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Sleep Apnea and Metabolic Dysfunction: Cause or Co-Relation?

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Introduction

Obesity is a global epidemic with far reaching economic and public health implications (1;2). The increasing prevalence of excess weight is a widespread phenomenon that has affected children and adults of all ages and ethnic backgrounds. Although the prevalence of obesity was relatively stable in the U.S. from 1960 through 1980 (3), the shift in average body mass index (BMI) in American adults occurred well before 1960 (4). Findings from 1999–2000 National Health and Nutrition Examination Survey indicate that approximately 34% of adults in the U.S. are overweight and an additional 31% are obese (1). Excess body weight is a risk factor for hypertension, cardiovascular disease, stroke, dyslipidemia, type 2 diabetes mellitus, sleep apnea, osteoarthritis, and depression (5-7). The economic consequences of obesity are overwhelming, costing the United States upwards of \$78.5 billion in 1998 and \$92.6 billion in 2002 (8).

Type 2 diabetes mellitus has also become an epidemic that has grown in tandem with obesity. Approximately 20.8 million people in the U.S. (~7.0 % of the general population) have type 2 diabetes and over six million of those with the disease remain undiagnosed (9). The International Diabetes Federation estimates that the number of adults with type 2 diabetes worldwide will increase by 122% from 135 million in 1995 to 300 million in 2025 (10;11). Established risk factors for type 2 diabetes include an increase in body fat with a predominance of visceral adiposity (12). In addition, genetic susceptibility, sedentary lifestyle, and a shift towards a high energy diet also contribute to the risk of type 2 diabetes (13;14). In recent years, there is growing recognition that disorders of sleep may also increase the propensity for insulin resistance, glucose intolerance, and overt diabetes (15). Evidence from several observational and experimental studies suggests that habitually shortened sleep duration and disturbances of sleep imposed by conditions such as sleep apnea may confer additional risk for metabolic dysfunction. In fact, the past few years have witnessed an enormous growth in the scale of scientific activity devoted to assessing the possible link between sleep apnea and disorders of glucose metabolism. The explosion in research and clinical interest has been driven by the demonstration that short sleep duration can lead to glucose intolerance and insulin resistance (16). Subsequently a number of studies have provided strong support for an independent association between disorders such as sleep apnea, chronic sleep loss, and insomnia with metabolic dysfunction. The purpose of the current review is to summarize the body of literature implicating sleep apnea as an independent risk factor for abnormalities in glucose metabolism

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and discuss the possible physiological role of sleep fragmentation and intermittent hypoxemia as putative intermediates. A critical question that will be addressed within this context is whether there is sufficient evidence implicating sleep apnea as an etiologic factor in altering glucose homeostasis. Finally, the possibility of reverse causation (i.e., type 2 diabetes leading to sleep apnea) will also be reviewed. Prior to embarking on the research advancements associating sleep apnea and glucose metabolism, a brief summary of the terminology used to describe metabolic and sleep-related abnormalities is presented.

Disease Definitions and Diagnosis

The American Diabetes Association defines diabetes mellitus as a group of conditions that are characterized by hyperglycemia resulting either from defects in insulin secretion, insulin action, or both (17). Four distinct categories of diabetes have been proposed. Type 1 diabetes mellitus, which accounts for approximately 5% of all cases, results from cell-mediated autoimmune destruction of the pancreatic β -cells. Although patients with type 1 diabetes are generally not obese at presentation, obesity is not incompatible with the diagnosis. Type 2 diabetes mellitus, which accounts for approximately 90% of all diabetes cases, results from a deficit of both insulin sensitivity and insulin secretion. Most patients with type 2 diabetes are obese with many often going undiagnosed for several years. The third category of diabetes encompasses a repertoire of disorders that include genetic defects of the pancreatic β -cell or of insulin action, endocrinopathies, drug or chemical-induced pancreatic injury, infections, and other uncommon forms of immune-mediated diabetes. Finally, the fourth category of gestational diabetes mellitus is defined as any degree of glucose intolerance that develops during pregnancy. The diagnostic criteria (17) for diabetes are as follows: (a) symptoms of polyuria, polydipsia, or unexplained weight loss and a random glucose level ≥ 200 mg/dl; or (b) fasting glucose level ≥ 126 mg/dl; or (c) a 2-hour post challenge glucose level ≥ 200 during an oral glucose tolerance test (OGTT). In addition, two pre-diabetic conditions of clinical relevance include impaired fasting glucose and impaired glucose tolerance. Impaired fasting glucose is defined as a fasting glucose level between 100 mg/dl and 126 mg/dl. Impaired glucose tolerance is defined as a 2-hour post-challenge glucose level between 140 mg/dl and 200 mg/dl during the OGTT.

