

Obstructive Sleep Apnea as a Risk Factor for Type 2 Diabetes

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ABSTRACT

PURPOSE: Cross-sectional studies have documented the co-occurrence of obstructive sleep apnea (hereafter, sleep apnea) with glucose intolerance, insulin resistance, and type 2 diabetes mellitus (hereafter, diabetes). It has not been determined, however, whether sleep apnea is independently associated with the subsequent development of diabetes, accounting for established risk factors.

METHODS: This observational cohort study examined 1233 consecutive patients in the Veteran Affairs Connecticut Healthcare System referred for evaluation of sleep-disordered breathing; 544 study participants were free of preexisting diabetes and completed a full, attended, diagnostic polysomnogram. The study population was divided into quartiles based on severity of sleep apnea as measured by the apnea-hypopnea index. The main outcome was incident diabetes defined as fasting glucose level >126 mg/dL and a corresponding physician diagnosis. Compliance with positive airway pressure therapy, and its impact on the main outcome, also was examined.

RESULTS: In unadjusted analysis, increasing severity of sleep apnea was associated with an increased risk of diabetes (P for linear trend <.001). After adjusting for age, sex, race, baseline fasting blood glucose, body mass index, and weight change, an independent association was found between sleep apnea and incident diabetes (hazard ratio per quartile 1.43; confidence interval 1.10-1.86). Among patients with more severe sleep apnea (upper 2 quartiles of severity), 60% had evidence of regular positive airway pressure use, and this treatment was associated with an attenuation of the risk of diabetes (log-rank test $P = .04$).

CONCLUSION: Sleep apnea increases the risk of developing diabetes, independent of other risk factors. Among patients with more severe sleep apnea, regular positive airway pressure use may attenuate this risk. Published by Elsevier Inc. • *The American Journal of Medicine* (2009) 122, 1122-1127

KEYWORDS: Sleep apnea syndrome; Type 2 diabetes mellitus

The prevalence of type 2 diabetes continues to increase in the US, and currently affects an estimated 18 million people.¹ Although lifestyle changes such as weight loss and

physical activity are the cornerstone of diabetes prevention, efforts are needed to better understand other disease determinants and to develop additional strategies for prevention. Understanding the link between obstructive sleep apnea and diabetes might represent one such effort.

Obstructive sleep apnea (hereafter, sleep apnea) is a common and treatable form of sleep-disordered breathing, involving upper airway collapse during sleep. This collapse results in a cycle of physiologic events that occur repeatedly throughout the night, including intermittent hypoxemia and arousal from sleep. Sleep apnea is present in 9%-24% of the middle-aged adult population² and has been associated with increased rates of hypertension, atherosclerosis, cardiovascular morbidity and mortality (including stroke), and all-cause mortality.³⁻⁷

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Recent short-term studies have demonstrated striking alterations in metabolic function, including glucose intolerance and insulin resistance, associated with short-term sleep restriction^{8,9} and sleep apnea.^{8,10-15} These findings raise the question of whether sleep apnea may have a role in development of overt clinical diabetes. The current study evaluated longitudinally whether sleep apnea is an independent risk factor for diabetes. In addition, we explored whether positive airway pressure, as the main medical therapy for sleep apnea, had an impact on this risk.

METHODS

Study Design and Patient Population

This observational cohort study examined nondiabetic patients referred to the Veterans Affairs (VA) Connecticut Sleep Center from January 2000 to December 2005. Eligible participants include patients referred for initial evaluation of sleep-disordered breathing who had at least 2 hours of sleep monitoring and a fasting glucose level <126 mg/dL. Participants were excluded if the entire polysomnographic study was performed with airway pressurization for therapeutic purposes. The study was approved by the institutional review board at the VA Connecticut Healthcare System.

