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Impact of Untreated Obstructive Sleep Apnea on Glucose Control in Type 2 Diabetes

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Abstract

Rationale: Obstructive sleep apnea (OSA), a treatable sleep disorder that is associated with alterations in glucose metabolism in individuals without diabetes, is a highly prevalent comorbidity of type 2 diabetes. However, it is not known whether the severity of OSA is a predictor of glycemic control in patients with diabetes.

Objectives: To determine the impact of OSA on hemoglobin A1c (HbA1c), the major clinical indicator of glycemic control, in patients with type 2 diabetes.

Methods: We performed polysomnography studies and measured HbA1c in 60 consecutive patients with diabetes recruited from outpatient clinics between February 2007 and August 2009.

Measurements and Main Results: A total of 77% of patients with diabetes had OSA (apnea-hypopnea index [AHI] ≥5). Increasing OSA severity was associated with poorer glucose control, after controlling for age, sex, race, body mass index, number of diabetes medications, level of exercise, years of diabetes and total sleep time. Compared with patients without OSA, the adjusted mean HbA1c was increased by 1.49% ($P = 0.0028$) in patients with mild OSA, 1.93% ($P = 0.0033$) in patients with moderate OSA, and 3.69% ($P < 0.0001$) in patients with severe OSA ($P < 0.0001$ for linear trend). Measures of OSA severity, including total AHI ($P = 0.004$), rapid eye movement AHI ($P = 0.005$), and the oxygen desaturation index during total and rapid eye movement sleep ($P = 0.005$ and $P = 0.008$, respectively) were positively correlated with increasing HbA1c levels.

Conclusions: In patients with type 2 diabetes, increasing severity of OSA is associated with poorer glucose control, independent of adiposity and other confounders, with effect sizes comparable to those of widely used hypoglycemic drugs.

sleep disordered breathing glycemic control diabetes

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obstructive sleep apnea (OSA) is associated with alterations in glucose metabolism in non-diabetic individuals and is a highly prevalent co-morbidity of type 2 diabetes, but its effect on glycemic control in patients with diabetes was not known.

What This Study Adds to the Field

In patients with type 2 diabetes, there is a robust graded relationship between the severity of OSA and glycemic control.

Given the enormous public health burden of the type 2 diabetes epidemic, and growing concerns about the safety profiles of current pharmacologic treatments (1, 2), a better understanding of the impact of comorbidities on

glucose control is needed to develop additional preventive and therapeutic strategies. Obstructive sleep apnea (OSA) is a treatable sleep disorder characterized by repetitive upper airway closures, leading to oxygen desaturations and sleep fragmentation. OSA has been identified as a highly prevalent comorbidity of type 2 diabetes (3–5). In particular, among obese patients with type 2 diabetes, who represent the vast majority of individuals with type 2 diabetes in the United States, the prevalence has recently been estimated at a staggering 86% (5).

OSA is a well documented risk factor for cardiovascular disease and mortality (6–9). Multiple epidemiologic and clinical studies have revealed that individuals without diabetes suffering from OSA show alterations in glucose metabolism, including insulin resistance and impaired glucose tolerance, independent of adiposity (10–13).

Despite these independent associations between OSA and abnormal glucose metabolism and the high prevalence of OSA in patients with type 2 diabetes, data on whether the presence and severity of OSA compromises glycemic control in patients with type 2 diabetes is lacking. The majority of patients with type 2 diabetes need multiple drugs, in addition to lifestyle modifications, to control glucose levels and avoid or delay the development of serious complications (14). Currently, both physicians and patients are challenged by rising concerns about the safety of widely used pharmacologic treatment options. Therefore, determining whether OSA has an adverse effect on glucose control in patients with diabetes has major clinical implications, because effective treatment of OSA could be a nonpharmacologic strategy to improve glucose control in the management of millions of patients with type 2 diabetes.

In the present study, we therefore evaluated the impact of untreated OSA on hemoglobin A1c (HbA1c), the major clinical indicator of glycemic control, in patients with type 2 diabetes. Preliminary findings from this study have been previously reported in abstract form (15, 16).