The term 'sleep apnea' encompasses sleep-related breathing abnormalities that are characterized by the occurrence of recurrent apneas (complete cessation of airflow) and/or hypopneas (decrease in airflow). Included in the rubric of 'sleep apnea' are the syndromes of obstructive and central sleep apnea. Although these two types of disordered breathing patterns can co-occur, the obstructive form is by far the most common. For the purpose of this review, the term 'sleep apnea' will be used to refer to obstructive sleep apnea which is the more prevalent of the two disorders. While the exact pathogenesis of obstructive sleep apnea remains elusive, repetitive upper airway collapse due to a decrease in pharyngeal muscle tone during sleep is considered a principal feature. In contrast, central sleep apnea is characterized by a decrease in ventilatory effort in the setting of a patent upper airway. Irrespective of the type of event, the number of apneas and hypopneas per hour of sleep or the apnea-hypopnea index (AHI) is used as a disease-defining metric for central and obstructive sleep apnea. In the following sections, the topic of whether obstructive sleep apnea is associated with abnormalities of glucose metabolism is reviewed with a particular emphasis on whether the association is independent factors such as obesity.

Sleep Apnea as a Risk Factor for Altered Glucose Metabolism

Considerable progress has been made in our understanding of the pathogenesis of type 2 diabetes (13;14). Although the focus of this review does not permit an extensive discussion of the complex relationships between insulin resistance and the clinical syndromes of glucose

intolerance and type 2 diabetes, it is important to briefly outline the natural history of type 2 diabetes. It has now well recognized that development of hyperglycemia and diabetes is a multi-step process along a continuum that is influenced substantially by genetic and environmental factors. The natural history of type 2 diabetes is characterized at the outset by normal glucose tolerance followed initially by insulin resistance and compensatory hyperinsulinemia. With ongoing and persistent insulin resistance, glucose intolerance eventually develops and finally culminates in the clinical expression of type 2 diabetes and its associated complications. Although there has been much controversy for many years, the body of available data indicates that insulin resistance and pancreatic β -cell dysfunction are both present early in the course that terminates with the development of frank diabetes.

Given that insulin resistance, even in the absence of diabetes, is a risk factor for cardiovascular disease (18-21), there is scientific and clinical merit in understanding whether sleep apnea has a role in the development of glucose intolerance and insulin resistance. Reports from several clinical and non-clinical samples suggesting a possible link between sleep apnea and altered glucose metabolism started appearing in the early 1990s. A comprehensive analysis of the literature conducted in 2003 (22) summarized the available evidence based on the type of approach used to delineate the association. Several investigators have examined metabolic function in relation to (a) sleep apnea-related symptoms; (b) polysomnographically defined sleep apnea; and (c) effects of continuous positive airway pressure (CPAP) therapy. Based on the 2003 systematic review, it is readily evident that some of the initial studies suffered from methodological limitations including relatively small sample sizes, use of highly select clinic-based samples, and inadequate adjustment for confounding covariates such as obesity. Fortunately, studies within the first category (23-30) avoided many such pitfalls by including large samples of community-based cohorts and accounting for the possible effects of several confounding covariates. Moreover, some have also provided longitudinal data further strengthening the notion that sleep apnea may play causative role in altering glucose metabolism. However, the use of surrogate measures (e.g., snoring, witnessed apneas, or excessive sleepiness) to assess the presence of sleep apnea in these studies represents a major weakness as it provides little insight into the putative mechanisms responsible for the observed association.

