Association of Obstructive Sleep Apnea in Rapid Eye Movement Sleep With Reduced Glycemic Control in Type 2 Diabetes: Therapeutic Implications

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CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

OBJECTIVE

Severity of obstructive sleep apnea (OSA) has been associated with poorer glycemic control in type 2 diabetes. It is not known whether obstructive events during rapid eye movement (REM) sleep have a different metabolic impact compared with those during non-REM (NREM) sleep. Treatment of OSA is often limited to the first half of the night, when NREM rather than REM sleep predominates. We aimed to quantify the impact of OSA in REM versus NREM sleep on hemoglobin A_{1c} (HbA_{1c}) in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

All participants underwent polysomnography, and glycemic control was assessed by HbA_{1c}.

RESULTS

Our analytic cohort included 115 subjects (65 women; age 55.2 ± 9.8 years; BMI 34.5 ± 7.5 kg/m^2). In a multivariate linear regression model, REM apnea–hypopnea index (AHI) was independently associated with increasing levels of HbA_{1c} (P = 0.008). In contrast, NREM AHI was not associated with HbA_{1c} (P = 0.762). The mean adjusted HbA_{1c} increased from 6.3% in subjects in the lowest quartile of REM AHI to 7.3% in subjects in the highest quartile of REM AHI (P = 0.044 for linear trend). Our model predicts that 4 h of continuous positive airway pressure (CPAP) use would leave 60% of REM sleep untreated and would be associated with a decrease in HbA_{1c} by approximately 0.25%. In contrast, 7 h of CPAP use would cover more than 85% of REM sleep and would be associated with a decrease in HbA_{1c} by as much as 1%.

CONCLUSIONS

In type 2 diabetes, OSA during REM sleep may influence long-term glycemic control. The metabolic benefits of CPAP therapy may not be achieved with the typical adherence of 4 h per night.

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In 2011, the Centers for Disease Control and Prevention reported that nearly 26 million American adults, 8.3% of the population, had type 2 diabetes (1). The alarming increase in overweight and obesity has played a pivotal role in the rise of type 2 diabetes prevalence. The obesity epidemic has also been associated with an increased prevalence of sleep disturbances, particularly obstructive sleep apnea (OSA) (2,3). Over the past decade, both laboratory and epidemiologic studies have identified poor sleep quality and OSA as putative novel risk factors for type 2 diabetes (4–6). OSA is a treatable chronic sleep disorder characterized by recurrent episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway. OSA leads to intermittent hypoxemia and hypercapnia, increased oxidative stress, cortical microarousals, sleep fragmentation, and chronic sleep loss. Indeed, prevalence estimates of OSA, defined as apnea–hypopnea index (AHI) $\geq$5 events per hour, in nondiabetic obese adults have ranged from 50 to 68% (7,8).

In recent years, evidence has accumulated to indicate that OSA is both a risk factor for type 2 diabetes and an exceptionally frequent comorbidity with an adverse impact on glycemic control. Five independent studies, totaling nearly 1,400 patients with type 2 diabetes, have shown that the prevalence of OSA (assessed by polysomnography [PSG]) ranges between 58 and 86% (9,10). Several studies have established a robust association—independent of adiposity and other known confounders—between the presence and severity of OSA and insulin resistance and glucose intolerance in nondiabetic adults (11–14). Two studies that used the gold standard of in-laboratory PSG to accurately quantify the severity of OSA reported a robust association between increasing OSA severity and increasing levels of hemoglobin A_{1c} (HbA$_{1c}$) in patients with type 2 diabetes, after controlling for multiple potential confounders (9,15). While the findings of these two studies suggested that the effective treatment of OSA may be a nonpharmacologic strategy to improve glucose control, the results of the only

randomized, placebo-controlled clinical trial examining the impact of continuous positive airway pressure (CPAP) treatment on HbA$_{1c}$ in patients with type 2 diabetes were surprisingly disappointing (16). One potential reason for the failure of OSA treatment to improve chronic glycemic control in patients with type 2 diabetes is insufficient CPAP use. Notably, the mean nightly CPAP use in this clinical trial was 3.6 h. As most of rapid eye movement (REM) sleep occurs in the early morning hours before habitual awakening, one possibility is that with suboptimal adherence to CPAP therapy, obstructive apneas and hypopneas during REM sleep were disproportionately untreated compared with events in non-REM (NREM) sleep. This may be relevant to glycemic control because it is now well established that compared with NREM sleep, REM sleep is associated with greater sympathetic activity in healthy subjects as well as in patients with OSA (17–19). Further, compared with events in NREM sleep, obstructive apneas and hypopneas during REM sleep last nearly 30 s longer and are associated with significantly larger oxygen desaturation (20–22). Therefore, obstructive events during REM sleep, as compared with NREM sleep, may have a larger adverse effect on insulin release and action. This issue has major clinical implications for the duration of CPAP use that is needed to reverse the negative consequences of OSA on glycemic control in type 2 diabetes. We have therefore performed a detailed analysis comparing the contributions of NREM versus REM OSA to glycemic control as assessed by levels of HbA$_{1c}$ in a large cohort of adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS
Participants
We prospectively recruited subjects with established type 2 diabetes using an advertisement posted in the primary care and endocrinology clinics at the University of Chicago, inviting participation in a research study on sleep and diabetes. Eligible individuals had to meet the criteria for type 2 diabetes based on physician diagnosis using standard criteria (23). In order to include individuals with newly