Baseline Assessment

Data on demographics, sleep, and medical history, and medication use/habits were extracted from each patient's medical record. Hypertension occurred if the average blood pressure was ≥ 140 mm Hg (systolic) or ≥ 90 mm Hg (diastolic) from 3 office visits before polysomnography or if patients had a history of hypertension. Hyperlipidemia was based on history or an appropriate drug prescription. Baseline fasting blood glucose values (with all patients routinely tested) were obtained within 3 months of initial polysomnogram. Each patient's body mass index (BMI) was calculated at the time of polysomnogram and at follow-up. The Epworth Sleepiness Scale, a measure of sleepiness,¹⁶ also was recorded.

Polysomnography

At baseline, participants underwent a full, attended, overnight polysomnography, with the use of Grass data-acquisition systems (Astro-Med®, Astro-Med Inc., West Warwick, RI). Recordings were manually scored according to standard criteria.¹⁷⁻¹⁹ Calculated variables included the arousal index (number of arousals/hour of sleep), minimum arterial oxygen

saturation, mean arterial oxygen saturation, T90% (percentage of total sleep time with oxygen saturation <90%), and the apnea-hypopnea index (the sum of apneas and hypopneas/hour of sleep). The study population was divided into quartiles based on severity of sleep apnea as measured by the apnea-hypopnea index.

CLINICAL SIGNIFICANCE

- Obstructive sleep apnea might represent an under-recognized independent risk factor for the development of diabetes.
- Increased severity of obstructive sleep apnea is associated with an increased risk of diabetes, and the risk might be partially explained by hypoxemia and arousals.
- Treatment with continuous positive airway pressure can add a potential therapeutic option, to diet and exercise alone, to attenuate the risk of diabetes in patients with obstructive sleep apnea.

Outcomes

The primary outcome was the development of diabetes, measured from the interval of the initial polysomnogram to the date of first office visit in which the diagnosis of diabetes occurred. Diabetes was defined by a physician diagnosis during routine office visit and fasting blood glucose >126 mg/dL²⁰ (using Hexokinase/G-6-PDH methodology through the Architect/Aeroset system; Abbott Laboratories, Ill). A physician investigator, unaware of patients' sleep apnea status, reviewed electronic medical records to ascertain incident diabetes. Censoring occurred at end of follow-up (last office visit before July 31, 2006) or the time of death (if death occurred).

Positive Airway Pressure Treatment Compliance

This VA study population received treatment according to consensus guidelines,²¹ and appliance and supplies were ordered by the institution and issued through a single respiratory home care company. Importantly, the orders for these services are documented in the electronic medical record. In addition, patients are followed closely for assessment of efficacy and treatment compliance through established sleep medicine and pulmonary clinics where positive airway pressure use is documented. Two physician-investigators, blinded to outcome status, categorized each patient's airway pressurization treatment use in categories of: not ordered; no use; intermittent use; and continuous or "regular" use of positive airway pressure. For the purposes of these analyses, airway pressurization compliance was dichotomized into "regular use" or not.

Statistical Analysis

Student's *t* test was used to compare mean values at baseline between subjects in the first quartile (comparison group) with the upper 3 quartiles (sleep apnea group). Categorical data were compared using the chi-squared test. A nonparametric comparison of medians was done with the Wilcoxon-Mann-Whitney test.

Kaplan-Meier analysis was used to compare event-free survival among patients with and without sleep apnea. An analysis using the chi-squared test for linear trend was done

Table 1 Baseline Characteristics of Patients in Quartiles* of Apnea-hypopnea Index