METHODS

Participants and Study Design

Patients with type 2 diabetes were consecutively recruited by one of the study investigators (R.S.A.), from the Primary Care and Endocrinology Clinics at the University of Chicago between February 2007 and August 2009. Sleep complaints or symptoms of OSA were not used as selection criteria. All participants were on stable medications for diabetes and other comorbidities for the preceding 3 months. Subjects were excluded if they: failed to meet the criteria for type 2 diabetes, based on physician diagnosis, in accordance with established guidelines (14); had unstable cardiopulmonary, neurological, or psychiatric disease; upper airway surgery; or used nocturnal oxygen, positive airway pressure therapy, or oral appliances. The study was approved by the University of Chicago Institutional Review Board, and all participants gave written informed consent.

During a 45-minutes interview, each patient completed surveys, including the University of Chicago Diabetes/Quality of Life Survey (17) (which includes self-report of medications, presence of diabetic complications [retinopathy, nephropathy, neuropathy, coronary artery disease, and peripheral vascular disease], and level of exercise [no = rarely, mild = once or twice a week, moderate = three times a week, and heavy = more than three times a week]), the Berlin Questionnaire (18) (used to assess the presence of snoring), and the Center for Epidemiologic Studies Depression Scale (19) (score ≥16 indicates depression). Height and weight were measured in all patients. Waist circumference was measured in 58 patients. Subjects underwent 5 consecutive days of ambulatory wrist actigraphy to determine habitual sleep habits. An overnight laboratory polysomnogram (PSG) was then performed to establish the presence and severity of OSA. Bedtimes in the laboratory were individually designed based on the subject's usual habits derived from actigraphy. However, each subject was recorded for a minimum of 7 hours. HbA1c values (%, defined as the proportion of hemoglobin that is glycosylated) were obtained from the patient's chart if assessed during the previous 3 months, or a single blood sample was drawn on the morning after PSG. HbA1c was measured by Bio-Rad Variant Classic boronate affinity-automated HPLC (Bio-Rad, Hercules, CA). The intra-assay coefficient of variation was 0.5–1.0%, and the interassay coefficient of variation ranges from 2.2–2.4%.

Polysomnography

PSG (Neurofax EEG 1100 system; Nihon Kohden, Foothill Ranch, CA) included recordings of six electroencephalogram channels, bilateral electro-oculograms, chin and tibialis electromyogram, electrocardiogram, airflow by nasal pressure transducer and oronasal thermocouples, chest and abdominal wall motion by piezo electrodes, and oxygen saturation by pulse oximeter. Recordings were visually scored in 30 seconds in stages 1–4 of non-rapid eye movement (REM) sleep and in REM sleep, according to standard criteria (20). Respiratory events and microarousals were scored according to established criteria (21, 22). Total cessation of airflow for at least 10 seconds was defined as apnea (obstructive if respiratory efforts were present and central if respiratory efforts were absent). Hypopneas were identified if there was a discernable reduction in airflow lasting at least 10 seconds and associated with at least 3% desaturation. The apnea-hypopnea index (AHI) was defined as the total number of obstructive apneas and obstructive hypopneas per hour of sleep. OSA severity categories were defined according to commonly used clinical cutoffs as follows: no OSA (AHI <5); mild OSA (AHI ≥5 but <15); moderate OSA (AHI ≥15 but <30); and severe OSA (AHI ≥30). Total oxygen desaturation index (ODI) was defined as the total number of desaturations of at least 3% per total sleep time in hours. REM ODI was defined as number of desaturations of at least 3% during REM sleep per REM sleep time in hours. The microarousal index was calculated as the total number of microarousals per hour of sleep.

Actigraphy

Habitual sleep duration was assessed at home by actigraphy using the Actiwatch (Mini-Mitter, Bend, OR) in accordance with previously described methods (23–25). Participants were asked to wear the Actiwatch for 5 consecutive days—3 weekdays and 2 weekend days—and to maintain their habitual bedtimes and fill out daily sleep logs. Of the 60 subjects who were included in the final analysis, 50 (83%) wore the Actiwatch for all 5 days, 7 (12%) wore the Actiwatch for 4 days, and 2 (3%) wore the Actiwatch for 3 days. One subject's data could not be downloaded due to a technical failure, thus data on habitual sleep duration are reported in 59 subjects.