diagnosed type 2 diabetes, we also recruited in the community using an advertisement inviting subjects at risk for type 2 diabetes based on age and adiposity to participate in a research study on sleep and metabolism. All participants without an established diagnosis of type 2 diabetes had to undergo a standard 75-g oral glucose tolerance test and meet the American Diabetes Association guidelines for the diagnosis of type 2 diabetes (23).

All participants were in stable condition and, when on pharmacological treatment, on a stable antidiabetic medication regimen for the preceding 3 months. Exclusion criteria were unstable cardiopulmonary conditions, neurological disorders, psychiatric disease, shift work, chronic insomnia, or any prior or current treatment for OSA (upper airway surgery, CPAP therapy, oral appliances, or supplemental oxygen). We previously reported the association of OSA severity categories (no, mild, moderate, and severe OSA) with chronic glycemic control in type 2 diabetes using 60 of the participants included in this analysis (9).

The study was approved by the University of Chicago Institutional Review Board, and all participants gave written informed consent.

Experimental Protocol
Subjects were admitted to the Clinical Resource Center or the Sleep Research Laboratory of the Sleep, Health, and Metabolism Center at the University of Chicago to undergo an overnight in-laboratory PSG. Height and weight were measured in all participants. Self-reported ethnicity-based diabetes risk was categorized as low-risk category (non-Hispanic whites) and high-risk category (African Americans, Hispanics, and Asians). The duration of type 2 diabetes and the number of medications were verified by questionnaires as well as review of the patients' medical records. Insulin use was defined as the current use of insulin by subject's report. HbA$_{1c}$ was used as clinical indicator of glycemic control. HbA$_{1c}$ values (defined as the proportion of hemoglobin that is glycosylated) were obtained from the patient's chart if assessed during the previous three

months (n = 17,15% of subjects) or measured on a single blood sample drawn on the morning after the PSG (n = 98, 85% of the subjects). HbA_{1c} was measured by Bio-Rad variant classic boronate affinity-automated high-performance liquid chromatography (Bio-Rad, Hercules, CA). The intra-assay coefficient of variation was 0.5–1.0%, and the interassay coefficient of variation was 2.2–2.4%.

PSG
Bedtimes were from 11:00 P.M.–12:00 A.M. until 7:00 A.M.–8:00 A.M. Each subject was recorded for a minimum of 7 h to determine the presence and severity of obstructive respiratory events across the entire night. PSG (Neurofax EEG 1100 system, Nihon Kohden, Foothill Ranch, CA) included recordings of six electroencephalographic channels, bilateral electro-oculograms, chin and tibialis electromyogram, electrocardiogram, airflow by nasal pressure transducer and oronasal thermocouples, chest and abdominal wall motion by piezo electrode belts, and oxygen saturation by finger pulse oximeter. All PSGs were staged and scored according to the 2007 American Academy of Sleep Medicine Manual for the Scoring of Sleep and Related Events (24). Apneas were defined as total cessation of airflow for at least 10 s (obstructive if respiratory effort was present and central if respiratory effort was absent). Hypopneas were scored if the magnitude of the ventilation signal decreased by at least 50% of the baseline amplitude of the nasal pressure transducer for at least 10 s and were associated with either a 3% or greater drop in oxygen saturation as measured by finger pulse oximetry or an electro-encephalographic microarousal (24). The total AHI was defined as the number of obstructive apneas and obstructive hypopneas per hour of sleep. Given the minimal presence of central apneas, we did not include these events in the calculation of AHI. The median central apnea index was 0.001 (interquartile range of 0.001–0.41), and the highest central apnea index was 5. OSA was defined as AHI ≥5. Severity of OSA was measured by the AHI. A subject was considered to have mild OSA if the AHI was 5–14, moderate OSA if the

AHI was 15–29, and severe OSA if the AHI was ≥30. REM AHI was calculated as the number of apneas and hypopneas during REM sleep divided by total time in REM sleep in hours. NREM AHI was calculated by dividing the number of apneas and hypopneas during NREM sleep by total time in NREM sleep in hours. The oxygen desaturation index (ODI) was defined as the total number of oxygen desat-urations of at least 3% per total sleep time (TST) in hours. The micro-arousal index (MAI) was calculated as the total number of microarousals per hour of sleep. ODI and MAI were also calculated during REM and NREM sleep.

Statistical Analysis
Continuous variables are presented as mean ± SD or median and interquartile ranges. Differences between subjects with and without OSA were tested using the Student t test or Mann–Whitney nonparametric test for continuous variables. Categorical variables were reported as proportions and were compared using the χ square test or Fisher's exact test. All tests of significance were two sided.