Characteristics	Quartile #1 (n = 142)	Quartile #2 (n = 136)	Quartile #3 (n = 132)	Quartile #4 (n = 134)	Quartiles #2-4 (n = 402)	P Value†
Mean age (years)	57.6	62.3	65.0	61.2	62.9	<.001
Male sex (%)	85.2	94.9	96.2	97.8	96.3	<.001
White race (%)	76.8	83.8	78.8	76.9	79.9	.45
Hypertension (%)	53.5	66.9	66.7	73.1	68.9	.001
Beta-blocker use (%)	20.4	33.1	37.1	33.6	34.6	<.001
Hyperlipidemia (%)	42.3	42.7	45.5	35.8	41.3	.43
Current alcohol consumption (%)	18.3	16.9	21.2	29.1	22.4	.31
Baseline fasting glucose	95.3	97.8	99.7	100.6	99.4	.05
Obesity (%)	48.6	58.8	67.4	84.3	70.2	<.001
Body mass index (BMI)	31.1	32.2	33.9	36.0	34.0	<.001
Change in BMI	-0.21	-0.21	-0.40	-0.80	-0.47	.07
Epworth Sleepiness Scale	7.9	7.7	8.5	8.1	8.1	.75
Apnea-hypopnea index (AHI)	2.9	13.7	32.6	78.2	41.5	<.001
Arousal index	22.4	29.9	45.4	82.4	50.5	<.001
Median T90%	0.4	2.0	5.0	12.0	5.0	<.001

*Quartile #1, AHI <8 (reference group); quartile #2, 8 ≤ AHI <20; quartile #3, 21 ≤ AHI <45; quartile #4, AHI ≥46.

†P value for comparison of quartile #1 vs quartiles #2-4.

to analyze whether increased severity of sleep apnea was associated with an increased risk of developing diabetes.

Subsequently, using proportional-hazards analysis, hazard ratios and 95% confidence intervals (CI) were generated for the unadjusted association between sleep apnea and incident diabetes. Adjusted hazard ratios were then calculated to account for the confounding effects of other baseline characteristics, including, age, sex, race, BMI, change in BMI (over the follow-up period), and baseline fasting glucose.

To examine the impact of positive airway pressure appliance use on diabetes, compliance (defined as percentage of patients with regular appliance use) was first examined by quartile of sleep apnea severity. Anticipating that regular use would be significantly higher among those with more severe sleep apnea, a prespecified subgroup analysis sought to investigate the impact of regular positive airway pressure use on incident diabetes among the upper 2 quartiles of severity (quartiles 3 and 4). This association was examined first using Kaplan-Meier analysis, and subsequently in multivariable analysis using Cox proportional hazards analysis.

Based on an available sample size of 544 participants, 90% power existed to detect a hazard ratio (HR) of 1.38 for 2-sided alpha at the 0.05 level²² for the primary outcome of diabetes. All statistical tests were performed with the use of SAS software (SAS Institute Inc., Cary, NC), with the exception of the Kaplan-Meier curves, for which S-Plus software (TIBCO; Palo Alto, Calif) was used.

RESULTS

Between January 2000 and July 2005, 1233 consecutive patients were referred to the VA Connecticut Sleep Center; 407 (33%) patients were ineligible because they were referred for conditions other than sleep-disordered breathing, or they had no initial diagnostic study. An additional 233

(19%) patients were ineligible because they had previously diagnosed diabetes, and 49 (4%) patients were excluded because they had incomplete polysomnographic data. Data for the remaining 544 patients were included in the study.

Table 1 shows the baseline characteristics of participants according to quartile of severity of the apnea-hypopnea index. The mean apnea-hypopnea index in the sleep apnea group was 41.5, compared with 2.9 in the comparison group. The baseline fasting blood glucose values were higher in the sleep apnea group compared with the comparison group (99.4 mg/dL vs. 95.3 mg/dL, respectively; $P = .05$). As expected, the prevalence of obesity (defined as BMI >30) was higher in the sleep apnea group, as was the prevalence of hypertension. The sleep apnea group also was older, with a mean age of 62.9 years vs 57.6 years, respectively. Obstructive apneas were the predominant apneic event; central apneas were rare.

Follow-up after the index sleep study took place between January 1, 2005 and July 31, 2006. Patients in groups with or without sleep apnea had a mean duration of follow-up of 2.7 years from baseline. Incident diabetes occurred in 61 patients, with 55 events occurring in the sleep apnea group compared with 6 events in the comparison group (5.5 vs 1.8 events per 100 person-years, respectively). Figure 1 shows the Kaplan-Meier (unadjusted) estimates of time to the endpoint of diabetes; the probability of developing diabetes was significantly higher for the sleep apnea group than for the comparison group (log-rank test, $P = .003$).