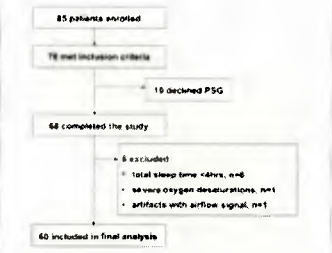
Statistical Analysis

Group data are expressed as means (±SD). Variables were examined for normality, and, if skewed, the log-transformed values were used. All categorical data were compared by Pearson's χ^2 test. Pair-wise comparisons of continuous variables in patients with and without OSA were examined by *t* test and confirmed by the nonparametric Mann-Whitney test. Unadjusted group differences across OSA severity categories were assessed by analysis of variance. A linear contrast was used to test for trends. We performed multivariate regression analyses to characterize the independent associations between measures of OSA severity and the primary outcome variable, HbA1c. The primary independent predictor was the OSA severity category, and we also examined total AHI, REM AHI, total ODI, and REM ODI. Potential confounding variables included in all multivariable models as covariates were: age; sex; race; body mass index (BMI); number of diabetes medications; level of exercise; years since diabetes diagnosis; and total sleep time by PSG. After log transformation, the distribution of HbA1c values remained skewed due to one outlier subject, thus a sensitivity analysis excluding this outlier value was performed and confirmed the significance of the association between severity of OSA and HbA1c. We also performed sensitivity analyses using waist circumference as covariate (instead of BMI) in all multivariate models. Data are presented in non-log-transformed values for ease of interpretation. All statistical analyses were performed using JMP version 6.0.3 statistical software (SAS Institute, Cary, NC). All reported *P* values are two sided.

RESULTS

Figure 1 shows the flow diagram of patient recruitment and selection. Patients who obtained less than 4 hours of total sleep time during the PSG, thus preventing accurate assessment of the degree of severity of OSA, were not included in the analysis ($n = 6$). One patient showed severe oxygen desaturations not explained by apneas or hypopneas (thus consistent with significant hypoventilation) and, in another patient, the PSG data could not be interpreted due to multiple artifacts in the airflow signal. Thus, 60 patients were included in the final analysis.

Figure 1.



Participant flow diagram

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Table 1 summarizes the demographic characteristics of the cohort, which comprised similar proportions of men and women and of whites and African Americans. The age range was 41–77 years. The BMI range was 20–57 kg/m². The sample included 7 lean, 14 overweight, and 39 obese patients.

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TABLE 1.

SAMPLE CHARACTERISTICS: PATIENTS WITH DIABETES ACCORDING TO OBSTRUCTIVE SLEEP APNEA STATUS

A total of 46 of the 60 patients (77%) had OSA (AHI ≥5). Only five patients had been previously evaluated for OSA, and none were receiving treatment. Mild, moderate, and severe OSA was found in 38.3% (n = 23), 25.0% (n = 15), and 13.3% (n = 8) of the sample, respectively.

Compared with patients without OSA, those with OSA were heavier and 6 years older on average (Table 1). Increasing severity of OSA was associated with increasing BMI (unadjusted P = 0.00042 for linear trend) and greater waist circumference (unadjusted P = 0.00038 for linear trend). Patients without OSA had fewer diabetic complications than those with OSA. Out of 60 patients, 6 (10%) did not take any diabetes medications (i.e., insulin, oral agents, or incretin-based therapies), 18 (30%) were on 1 medication, 24 (40%) were on 2 medications, 11 (18%) were on 3 medications, and 1 (2%) patient was on 4 medications. Out of 60 patients, 20 (33.3%) reported no exercise, 11 (18.3%) reported mild exercise, 14 (23.3%) reported moderate exercise, and 15 (25.0%) reported heavy exercise.

Sleep characteristics are summarized in Table 2. Habitual sleep duration was not significantly different between patients with and without OSA. In the laboratory, patients with OSA had shorter total sleep duration, decreased sleep efficiency, increased wake time after sleep onset, and less REM sleep than those without OSA. Increasing severity of OSA was associated with lower amounts of REM sleep (unadjusted P = 0.012 for linear trend), more stage 1 sleep (unadjusted P = 0.007 for linear trend), and more sleep fragmentation as assessed by the microarousal index (unadjusted P = 0.0001 for linear trend). The predominant respiratory disturbances were obstructive apneas and hypopneas, rather than central apneas.