Studies that have used polysomnography to characterize breathing abnormalities during sleep have by and large found an independent correlation between sleep apnea and alterations in glucose metabolism (31-43). Measures of sleep apnea severity such as the AHI, severity of nocturnal oxyhemoglobin desaturation, and degree of sleep fragmentation have been associated with a repertoire of metabolic parameters including fasting insulin and glucose levels, results of the oral glucose tolerance test, and the glucose clamp. Careful consideration for factors such as BMI and waist circumference in these studies supports the hypothesis that sleep apnea may be independent risk factor of metabolic dysfunction. Nevertheless, statistical adjustments for BMI and waist circumference even in the analyses of large datasets such as the Sleep Heart Health Study data (42) are insufficient to circumvent residual confounding due to visceral fat mass. Central obesity and visceral fat accumulation are associated with insulin resistance and diabetes more than the degree of overall obesity (44-50). Thus, accounting for the effects of visceral fat in the association between sleep apnea and glucose metabolism is essential and remains relatively unexplored (34;43). Studies in the pediatric populations, where there is less confounding secondary to medical comorbidities, have provided conflicting results. Data from these studies suggest that obesity rather than sleep apnea is the primary correlate of metabolic dysfunction (40;51;52).

Additional ways for identifying a causal association consist of examining whether CPAP therapy by mitigating sleep apnea favorably affects metabolic outcomes and/or investigating longitudinal changes in glucose metabolism in those with and without sleep apnea. Although

a number of studies conducted over the last decade failed to demonstrate consistent improvements with CPAP therapy (35;53-60), recent observations in patients with sleep apnea and type 2 diabetes indicate that CPAP therapy can improve insulin sensitivity (61;62) and glycemic control (63), respectively. Indeed, such findings add to the accruing evidence that implicate a possible causal link between sleep apnea and altered glucose metabolism. Unfortunately, prospective data from the Wisconsin sleep cohort have not aligned with this tenet. In a recent report, Reichmuth et al. (64) have shown that while the severity of sleep apnea is associated with prevalent diabetes in the Wisconsin sleep cohort, it does not predict incident disease. Despite the limited number of incident cases over the follow period, the Wisconsin study highlights the previous concern that the cross-sectional association between sleep apnea and glucose metabolism could well be simply due to obesity. Clearly, further research on the metabolic implications of sleep apnea is warranted to reconcile these disparate findings.

Metabolic Effects of Intermittent Hypoxemia and Sleep Fragmentation

If empirical evidence eventually establishes that sleep apnea negatively impact glucose metabolism, what then are the intermediate mechanisms in the causal pathway? While many of the putative links are not well elucidated, it is likely that intermittent hypoxemia and sleep fragmentation, the primary concomitants of sleep apnea, play an etiologic role. Several animal and human studies have shown that both short and longer-term exposure to hypoxia can disrupt glucose homeostasis. Elevations in fasting insulin levels have been demonstrated after hypoxic exposure for seven days in newborn rats (65;66) and as little as two hours in newborn calves (67). Studies using murine models also indicate that obesity can modulate the effects of hypoxia on glucose metabolism. Exposure to intermittent hypoxia has been shown to increase fasting insulin levels in leptin deficient obese mice (C57BL/6J-Lep^{ob}) but not in the lean wild type mice (68). Experimental evidence from human studies, although limited, corroborates the detrimental effects of hypoxia on glucose metabolism. Conditions of altitude hypoxia can markedly decrease insulin action and sensitivity in both men and women (69;70). Moreover, experimental exposure of normal subjects to acute hypoxia for about 30-minutes can diminish insulin sensitivity (71).

In addition to the effects of hypoxia, apnea-related sleep fragmentation may also negatively affect glucose metabolism. While direct evidence on the metabolic effects of sleep disruption is not yet available, experimental sleep restriction in normal volunteers has been shown to worsen glucose tolerance (72). Moreover, cross-sectional data from the Sleep Heart Health Study has demonstrated an increased prevalence of impaired glucose tolerance and diabetes in subjects habitually reporting six hour or less of sleep per night (73). Thus, sleep duration may have an essential role in maintaining normal glucose metabolism. Whether sleep fragmentation due to apneas and hypopneas has similar untoward effects on glucose metabolism remains to be determined. Nonetheless, there are several biologically plausible mechanisms through which sleep fragmentation and intermittent hypoxemia may be involved in the pathogenesis of insulin resistance. These include (a) increase in sympathetic activity; (b) alterations in neuroendocrine function; and (c) release of proinflammatory cytokines (e.g., interleukin-6 [IL-6] and tumor necrosis factor- α [TNF- α]) and adipocyte derived factors (e.g., leptin, adiponectin, and resistin).