Five multivariate linear models were successively fitted to examine associations between HbA_{1c} and measures of OSA severity after controlling for multiple covariates. Model 1 included demographic variables traditionally associated with glycemic control, namely, age, sex, ethnicity-based diabetes risk, BMI, years of type 2 diabetes, and insulin use. Model 2 included all the covariates in model 1 plus total AHI. Model 3 included all the covariates in model 1 plus NREM AHI. Model 4 included all the covariates in model 1 plus REM AHI. Lastly, model 5 included all the covariates in model 1 plus NREM AHI and REM AHI. Since there are individuals who have a significant number of apneas and hypopneas during REM sleep while having an overall AHI below 5 (hence no OSA based on current definitions), we included all 115 subjects (with or without OSA) in the multivariate regression models in order to explore the entire spectrum of REM and NREM events (AHI, ODI, and MAI). We formally ruled out any evidence of collinearity among the variables entered in the models using standard statistics,

including "tolerance" and "variance inflation factor" (SPSS Statistics v20, IBM, Armonk, NY). Values for HbA_{1c}, years of type 2 diabetes, and REM and NREM AHI were submitted to natural log (Ln) transformation. In order to deal with zero values, the total AHI, REM AHI, and NREM AHI were log transformed using the formula AHI = log(AHI + 0.01). A similar procedure was used for years of type 2 diabetes. We used casewise diagnostics to identify any outliers. Only one outlier was identified (low HbA_{1c}), and sensitivity analysis excluding this subject was performed confirming the association between HbA_{1c} and measures of REM OSA severity. Goodness of fit of the models was assessed using diagnostic plots.

In order to estimate the effect size of increasing severity of OSA on HbA_{1c} in a clinically useful manner, models were fitted to estimate the change in adjusted HbA_{1c} based on quartiles of REM and NREM AHI. The models included all the covariates in model 5 (age, sex, ethnicity-based diabetes risk, BMI, years of type 2 diabetes, and insulin use) and replaced LnREM AHI with REM AHI quartiles while keeping LnNREM AHI in the model. This process was repeated, and LnNREM AHI was replaced with NREM AHI quartiles while keeping LnREM AHI in the model. Similar models were fitted for REM and NREM ODI and MAI quartiles.

To simulate the impact of various durations of nocturnal CPAP therapy on HbA_{1c}, we calculated the mean profiles of cumulative minutes of REM and NREM sleep over 8 h of total recording time from the 115 polysomnograms. We then estimated mean percentages of REM and NREM sleep left untreated after 4, 6, and 7 h of optimal CPAP treatment eliminating all events. For each duration of CPAP use, we entered the number of REM and NREM obstructive events left untreated in a regression model predicting HbA_{1c} after adjustment for age, sex, ethnicity-based diabetes risk, BMI, years of type 2 diabetes, and insulin use.

All statistical analyses were performed using SPSS Statistics v20 and verified using Stata (v10.1, College Station, TX).

RESULTS
Inclusion criteria were met in 141 participants. Ten participants declined

to undergo in-laboratory PSG. Therefore, the study was completed by 131 participants. Those who obtained less than 4 h of TST during the PSG were not included in the analysis (n = 7). Participants were also excluded if the PSG data could not be interpreted due to multiple artifacts in the airflow signal (n = 8). One patient showed severe oxygen desaturation not explained by apneas or hypopneas consistent with significant hypoventilation. Thus the final analytic cohort included 115 subjects with type 2 diabetes.

The demographic and clinical characteristics of our cohort are summarized in Table 1. Of the 115 subjects included in the study, 56.5% were women, 58.3% were African American, 68.7% were obese, and the mean BMI was 34.5 kg/m^2. The median duration of type 2 diabetes was 4 years, and a quarter of the subjects were not on any antidiabetic medication. At least one type of diabetes complication was present in 33% of the subjects (i.e., neuropathy, nephropathy, retinopathy, coronary artery disease, or peripheral arterial disease). OSA was present in

85.2% of the participants. Mild OSA was present in 27%, moderate OSA in 28.7%, and severe OSA in 29.6% of the subjects. There were no significant differences in sex, race, BMI, years of type 2 diabetes, number of antidiabetic medications, insulin use, and HbA$_{1c}$ level between subjects with and without OSA, but participants without OSA were on average 9 years younger than those with OSA. The lack of statistically significant differences in BMI and HbA$_{1c}$ may have been related to the small number of subjects without OSA. The polysomnographic findings in our cohort are summarized in Supplementary Table 1. There were no significant differences in total recording time and percentage of slow wave sleep between subjects with and without OSA. However, subjects with OSA had significantly less TST and percentage of REM sleep and significantly higher wake after sleep onset. Within the participants with OSA (n = 98), REM AHI, REM ODI, and REM MAI were all significantly higher than NREM AHI, NREM ODI, and NREM MAI. The ODI was more than fourfold higher during REM

than NREM sleep, but differences in MAI were more modest.