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TABLE 2.

SLEEP CHARACTERISTICS: PATIENTS WITH DIABETES ACCORDING TO OBSTRUCTIVE SLEEP APNEA STATUS

Increasing severity of OSA was associated with poorer glucose control after controlling for age, sex, race, BMI, number of diabetes medications, level of exercise, years of diabetes, and total sleep time on PSG (P < 0.0001 for linear trend). Figure 2 shows the adjusted mean values of HbA1c in each OSA category. Compared with patients without OSA, the adjusted mean HbA1c was increased by 1.49% (P = 0.0028) in patients with mild OSA, 1.93% (P = 0.0033) in patients with moderate OSA, and 3.69% (P < 0.0001) in patients with severe OSA (P < 0.0001 for linear trend). Associations between OSA severity and HbA1c levels remained robust when "number of diabetes medications" was replaced by "oral hypoglycemic medication use" (P < 0.0001 for linear trend) or

"insulin use" ($P = 0.0002$ for linear trend) in the regression model. Similar associations between the severity of OSA and glycemic control were found when the presence of diabetic complications was added to the regression model ($P < 0.0001$ for linear trend). A sensitivity analysis including waist circumference (instead of BMI) in the regression model also showed similar linear associations between increasing severity of OSA and higher HbA1c levels ($P = 0.0001$ for linear trend).

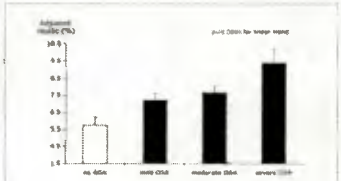

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Figure 2.

Adjusted mean hemoglobin A1c (HbA1c) values for patients with no, mild, moderate and severe obstructive sleep apnea (OSA). Data were adjusted for age, sex, race, body mass index, number of diabetes medications, level of exercise, years of diabetes, and total sleep time on polysomnogram. *Bars* represent SEM; $P < 0.0001$ for linear trend.

Other measures of OSA severity, including total AHI ($P = 0.004$), REM AHI ($P = 0.005$), total ODI ($P = 0.005$), and REM ODI ($P = 0.008$), were positively correlated with increasing HbA1c levels after adjusting for age, sex, race, BMI, number of diabetes medications, level of exercise, years of diabetes, and total sleep time on PSG. We did not detect significant associations between HbA1c levels and the microarousal index ($P = 0.75$) or the amount of slow wave sleep ($P = 0.67$) after adjusting for age, sex, race, BMI, number of diabetes medications, level of exercise, years of diabetes, and total sleep time.

DISCUSSION

The present study indicates that OSA is highly prevalent in patients with type 2 diabetes, and demonstrates, for the first time, a clear, graded, inverse relationship between OSA severity and glucose control in patients with type 2 diabetes, after controlling for the degree of adiposity and multiple other potential confounders. A total of 46 of our 60 subjects (77%) had OSA. In nearly 90% of these patients, the presence of OSA had not been previously evaluated. Relative to patients without OSA, the presence of mild, moderate, or severe OSA increased mean adjusted HbA1c values by 1.49, 1.93, and 3.69%, respectively. These effect sizes are comparable to, if not exceeding, those of widely used hypoglycemic medications (26–28). Our findings have important clinical implications, as they support the hypothesis that reducing the severity of OSA may improve glycemic control. Thus, effective treatment of OSA may represent a novel nonpharmacologic intervention in the management of millions of patients with type 2 diabetes.