The Sympathetic Nervous System as a Causal Intermediate

A number of studies have unequivocally shown that sleep apnea is associated with an increase in sympathetic activity during sleep and wakefulness (74-77). Although hypoxemia is considered to be a major stimulus (75;78-82), arousal from sleep most likely intensifies the sympathetic activation accompanying each obstructive event (83-85). Interestingly, the increase in sympathetic neural traffic associated with sleep apnea persists into the waking period as evidenced by higher levels of plasma and urinary catecholamines (86-88). Finally,

and more importantly, is the consistent observation across several studies that sympathetic neural activity in sleep apnea decreases with appropriate treatment (89-94). The sympathetic nervous system has a central role in the regulation of glucose and fat metabolism (95). Sympathetic activation reduces insulin-mediated glucose uptake in muscle and thus diminish insulin sensitivity (96). Moreover, infusion of epinephrine in normal subjects inhibits insulin-mediated glycogenesis, enhances glycolysis, and decreases the ability of glucose to stimulate its own disposal (97;98). Studies using animal models have also shown that administration of β -agonists can alter muscle composition with a transition to a more insulin-resistant type II skeletal muscle fiber (99). Finally, sympathetic activity has well known lipolytic effects through signaling pathways that activate hormone-sensitive lipase, thus mobilizing nonesterified fatty acids (NEFA) through triglyceride hydrolysis (100). Within hours, an acute elevation in circulating NEFA levels can diminish insulin sensitivity in healthy subjects (101). Conversely, lowering NEFA levels with antilipolytic agents reduces insulin resistance, hyperinsulinemia, and improves glucose tolerance (102). At present, the state-of-the art on the effects of sleep apnea on circulating NEFA levels is limited with only one study showing an *increase* in NEFA concentration following a night of CPAP therapy (57). Obviously, there are significant gaps in our understanding of the intermediate mechanisms linking sleep apnea-related alterations in sympathetic activity to increases in NEFA levels and the resulting changes in glucose metabolism.

The Hypothalamic-Pituitary-Adrenal Dysfunction as a Causal Intermediate

Sleep apnea could also influence glucose metabolism by modulating the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, intermittent hypoxemia and sleep fragmentation may elicit a stress-related increase in HPA activity and lead to excessive cortisol secretion. As with several neuroendocrine axes, HPA activity exhibits a diurnal profile that is characterized by a progressive increase in circulating cortisol which starts shortly after sleep onset and reaches a maximum in the early morning. Experimental manipulation of sleep with recurrent arousals in normal subjects leads to pulsatile increases in serum cortisol (103). Moreover, sleep curtailment can elevate the circadian trough in the cortisol profile on the following day (104). Complementary data based on observations at high altitude also show that hypoxia modifies the diurnal pattern of cortisol secretion (105-111). Thus, there is ample biological basis to speculate that apnea-related intermittent hypoxemia and recurrent arousals may negatively impact HPA function. Despite the wealth of indirect evidence, conclusive data on HPA dysfunction in sleep apnea are lacking (112-117). A notable limitation in the available research is that HPA activity in most reports was assessed with a single measurement of serum cortisol. Isolated serum cortisol measurements while convenient cannot reveal temporal variations and/or changes in secretory activity that may occur at other times. Understanding the relationship between sleep apnea and HPA function is of paramount significance to better understand whether sleep apnea confers additional risk for glucose intolerance, insulin resistance, and type 2 diabetes. It is well established that cortisol and other glucocorticoids interfere with glucose metabolism at several different levels. Cortisol can inhibit β -cell secretion of insulin and induce insulin resistance by sequentially modifying multiple aspects of the insulin-mediated glucose transport system (118-122). Thus, future research efforts are desperately needed to address whether abnormalities in the amplitude or phase of the cortisol rhythm can explicate the higher prevalence of impaired glucose metabolism in sleep apnea.