Table 2 describes the results of the five multivariate linear regression models predicting HbA$_{1c}$. Model 1 demonstrates the association of HbA$_{1c}$ with nonsleep variables. In model 2, the total AHI was significantly associated with higher HbA$_{1c}$ (P = 0.019). Model 3 shows that NREM AHI was not associated with HbA$_{1c}$ (P = 0.070). In contrast, in model 4, REM AHI was independently associated with HbA$_{1c}$ (P = 0.001). In model 5, REM AHI (P = 0.008) remained a significant predictor of HbA$_{1c}$ even after adjusting for NREM AHI (P = 0.762). In the final fully adjusted model 5, the independent predictors of increased HbA$_{1c}$ were REM AHI (P = 0.008), race risk (P = 0.001), years of type 2 diabetes (P = 0.001), and insulin use (P < 0.001). Age, sex, BMI, and NREM AHI were not significant. Similar results were obtained when NREM AHI and REM AHI were replaced by the total number of events in NREM and REM sleep, respectively (P = 0.023 for REM events and P = 0.355 for NREM events).

In order to estimate the effect size of increasing levels of REM AHI and NREM AHI on HbA$_{1c}$, we performed multivariate linear regression models using quartiles of REM AHI and NREM AHI. As can be seen in Fig. 1, after adjustment for age, sex, BMI, race risk, years of type 2 diabetes, insulin use, and LnNREM AHI, increasing quartiles of REM AHI were significantly associated with increasing levels of HbA$_{1c}$ (P = 0.044 for linear trend). The mean adjusted HbA$_{1c}$ increased from 6.3% in subjects with REM AHI <12.3 events per hour (lowest quartile) to 7.3% in subjects with REM AHI >47 events per hour (highest quartile). Similarly, quartiles of REM ODI and REM MAI were significantly associated with increasing levels of HbA$_{1c}$. The mean adjusted HbA$_{1c}$ increased from 6.5% in the lowest quartile of REM ODI to 7.5% in the highest quartile (P = 0.039 for linear trend). Similarly, the mean adjusted HbA$_{1c}$ increased from 7.6% in the lowest quartile of REM MAI to 8.9% in the highest quartile (P = 0.003 for linear trend). In contrast, increasing levels of NREM AHI, NREM ODI, and NREM MAI quartiles were not associated with HbA$_{1c}$ (Fig. 1).

Table 1—Demographic and clinical features of 115 patients with type 2 diabetes

Characteristics	All subjects (n = 115)	No OSA (n = 17)	OSA (n = 98)	P
Age, years	55.2 ± 9.8	47.5 ± 8.0	56.5 ± 9.4	<0.001
Sex				0.59
Women, %	56.5	64.7	55.1	
Men, %	43.5	35.3	44.9	
Race, %				0.37
African American	58.3	76.5	55.1	
White	36.5	23.5	38.8	
Hispanic	4.3	0	5.1	
Asian	0.9	0	1.0	
BMI, kg/m^2*	34.5 ± 7.5	31.8 ± 7.4	35.0 ± 7.4	0.10
HbA$_{1c}$, %	7.36 ± 1.7	6.7 ± 1.3	7.4 ± 1.7	0.10
HbA$_{1c}$, mmol/mol	56.5 ± 18.6	50 ± 14.2	57 ± 18.6	0.10
Diabetes diagnosis, years	4 (1–12)	4 (0–8)	4 (1–13)	0.71
Diabetes medications, %				0.59
No medication	25.2	35.3	23.5	
One medication	29.6	35.3	28.6	
Two medications	33.9	17.6	36.7	
Three medications	10.4	11.8	10.2	
Four medications	0.9	0	1.0	
Insulin use, %	20.9	35.3	18.3	0.19

Medications included insulin or oral hypoglycemic agents such as metformin, sulfonylurea, and thiazolidinedione. Data are presented as mean ± SD and compared using Student t test or median (interquartile range) and compared using Mann–Whitney nonparametric test. Categorical data are presented as proportions and compared using the χ^2 test or Fisher's exact test where appropriate. *Information on BMI was missing on one subject.

Table 2—Multivariate linear regression models predicting natural log of HbA$_{1c}$ in patients with type 2 diabetes