An initial analysis of linear trend revealed an increased risk of incident diabetes as a function of an increased severity of sleep apnea ($P < .001$; data not shown). In unadjusted analysis (Table 2), a significant association was found between sleep apnea (categorized by quartiles with increasing severity) and incident diabetes (HR per quartile 1.53; 95% CI, 1.21-1.94;

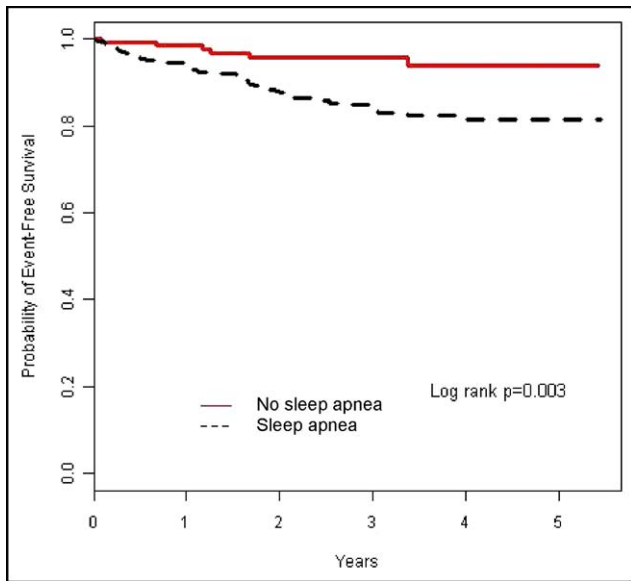


Figure 1 Kaplan-Meier curves for the association of sleep apnea and diabetes. Sleep apnea is defined as apnea-hypopnea index ≥ 8 .

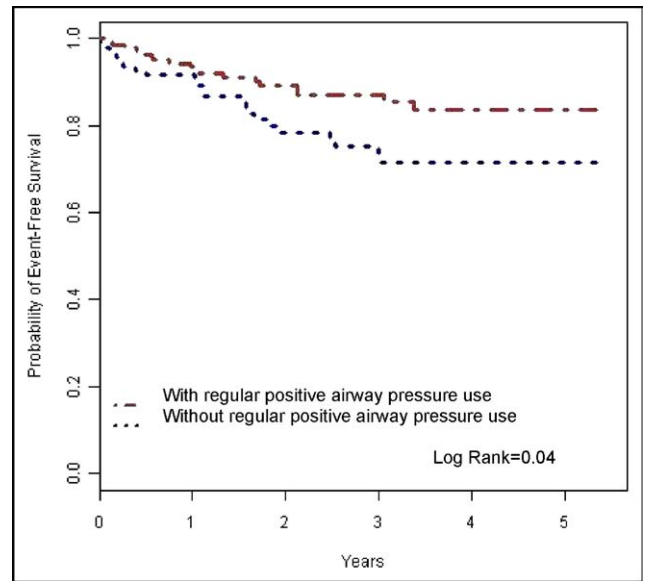


Figure 2 Kaplan-Meier curves examining the impact of regular continuous positive airway pressure on the risk of incident diabetes among patients in the upper 2 quartiles of apnea-hypopnea index severity (quartiles 3 and 4).

$P \leq .001$). In particular, the unadjusted risk of incident diabetes for subjects in the fourth quartile of severity was more than 4 1/2 times that in the comparison group (HR 4.67; 95% CI, 1.92-11.34; $P = .0007$).

After adjusting for age, sex, race, baseline fasting blood glucose, BMI, and change in BMI, sleep apnea retained a statistically significant association with diabetes (adjusted HR per quartile 1.43; 95% CI, 1.10-1.86; $P = .008$) (Table 2). The association of both fasting blood glucose and change in BMI with incident diabetes persisted after adjustment. In a secondary, explanatory analysis, both T90 (as measures of hypoxia) and arousal index also had statistically significant hazard ratios for their association with diabetes; data not shown.