Systemic Inflammation and the Adipocyte-derived Factors as Causal Intermediates

In recent years, the question of whether sleep apnea promotes systemic inflammation and thus increases the propensity for cardiovascular and metabolic abnormalities has been the focus of significant research. Several investigators have demonstrated abnormalities in several inflammatory markers in sleep apnea. Compared to normal subjects, sleep apnea patients have higher levels of circulating adhesion molecules (123-129) and inflammatory cytokines

including IL-6 and TNF- α which decrease with effective CPAP therapy (34;112;130-135). In addition, studies examining specific leukocyte populations reveal that patients with sleep apnea also exhibit monocyte and lymphocyte activation which improves with CPAP therapy (136-139). While the mechanisms through which sleep apnea disrupts normal immune function are poorly understood, intermittent hypoxemia is likely to play a leading role. Experimental studies in normal subjects have shown that hypoxia can modulate an array of immune related functions including increase in leukocyte concentration and alterations in the functional characteristics of circulating lymphocytes (140-142). Furthermore, there is ample evidence favoring a direct effect of increased sympathetic activity and circulating catecholamines on the regulation of the innate immune response. Adrenergic receptors expressed on macrophages and lymphocytes can influence their activity and alter proliferation, circulation, and cytokine production. (143;144). Another possibility that should be considered is that perhaps sleep fragmentation can also affect immune response. Of relevance to the latter notion are the findings that experimental total or partial sleep loss in healthy subjects can increase CRP levels (145). However, data on the effects of sleep fragmentation on inflammatory parameters are nonexistent.

Systemic inflammation is being increasingly recognized as a fundamental component in the pathogenesis of insulin resistance and type 2 diabetes. Animal studies have shown TNF- α to be an important intermediate in the development of insulin resistance. Both *in vivo* and *in vitro* studies have demonstrated that TNF- α can impair insulin signaling causing disruption of glucose homeostasis (146-150). While high levels of IL-6 and CRP have been found to predict the development of type 2 diabetes (151;152), there are some data suggesting that acute administration of IL-6 to healthy subjects does not diminish glucose disposal or muscle glucose uptake (153;154). Although such discrepancies could be attributed to the duration of exposure to IL-6 in studies of normal subjects, the role of IL-6 in modulating insulin sensitivity remains controversial (155). A major challenge in invoking systemic inflammation as an intermediate between sleep apnea and metabolic dysfunction is the confounding effects of obesity. There is general agreement that adipose tissue can increase systemic inflammation, with visceral adiposity having an enhanced capacity to produce specific cytokines of interest (e.g., IL-6 and TNF- α). However, it appears that even after considering the effects of body mass and regional adiposity, indices of SDB and correlate with the degree of inflammatory burden (156).

Even if systemic inflammation in patients with sleep apnea is solely due to the effects of obesity, glucose dysmetabolism in these patients could also be ascribed to the apnea-related effects on adipocyte-derived factors including leptin, adiponectin, and resistin. Leptin regulates hunger and weight gain by increasing anorexigenic and decreasing orexigenic neuropeptide expression in the hypothalamus (157). Peripherally, leptin appears to be involved in governing glucose homeostasis but studies concerning the direct effects of leptin on insulin sensitivity have yielded conflicting results (158;159). A growing body of literature shows that patients with sleep apnea have higher leptin levels (34;39;58;160-169) which decrease with CPAP treatment (59;170;171). Whether higher levels of leptin in sleep apnea patients adversely affect glucose metabolism remains to be determined.

Adiponectin is also synthesized by the adipocyte and has been shown to have endogenous insulin-sensitizing properties. Animal models lacking adiponectin develop insulin resistance (172;173) and a high adiponectin level in humans has been shown to protect against type 2 diabetes (174). Given that alterations in adiponectin levels appear to influence glucose regulation, there is inherent value in assessing whether sleep apnea is associated with altered adiponectin levels. While some groups have not found an association between sleep apnea and adiponectin levels (43;169;175;176), others have shown lower adiponectin levels in patients with sleep apnea (177-179) and have correlated it with nadir oxygen saturation (179). Resistin is the third adipocytokine of recent interest in sleep apnea. Initially, thought to impair glucose

tolerance and insulin sensitivity (180-182), recent studies have not been able to correlate resistin measures of insulin resistance (183-185). At present, there is only one available study on resistin levels in sleep apnea which failed to document any change in serum resistin with two months of CPAP therapy (186). Given the number of uncertainties regarding the impact of sleep apnea role on adipocyte-derived factors and their potential role in glucose metabolism, further work is needed to determine how these proteins influence insulin signaling, if at all, in tissues such as liver and muscle.