Variables	Model 1		Model 2		Model 3		Model 4		Model 5	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
R	0.560		0.591		0.578		0.614		0.615	
R²	0.313		0.349		0.334		0.377		0.378	
R² adjusted	0.275		0.306		0.290		0.336		0.331	
P value for R² change			0.017*		0.070*		0.001*		0.006*	
Age	−0.002 (−0.006 to 0.002)	0.395	−0.004 (−0.008 to 0.000)	0.158	−0.003 (−0.007 to 0.001)	0.128	−0.005 (−0.009 to −0.001)	**0.028**	−0.005 (−0.009 to −0.001)	**0.028**
Sex	0.046 (−0.027 to 0.120)	0.214	0.024 (−0.050 to 0.098)	0.377	0.031 (−0.044 to 0.105)	0.415	0.035 (−0.036 to 0.105)	0.334	0.032 (−0.040 to 0.105)	0.379
Race risk	0.115 (0.040–0.190)	**0.003**	0.121 (0.048–0.195)	**<0.001**	0.123 (0.048–0.197)	**0.002**	0.119 (0.047–0.191)	**0.001**	0.120 (0.048–0.193)	**0.001**
BMI	0.006 (0.001–0.011)	**0.012**	0.004 (−0.002 to 0.009)	0.263	0.005 (0.000–0.010)	0.071	0.002 (−0.004 to 0.007)	0.526	0.002 (−0.004 to 0.007)	0.542
Ln years T2DM	0.021 (0.007–0.036)	**0.004**	0.024 (0.009–0.038)	**0.008**	0.023 (0.009–0.037)	**0.002**	0.024 (0.011–0.038)	**0.001**	0.025 (0.011–0.039)	**0.001**
Insulin use	0.151 (0.062–0.240)	**0.001**	0.159 (0.072–0.246)	**0.001**	0.153 (0.066–0.241)	**0.001**	0.164 (0.078–0.249)	**<0.001**	0.163 (0.078–0.249)	**<0.001**
LnAHI	—		0.046 (0.008–0.084)	**0.019**	—		—		—	
LnNREM AHI	—		—		0.028 (−0.002 to 0.059)	0.070	—		0.005 (−0.029 to 0.039)	0.762
LnREM AHI	—		—		—		0.063 (0.025–0.101)	**0.001**	0.060 (0.016–0.104)	**0.008**

Model 1 includes age, sex, race risk, BMI, Ln years type 2 diabetes, and insulin use. Model 2 includes age, sex, race risk, BMI, Ln years type 2 diabetes, insulin use, and LnAHI. Model 3 includes age, sex, race risk, BMI, Ln years type 2 diabetes, insulin use, and LnNREM AHI. Model 4 includes age, sex, race risk, BMI, Ln years type 2 diabetes, insulin use, and LnREM AHI. Model 5 includes age, sex, race risk, BMI, Ln years type 2 diabetes, insulin use, LnREM AHI, and LnNREM AHI. All models included 114 subjects (1 subject was dropped from the model for missing BMI, T2DM, type 2 diabetes mellitus; CI, confidence interval. *Compared with model 1. Race risk, 0 low race risk and 1 high race risk; sex, 0 women and 1 men; insulin use, 0 no insulin use and 1 insulin use. Statistically significant P values are in boldface.
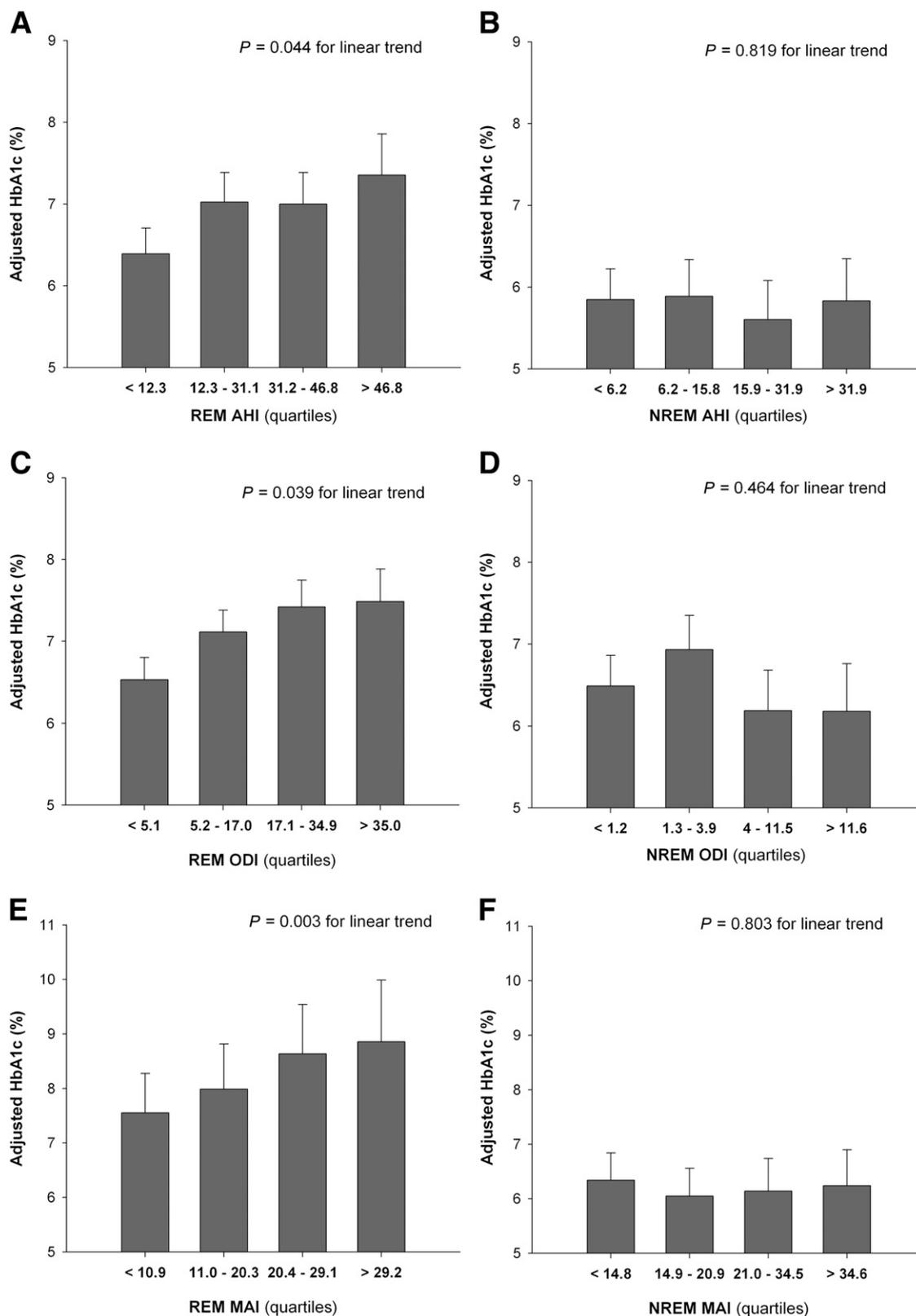
Figure 2*A* illustrates the predominance of REM sleep in the later part of sleep. In our cohort, 3 and 4 h after lights off, on average only 25 and 40% of REM sleep had occurred, respectively. Therefore, optimally titrated CPAP use for 3 or 4 h would treat only 25 or 40% of REM sleep, respectively, and would leave most obstructive events during REM sleep untreated. Figure 2*B* and *C* illustrate the simulated impact of 4, 6, and 7 h of CPAP use in men and women with low and high race/ethnicity-based diabetes risk. This simulation clearly shows that the metabolic benefit of 4 h of CPAP use, often considered as adequate CPAP compliance, is modest, while a much more clinically significant effect can be obtained when treatment is extended to 6 h and beyond.