Obstructive apneas and hypopneas were more frequent during REM sleep than during other sleep stages, indicating that the prevalence and the degree of severity of OSA in patients with type 2 diabetes may be underestimated when recording times are too short to allow for sufficient amounts of REM sleep to occur. Our findings contrast with the negative results of the only previous study that examined associations between the severity of OSA and HbA1c in patients with type 2 diabetes (4). It is possible that the lack of association in the previous study was due to the short duration of PSG recording (reported to be as low as 4 h), and thus perhaps insufficient to detect an association between OSA severity and HbA1c. In contrast, our study design specified a minimum duration of PSG recording of 7 hours, and our subjects achieved 6.6 hours of sleep on average. Of note, in an exploratory reanalysis of our own data set using only the first 4 hours of recording, the robust relationship between severity of OSA and HbA1c found with a PSG recording time of at least 7 hours was much weaker. Compared with patients without OSA (mean adjusted HbA1c = 7.05%), when only 4 hours of recording were analyzed, the adjusted mean HbA1c levels were not different in patients with mild OSA (mean adjusted HbA1c = 6.83%; $P = 0.67$), moderate OSA (mean adjusted HbA1c = 7.79%; $P = 0.28$), and severe OSA (mean adjusted HbA1c = 8.53%; $P = 0.10$), indicating that the shorter duration of PSG recording, which precludes observing normal amounts of REM sleep, fails to detect the robust relationship observed with the longer recording time. These findings highlight the importance of obtaining

PSG recordings longer than the commonly used minimum of 4 hours to examine associations between OSA severity and metabolic variables.

In our sample, OSA was characterized by a clear predominance of obstructive, rather than central, disease. This is in contrast with findings from the Sleep Heart Health Study (SHHS) (3), in which self-reported diabetes was associated with a significant increase in periodic breathing, an abnormality reflecting disruption of central control of breathing, and a nonstatistically significant increase in the occurrence of central apneas. By contrast, we did not observe periodic breathing pattern in any participant in our study. Consistent with our findings, two previous studies in patients with diabetes with autonomic neuropathy have reported a high frequency of obstructive, rather than central, respiratory events (29, 30). The finding of predominantly obstructive disease in patients with diabetes has important clinical implications, as it would indicate that the available therapies to improve obstructive disease, such as positive airway pressure therapy, oral appliances, and surgical options (31), could have a significant effect on glucose control in patients with type 2 diabetes and OSA. To date, six studies, including a total of 120 patients, have examined the impact of continuous positive airway pressure (CPAP) treatment of OSA on measures of glucose tolerance in type 2 diabetes (32–37). The study by Babu and colleagues (32) involving 25 obese patients with diabetes showed beneficial effects of 3 months of CPAP use on HbA1c and postprandial glucose levels, and two other studies (33, 36) reported improvements in nocturnal glucose levels after CPAP. Two earlier studies, including only a total of 10 subjects (34, 35), showed no change in HbA1c levels, but reported improvements in insulin sensitivity (by hyperinsulinemic eugylcemic clamps) after 3–4 months of CPAP. The only randomized controlled study, by West and colleagues (37), which included 20 obese patients with diabetes randomized to the active CPAP arm, found no effect of active CPAP on HbA1c levels or insulin sensitivity, but reported significant improvements in sleepiness measures. Of note, in this study, the average nightly CPAP use over a 3-month period was only about 3.3 hours. By contrast, the positive study by Babu and colleagues found that, in patients who used CPAP for more than 4 hours per night (average nightly use of ~6.6 h/night), the reduction in HbA1c levels was strongly correlated with CPAP use, suggesting that the negative findings on HbA1c in the study by West and colleagues could be explained, at least in part, by low CPAP adherence. It is also possible that the efficacy of CPAP varies according to the outcome (i.e., sleepiness versus glucose control), such that the duration and nightly use of CPAP needed to observe significant benefits may not be the same for cognitive versus metabolic outcomes.

Our findings regarding the prevalence of OSA in patients with type 2 diabetes are consistent with those of the most recent and largest study, the Sleep AHEAD (Action for Health in Diabetes) study, which included 306 obese patients with diabetes, and reported a prevalence of 86% (5). Two earlier studies had estimated the prevalence of OSA in patients with type 2 diabetes using full overnight PSG. First, the SHHS involving older individuals (about 50% >65 yr of age), in whom the diagnosis of diabetes was based on self-report only, found an OSA prevalence of 58% (3). Furthermore, in the SHHS, the definition of hypopneas was based on at least 4% desaturation, whereas, in our study, we used a cutoff of 3% desaturation, which could explain the difference in prevalence estimations (38). The second study (4), which did not specify respiratory event definitions, reported a prevalence of 71%, similar to our findings. Of note, in an exploratory reanalysis of our data using a definition of hypopneas based on a minimum of 4% desaturation, the prevalence of OSA was 58% (versus 77% with a cutoff of 3% desaturation), similar to that reported in the SHHS. Importantly, the associations between OSA severity and HbA1c levels that we observed with a cutoff of 3% desaturation remained significant, albeit somewhat weaker, when the 4% desaturation criterion was used ($P = 0.007$ and $P = 0.013$ for total AHI and REM AHI, respectively). These findings suggest that the reliance on strict criteria in defining OSA may fail to detect patients with milder disease who could nonetheless potentially benefit from treatment.