Regular use of positive airway pressure was observed in 28% of patients in the second quartile, and no significant impact of this use was observed. Regular use increased to 58% and 62% in the third and fourth quartiles, respectively, and Figure 2 shows the Kaplan-Meier estimates of the time to incident diabetes in this subgroup. The probability of incident diabetes was attenuated for those with regular pos-

itive airway pressure use compared with those without (log-rank test, $P = .04$). In adjusted analyses among these same participants, regular use of positive airway pressure was independently associated with a significantly attenuated risk of incident diabetes (HR 0.53; 95% CI, 0.28-0.99; $P = .04$), even after adjusting for baseline fasting blood glucose, BMI, and change in BMI at follow-up.

DISCUSSION

We conducted an observational cohort study examining the impact of sleep apnea on the development of type 2 diabetes mellitus. Our results show that sleep apnea is a risk factor for the development of diabetes; increasing severity of sleep apnea is associated with an increasing risk for the development of diabetes; and among patients with moderate to severe sleep apnea (upper 2 quartiles of severity), regular use of positive airway pressure is associated with an attenuated risk for the development of incident diabetes.

Table 2 Unadjusted and Adjusted Hazard Ratios for the Risk of Diabetes (n = 544)

Factor	Unadjusted Hazard Ratio (95% CI, P Value)	Adjusted Hazard Ratio (95% CI, P Value)
Age	0.99 (0.98-1.02; $P = .92$)	1.00 (0.97-1.02; $P = .71$)
Male sex	1.41 (0.44-4.51; $P = .56$)	0.43 (0.13-1.48; $P = .18$)
Non-Caucasian	1.35 (0.64-2.85; $P = .43$)	1.13 (0.56-2.30; $P = .73$)
Fasting glucose	1.04 (1.04-1.05; $P \leq .001$)	1.04 (1.03-1.05; $P \leq .001$)
BMI	1.06 (1.03-1.09; $P \leq .001$)	0.99 (0.96-1.03; $P = .72$)
Change in BMI	0.73 (0.69-0.78; $P \leq .001$)	0.76 (0.70-0.83; $P \leq .001$)
Sleep apnea	1.53 (1.21-1.94; $P \leq .001$)	1.43 (1.10-1.86; $P = .008$)

CI = confidence interval; BMI = body mass index.

Our findings are consistent with previous cross-sectional data showing an association between sleep apnea and insulin resistance, glucose intolerance, and diabetes.^{8,11,13,14,23-25} The causal direction of these associations, however, has been questioned.²⁶⁻²⁸ The few studies assessing longitudinal associations between sleep apnea and diabetes have had limitations. For example, sleep apnea was associated with development of diabetes during a 10-year follow-up period, but sleep apnea was determined by a self-report of snoring as a surrogate for a confirmed diagnosis.^{29,30} In addition, a longitudinal analysis of the Wisconsin Cohort found an association between sleep apnea and diabetes, but the impact of sleep apnea was not statistically significant when adjusted for BMI.²⁴ Finally, a recent longitudinal analysis of the Busselton Health Study detected an association between moderate-severe sleep apnea and diabetes using portable monitoring, but the small sample size, limited distribution of sleep apnea severity, and few incident cases of diabetes resulted in a wide confidence interval.³¹ Our study is novel in that it used a longitudinal design that was powered to demonstrate an independent association between confirmed sleep apnea and diabetes, used the gold standard test for diagnosis, assessed a broad range of sleep apnea severity, and examined the impact of sleep apnea treatment.

