitro* data indicate that leptin downregulates insulin gene transcription and insulin secretion by pancreatic islets (63, 103–105). Leptin also improves insulin sensitivity of peripheral tissues, acting both centrally via the melaninocortin system in the brain (82) and peripherally via insulin signaling pathways (7). Leptin-induced suppression of insulin secretion and improvement in insulin sensitivity account for the hyperinsulinemia and insulin resistance reported in leptin-deficient *ob/ob* mice. In the clinical setting, however, the role of leptin is more complicated than in leptin-deficient mice because the vast majority of obese humans have elevated leptin levels. This has led to the concept that there is a link between insulin resistance and leptin resistance in obese individuals (13). Although serum leptin is primarily determined by the degree of adiposity, recent evidence suggests that it can be increased in response to hypoxia. Normal subjects when exposed to altitude

hypoxia manifest increased levels of plasma leptin (125). C57BL/6J mice exposed to intermittent hypoxia also exhibit increases in leptin gene expression and serum protein levels (86). Furthermore, *in vitro* studies performed with rat adipocytes (44) and trophoblast-derived cell lines (39) show that hypoxia can increase leptin gene expression, an effect that is due to HIF-1 (38). It has also been reported that patients with sleep apnea manifest higher leptin levels that decrease with CPAP therapy (15, 58, 99, 106).

Besides leptin, other hormones produced by adipose tissue may affect insulin resistance in patients with sleep apnea. It has been shown that serum adiponectin levels inversely correlate with obesity and insulin resistance (124). Evidence for the role of adiponectin in metabolic consequences of sleep apnea remains controversial, with some investigators describing a decrease (52, 139) but others reporting an increase in this hormone (134). The role of resistin, an adipokine conferring insulin resistance, has not been adequately studied in sleep apnea (49).

#### FUTURE DIRECTIONS

Although the cause-and-effect sequence is uncertain, it is likely that sleep apnea is a precursor of adverse metabolic outcomes. Clearly, there is a relative paucity of data to draw definitive conclusions regarding causation. An added difficulty in interpreting the available data is that central obesity, a cardinal feature of sleep apnea and disorders of glucose metabolism, has not been adequately considered. Here, part of the uncertainty is due to the fact that most studies on sleep apnea and glucose metabolism have used anthropometric measures such as waist circumference or waist-to-hip ratio to account for the effects of body fat distribution. Although waist circumference and waist-to-hip ratio are widely used as indexes of regional fat distribution in epidemiologic field studies, these indexes cannot distinguish between the amount of intra-abdominal (i.e., visceral fat) and subcutaneous abdominal fat. Techniques, including computerized tomography and magnetic resonance imaging, can differentiate fat from other tissues and quantify the amount of visceral and subcutaneous abdominal fat. Numerous studies have shown that the detrimental influence of central obesity on metabolic processes can be attributed to the visceral fat depot (131). Deposition of fat within the abdomen confers greater risk of metabolic and cardiovascular consequences than fat accumulation elsewhere (64, 79). Excess visceral fat has been associated with higher glucose and insulin levels, insulin resistance, dyslipidemia, and hypertension (22, 23, 35, 72, 84, 87). The adverse effects of visceral fat on glucose metabolism are independent of total body and subcutaneous abdominal fat, and no association is noted between glucose tolerance and these variables after adjustments for the amount of visceral fat (23, 87). Thus future studies must carefully consider the potential effects of central obesity in assessing the relationship between sleep apnea and glucose metabolism. Although sleep-related pathology is likely to be an important risk factor for metabolic and cardiovascular consequences, several other questions remain unanswered. For example, what are the intermediate mechanisms relating abnormalities in sleep and glucose metabolism? To that end, what is the relative contribution of intermittent hypoxemia and sleep fragmentation in altering metabolic function? What are the key

intermediates that define the physiological cascade from intermittent hypoxemia and recurrent arousals to fasting hyperglycemia, insulin resistance, and Type 2 diabetes mellitus? Does the common habit of curtailing sleep in the current 24/7 society further compound the metabolic abnormalities attributed to sleep apnea? Can CPAP completely mitigate the effects of sleep apnea on glucose metabolism, or is there a component of irreversibility? What impact, if any, do alterations in glucose metabolism in sleep apnea have on vascular risk? There is no doubt that research on such questions will likely yield new challenges and findings that will one day perhaps prove that the English playwright Thomas Dekker was correct in his statement that "sleep is that golden chain that ties health and our bodies together."

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