Our study was not designed to examine the mechanisms linking OSA and glucose control in type 2 diabetes. Although it remains possible that hyperglycemia may promote sleep disturbances, the current evidence supports the hypothesis that OSA, and its inherent characteristics, such as intermittent hypoxia, elevated sympathetic nervous activity (39, 40), sleep fragmentation and low amounts of slow wave sleep (41), and cumulative sleep loss (42, 43), has adverse effects on glucose tolerance. Multiple prospective epidemiologic studies have indicated that short sleep and/or poor sleep quality, as is typical

of OSA, is associated with an increased incidence of diabetes over time (44-49). In a recent prospective population study, the presence of moderate to severe OSA was found to be a significant risk factor for incident diabetes during a 4-year follow-up period (50).

The present study reveals that the majority of patients with type 2 diabetes have undiagnosed OSA, and that untreated OSA is associated with poorer glucose control, which may instigate the need for more intensive pharmacotherapy. Conversely, treating OSA may have clinically significant beneficial effects on glucose control and reduce the number of drugs needed and/or their dose regimen. Pharmacotherapy of type 2 diabetes with drugs that promote weight gain may have the undesirable consequence of promoting the development of OSA or exacerbating the severity of existing OSA, thereby compromising glycemic control and elevating cardiovascular risk. The high prevalence of OSA and its cardiovascular consequences in type 2 diabetes may help in understanding possible adverse effects of antidiabetic pharmacotherapy. Noteworthy examples are the recent findings of the Action to Control Cardiovascular Risk in Diabetes and Action in Diabetes and Vascular Disease trials that examined the impact of intensive glucose lowering on cardiovascular risk (51, 52). Based on the data from our study, it is likely that OSA was present in most participants in both trials, and that this unrecognized comorbidity may explain the failure of near-normal glucose control to decrease the incidence of major macrovascular events. Consistent with a putative role of OSA in these findings, the ACCORD trial, which had to be terminated early due to unexpected mortality (particularly from cardiovascular causes), enrolled participants who were on average 15 kg heavier at baseline (thus, more likely to have OSA as well as more severe OSA) than those participating in the ADVANCE trial, which did not observe increased mortality or higher incidence of cardiovascular disease. Furthermore, those in the intensive treatment arm of ACCORD gained substantially more weight (>10 kg in about one-third of the patients) than those in the standard therapy arm, whereas the difference in weight gain between the two treatment arms of ADVANCE was less than 1 kg. It is well documented that weight gain increases the severity of OSA (53, 54) and thus obese participants in the intensive treatment arm of ACCORD may have been at increased risk for more severe OSA, and thus at increased risk for major cardiovascular events and death. Our findings are also noteworthy in the context of recent reports discussing a possible link between the use and dose of insulin glargine and cancer risk (2). Although the evidence is inconclusive, the questions raised by these reports clearly highlight the importance of developing additional, nonpharmacologic alternatives to offer patients with type 2 diabetes.

There is a relentless increase in type 2 diabetes worldwide. Diligent control of glucose levels is needed to prevent or delay the development of life-threatening complications. Most patients are treated with multiple drugs, and a substantial proportion requires insulin injections. This pharmacotherapy is not without risk, and may promote further weight gain. Our findings indicate that the role of OSA in the management of type 2 diabetes is in urgent need of further rigorous assessment. Current practice approaches should be updated to include systematic evaluation and treatment of OSA in patients with type 2 diabetes.

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this manuscript; E.V.C. received more than $100,001 as an investigator-initiated research grant from Respironics/Philips, $50,001-$100,000 as an investigator-initiated research grant from the ResMed Foundation, more than $100,001 (pending) as an investigator-initiated research grant from Amylin, Inc.; E.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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