Diabetes as a Risk Factor for Sleep Apnea

Although much of the foregoing discussion has focused on the possibility of sleep apnea as a risk factor for metabolic abnormalities, the possibility of reverse causation (i.e., metabolic abnormalities such as diabetes leading to sleep apnea) cannot be completely excluded. Indeed, a series of clinic-based studies have shown that diabetic patients are more likely to have obstructive and central sleep apnea (187-193). A remarkable feature across these studies was the observation that coexisting autonomic neuropathy substantially increases the prevalence of sleep apnea in these patients. However, numerous methodological limitations that often accompany pioneering work prohibit inferences regarding cause and effect and greatly limit the generalizability of the available data. Recently, investigators from the Sleep Heart Health Study showed that even after adjusting for confounders such as obesity and prevalent cardiovascular disease, those with longstanding diabetes in the general community are more likely to show evidence of periodic breathing during sleep (194). Surprisingly, no differences were observed between diabetic and nondiabetic subjects in the frequency of obstructive events. Mechanisms underlying the high prevalence of central sleep apnea in diabetes are not well understood. Animal models with chemically induced diabetes suggest that abnormal ventilatory responses to hypoxia and/or hypercapnia may be partially responsible (195;196). Studies in diabetic patients also show that abnormalities in O₂ and CO₂ sensitivity may have an important role in increasing respiratory control instability during sleep (197-201). Whether diabetes also contributes to mechanical alterations in the upper airway and thus increasing upper airway collapsibility during sleep remains an open question.

Sleep Apnea as a Component of the Metabolic Syndrome

The focus of this review thus far has been of a possible bi-directional association between sleep apnea and metabolic abnormalities. An alternate, but not mutually exclusive, view of the available data is that sleep apnea is yet another component of the metabolic syndrome. The World Health Organization defines the metabolic syndrome as the presence of hyperglycemia and/or insulin resistance in association with two or more related metabolic abnormalities (i.e., elevated blood pressure, dyslipidemia, central obesity, or microalbuminemia) (202). Proponents of this perspective argue that common genetic determinants may give rise to pleiotropic effects which include sleep apnea in addition to the aforementioned conditions including hypertension, central obesity, and dyslipidemia. Such clustering of sleep apnea with other components of the metabolic syndrome was first proposed by Wilcox et al. (203) and more recently reiterated by others (204-207). Even if a common predisposition for and clustering of these conditions is identified, it does not preclude the possibility of causal associations between the individual components of the metabolic syndrome. Substantiating the possibility of this idea is the bidirectional link between obesity and insulin resistance. It is well established that weight gain leads to insulin resistance which increases the propensity for further weight gain (208-214). Similar feed forward interactions may also exist between sleep apnea and the other components of metabolic syndrome. The clustering of individual components of the metabolic syndrome has important clinical and public health implications as the morbidity and possibly mortality associated with a collection of components may be multiplicative, and, therefore have more significant cardiovascular repercussions.

Future Research Agenda

In light of the evidence summarized, there is little doubt that the past decade has seen major advances in our understanding of the relationships between sleep apnea, glucose intolerance, insulin resistance, and type 2 diabetes. Despite these remarkable advancements, our enthusiasm to implicate causal links between sleep apnea and metabolic dysfunction has to be tempered by the fact that both conditions share common risk factors, such as obesity and increasing age. Thus, the challenge that clearly lies ahead is to collect unambiguous evidence that will either support or refute the hypothesis of a causal association. Only a concerted multi-disciplinary effort from the basic and clinical sciences will provide the foundation on which the deleterious effects of sleep apnea on metabolic function can be better delineated. Fortunately, the interest in the overlap of these conditions is in its infancy and a substantial number of studies have been undertaken to enhance our ability to answer the question of whether sleep apnea causes metabolic dysfunction.

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