Several potential mechanistic pathways might explain how sleep apnea and its physiologic sequelae (intermittent hypoxemia and recurrent arousals) ultimately lead to metabolic abnormalities. Previous studies found that severity of hypoxemia is related to the degree of glucose intolerance and insulin resistance.^{8,32,33} Although insulin levels were not available in the current study, hypoxemia (T90, defined as >2% of the night spent with an oxygen saturation <90%) was significantly associated with the outcome of diabetes (data not shown); intermittent hypoxemia may act through mechanisms of oxidative stress to mediate alterations in glucose metabolism.^{34,35} We also observed that the arousal index was associated with development of diabetes. Recurrent arousals (and sleep loss) may act through sympathetic activation and subsequent alterations in hypothalamic-pituitary-adrenal axis, leading to altered cortisol levels, decreased pancreatic beta-cell activity, elevated growth hormone levels, and alterations in neuroendocrine control of appetite.³⁵⁻³⁹

Our findings suggest an increased risk of diabetes among patients with sleep apnea, despite "usual care" administration of various therapies, primarily positive airway pressure. A few explanations might account for this finding. First, it is likely that our population had untreated sleep apnea for years before seeking diagnosis and treatment, resulting in prolonged exposure to an associated metabolic risk. Second, diabetes may develop even if patients receive effective therapy for sleep apnea. Finally, reduced compliance with positive airway pressure and limited efficacy of other treatments may have played a role in reducing the potential benefit of therapy.

We observed that regular use of positive airway pressure among patients in the upper 2 quartiles of severity was associated with a significant attenuation of incident diabetes, even after adjusting for subsequent weight loss. These findings are

consistent with several treatment studies that have demonstrated improvements in insulin sensitivity and postprandial glucose with airway pressurization therapy.⁴⁰⁻⁴² In contrast, other studies, including 2 short-term randomized controlled trials, have not shown a benefit.^{23,25} Future longitudinal and randomized studies examining the impact of treatment in various patient populations (eg, sleepy and nonsleepy patients) are needed.

Several methodologic issues should be considered in the interpretation of our results. First, as with any observational study, it is possible that residual confounding affected our adjusted hazard ratios, despite our attempts to control for major risk factors. For example, family history of diabetes could not be reliably ascertained through electronic medical record extraction and was not included in our analysis. In addition, BMI might not fully adjust for visceral obesity, known to be associated with components of the metabolic syndrome.^{43,44} Our comparison group also consisted of mainly obese males referred for suspected sleep apnea, however, thereby reducing the potential for residual confounding, given that similar risk factors were prominent in the comparison group. Change in BMI also was accounted for, to exclude the possibility that differential weight gain in one group may account for the difference in incident diabetes during the study.

Second, tracking of positive airway pressure treatment status was done through documentation in the electronic record, based on clinical assessment by treating physicians in conjunction with documentation of equipment and supply orders. Although the possibility of misclassification of treatment status exists (with a bias towards the null hypothesis), this scenario would not explain our observed findings of the attenuation of incident diabetes conferred by positive airway pressure use among our patients in the upper 2 quartiles of sleep apnea severity. In addition, our moderate long-term rates (~60%) of regular continuous positive airway pressure use are similar to those described using direct data card measures that track hours of use.⁴⁵

Third, treatment status in this observational cohort study was not randomly assigned. Patients who complied with positive airway pressure also might have been leading healthier lifestyles and complying with other therapies for the prevention of diabetes (eg, diet and exercise). Yet, this possibility would not explain the attenuation of incident diabetes among patients in the upper 2 quartiles of severity that was observed even after adjustment for weight loss.

Finally, the relatively low observed values for the Epworth Sleepiness Scale (mean <9; Table 1) might prompt questions about thresholds for initiating continuous positive airway pressure in the context of risk of future diabetes. Virtually all patients in our study were symptomatic, however, with episodes such as gasping during sleep, loud habitual snoring, or a bed-partner noting witnessed apneas; many of these patients also had coexistent cardiovascular risk factors and some had prevalent cardiovascular disease. Thus, caution is warranted in extrapolating our findings to healthier populations.

In summary, sleep apnea is significantly associated with the risk of type 2 diabetes, independently of other risk

factors, including age, race, sex, baseline fasting glucose, BMI, and changes in BMI. Increased severity of sleep apnea is associated with an increased risk of diabetes, and the risk might be partially explained by hypoxemia and arousals. As a treatable condition, sleep apnea might represent a modifiable risk factor for development of diabetes.

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