CONCLUSIONS

This study reveals that HbA$_{1c}$, a measure of chronic glycemic control in patients with type 2 diabetes, is adversely associated with obstructive apneas and hypopneas that occur in REM sleep (REM AHI) but not in NREM sleep (NREM AHI). The independent association between REM AHI, REM ODI, and REM MAI and HbA$_{1c}$ is robust and of clinical significance, with a difference of 1.0% HbA$_{1c}$ between the lowest and highest quartiles of REM AHI as well as REM ODI and of 1.3% HbA$_{1c}$ between the lowest and highest quartiles of REM MAI after adjusting for all the covariates. These effect sizes are comparable to what would be expected from widely used antidiabetic medications.

The severity of OSA in our cohort was greater in REM sleep than in NREM sleep, as evidenced by a higher AHI and a nearly fourfold higher ODI. Thus, despite the shorter duration of REM sleep, exposure to the adverse consequences of OSA, particularly intermittent hypoxemia, was greater during REM than NREM sleep. Surprisingly, in our diabetic participants with OSA, NREM AHI only predicted approximately 25% of the variance of REM AHI. Whether hyperglycemia plays a role in this relative independence of the severity of REM OSA relative to NREM OSA remains to be determined.

Multiple mechanistic pathways are likely to be involved in the link between REM OSA and poorer glycemic control in

Figure 1—Adjusted mean HbA$_{1c}$ values for REM and NREM AHI, ODI, and MAI quartiles. For all the panels, multivariate linear regression models were fitted to estimate the mean natural Ln HbA$_{1c}$ adjusted for demographic variables traditionally associated with glycemic control such as age, sex, ethnicity-based diabetes risk, BMI, Ln years of type 2 diabetes, and insulin use. In addition, panels are adjusted for (*A*) LnNREM AHI, (*B*) LnREM AHI, (*C*) LnNREM ODI, (*D*) LnREM ODI, (*E*) LnNREM MAI, and (*F*) LnREM MAI. Age and BMI are centered at their means: 55 years old and 35 kg/m^2, respectively. The corresponding β-coefficients for each quartile were then exponentiated to convert from Ln HbA$_{1c}$ to the standard values of HbA$_{1c}$. Bars represent SEM.
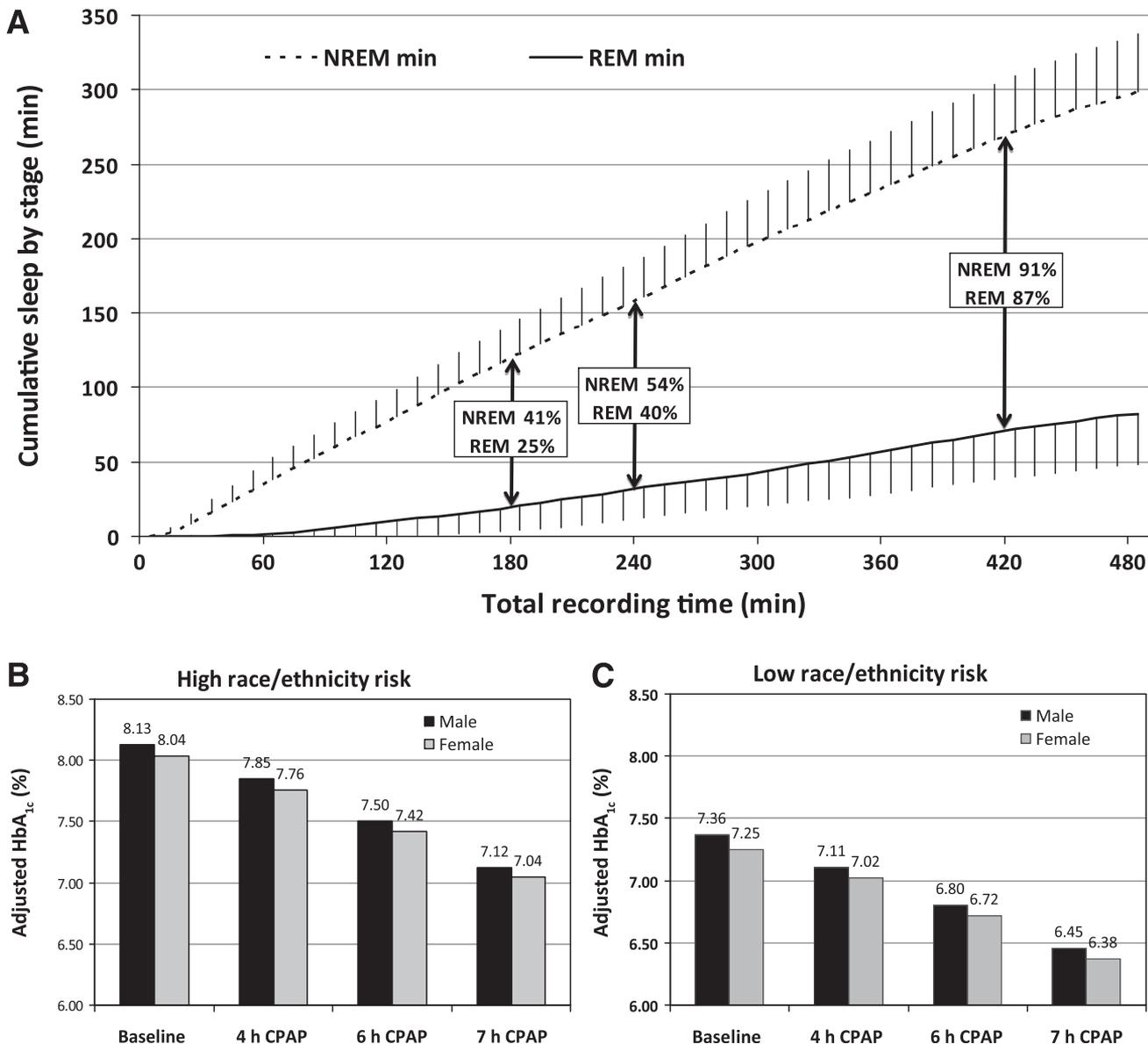
Figure 2—Cumulative minutes of REM and NREM sleep over 8 h of bedtime (A) and simulation of various hours of CPAP use in men and women with type 2 diabetes based on race/ethnicity-based diabetes risk (B and C). A: Data are summarized as mean ± SD of cumulative REM and NREM sleep minutes from lights off to lights on in 115 subjects with type 2 diabetes. The mean duration of REM and NREM sleep in our cohort was 82 and 298 min, respectively. Using CPAP for 3 or 4 h from the time lights are turned off will cover only 25 or 40% of REM sleep, respectively, and will leave most obstructive events during REM sleep untreated. In contrast, 7 h of CPAP use would treat 87% of REM sleep. B and C: Simulation of the impact of 4, 6, and 7 h of CPAP use in four groups of subjects based on sex and race/ethnicity-related diabetes risk. With this simulation, 4 h of CPAP use would treat 40% of REM sleep and would lead to a drop in adjusted HbA$_{1c}$ of 0.23–0.28%. In contrast, 7 h of CPAP therapy would treat 87% of REM sleep and lead to a decrease in adjusted HbA$_{1c}$ between 0.87 and 1.1%. High race/ethnicity risk includes African Americans, Hispanics, and Asians. Low race/ethnicity risk includes non-Hispanic whites.

subjects with type 2 diabetes. When compared with NREM sleep or quiet wakefulness, REM sleep is associated with increased sympathetic activation and reduced vagal tone in normal subjects and even more so in patients with OSA (17–19). Most endocrine organs releasing hormones involved in glucose regulation are sensitive to changes in sympathovagal balance. Well-documented examples relevant to

metabolic risk are pancreatic insulin secretion, hepatic glucose production, and adipocyte regulation of energy balance (25–27). In addition, peptidergic factors originating from the intestine (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide) augment the insulin response induced by nutrients. The secretion of these incretin hormones is intimately linked to autonomous nervous system (28–30).

However, it is important to point out that the impact of OSA on sympathetic activation in patients with type 2 diabetes of long duration remains unclear and that long-standing hyperglycemia may lead to reduction in sympathetic activity. Lastly, obstructive apneas and hypopneas during REM sleep lead to greater degrees of hypoxemia than in NREM sleep (21,22). In the present cohort, REM ODI was indeed much greater than NREM ODI.

Intermittent hypoxemia has been shown to be toxic to β-cell function in murine models of sleep apnea (31,32).

The findings from our analyses strongly suggest that REM-related obstructive respiratory events are of clinical significance for the severity of type 2 diabetes. Two recent studies that performed continuous interstitial glucose monitoring simultaneously with PSG directly support our hypothesis that REM-related OSA may have adverse metabolic consequences (33,34). One of these studies included 13 obese patients with type 2 diabetes with severe OSA and compared them with 13 obese patients with type 2 diabetes without OSA with similar demographic characteristics. Although there was no difference in the mean diurnal glycemic level between the two groups, the mean glycemic level was 38% higher during REM sleep in those with OSA (33). The second study included 11 nondiabetic subjects. They found that in the absence of OSA, REM sleep leads to a larger decline in interstitial glucose concentration than NREM sleep. OSA during REM sleep abolished the expected decline in interstitial glucose concentration. In contrast, OSA during NREM sleep had no impact on interstitial glucose concentrations (34). Taken together, the evidence from studies assessing interstitial glucose levels supports our finding that obstructive events during REM sleep are adversely associated with glucose metabolism.

While our participants did not meet any proposed definition of REM-related or REM-predominant OSA (35,36), our findings suggest that failure to recognize and treat OSA in REM sleep may be of critical clinical significance for glycemic control in diabetic patients. In clinical practice, 4 h of nightly CPAP use is considered adequate adherence to therapy (37). Indeed, a randomized controlled trial of CPAP therapy in patients with type 2 diabetes reported an average use of 3.6 h per night (16). The severity of residual OSA was not estimated. The disappointing results of CPAP trial in type 2 diabetes may reflect the failure to treat REM OSA due to insufficient CPAP use, leaving most obstructive events during REM sleep untreated. Alternatively, there may be other factors beyond poor CPAP

adherence that led to a lack of improvement in glycemic control such as a poor reserve in β-cell function. Our analyses show that based on the distribution of cumulative REM sleep in our cohort, CPAP therapy for the first 4 h after lights off would leave 60% of obstructive events during REM sleep untreated and would be associated with a decrease in the adjusted HbA_{1c} by only 0.25–0.28%. In contrast, 7 h of optimal CPAP therapy would be associated with a decrease in the adjusted HbA_{1c} by 0.87–1.1%.

Our study has several limitations. First, we used HbA_{1c}, the most commonly used measure in clinical practice, to assess glycemic control. Therefore, we cannot ascertain whether the mediating pathways linking REM AHI to HbA_{1c} involve increased insulin resistance or impaired β-cell function. Moreover, we only measured HbA_{1c} at a single time point, which was not consistently on the same day as PSG. However, treatment was stable for the preceding 3 months in all participants, and HbA_{1c} was measured on the morning after the PSG in 98 out of 115 participants (85%). Although HbA_{1c} reflects glycemic control 10 to 12 weeks before the assay, it mostly reflects glucose fluctuations during the last 6 weeks of the measurement. Despite our efforts to ensure treatment stability in the prior 3 months, we cannot exclude the possibility that fluctuations in adherence to medications may have influenced HbA_{1c} levels. Our study did not assess associations between REM OSA and glucose control in subjects with prediabetes or normal glucose tolerance. We also had a large proportion of African Americans and subjects requiring little or no antidiabetic medications. Therefore, it would be important for our findings to be replicated in larger and more diverse cohorts, including participants with more diabetes complications and/or longer disease duration as well as individuals with prediabetes or with normal glucose tolerance but at high risk for type 2 diabetes. Also, we did not have a measure of habitual sleep duration, which may be important in evaluating chronic exposure to REM OSA, and our only measure of adiposity

was the BMI. Lastly, the cross-sectional nature of the study does not address the direction of causality. Indeed, only rigorously designed intervention studies will provide causal evidence between disordered breathing during REM sleep and glucose metabolism dysregulation.

In summary, our findings support the notion that OSA in REM sleep has a strong and clinically significant association with glycemic control in subjects with type 2 diabetes. Since REM sleep is dominant during the latter part of the sleep period, REM-related OSA may often remain untreated with 4 h of CPAP use. Our analyses suggest that to achieve clinically significant improvement in glycemic control in patients with type 2 diabetes, CPAP use may need to be extended beyond 6 h per night. Further research is needed to elucidate the mechanistic pathways linking OSA during REM sleep and adverse metabolic outcomes.

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