Independent Association Between Obstructive Sleep Apnea Severity and Glycated Hemoglobin in Adults Without Diabetes

Pascaline Priou, md[1,2]
Marc Le Vaillant, phd[3]
Nicole Meslier, md[1,2]
Sylvaine Chollet, md[4]
Philippe Masson, md[5]
Marie P. Humeau, md[6]

Thierry Pigeanne, md[7]
Acya Bizieux-Thaminy, md[8]
François Goupil, md[9]
Frédéric Gagnadoux, md, phd[1,2]
The IRSR Sleep Cohort Group*

OBJECTIVE—We tested the hypothesis of an independent cross-sectional association between obstructive sleep apnea (OSA) severity and glycated hemoglobin (HbA_{1c}) in adults without known diabetes.

RESEARCH DESIGN AND METHODS—HbA_{1c} was measured in whole-blood samples from 2,139 patients undergoing nocturnal recording for suspected OSA. Participants with self-reported diabetes, use of diabetes medication, or HbA_{1c} value $\geq$6.5% were excluded from this study. Our final sample size comprised 1,599 patients.

RESULTS—A dose-response relationship was observed between apnea-hypopnea index (AHI) and the percentage of patients with HbA_{1c} >6.0%, ranging from 10.8% for AHI <5 to 34.2% for AHI $\geq$50. After adjustment for age, sex, smoking habits, BMI, waist circumference, cardiovascular morbidity, daytime sleepiness, depression, insomnia, sleep duration, and study site, odds ratios (95% CIs) for HbA_{1c} >6.0% were 1 (reference), 1.40 (0.84–2.32), 1.80 (1.19–2.72), 2.02 (1.31–3.14), and 2.96 (1.58–5.54) for AHI values <5, 5 to <15, 15 to <30, 30 to <50, and $\geq$50, respectively. Increasing hypoxemia during sleep was also independently associated with the odds of HbA_{1c} >6.0%.

CONCLUSIONS—Among adults without known diabetes, increasing OSA severity is independently associated with impaired glucose metabolism, as assessed by higher HbA_{1c} values, which may expose them to higher risks of diabetes and cardiovascular disease.

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Obstructive sleep apnea (OSA) is a highly prevalent disease characterized by recurrent episodes of partial or complete obstruction of the upper airways during sleep, leading to repeated falls in arterial oxygen saturation (SaO_2) and sleep fragmentation. OSA is recognized as an independent risk factor for cardiovascular disease (1), including stroke (2), coronary heart disease, and heart failure (3). OSA and type 2 diabetes are common comorbid conditions (4). There is growing evidence in support of an independent association between OSA and impaired glucose metabolism (5). Studies in animal and human models mimicking sleep-disordered breathing have identified several potential intermediate mechanisms linking OSA and impaired glucose metabolism, including intermittent hypoxia (6,7) and reduced sleep duration as a result of sleep fragmentation (8). Impaired glucose metabolism may be involved in the pathogenesis of the cardiovascular complications of OSA (9). Glycated hemoglobin (HbA_{1c}) values reflect the 2- to 3-month average endogenous exposure to glucose, including postprandial spikes in the blood glucose level, and present low intraindividual variability, particularly in persons without diabetes. HbA_{1c} is superior to fasting blood glucose for assessment of the long-term risk of subsequent cardiovascular disease in nondiabetic middle-aged adults, especially at values above 6.0% (10). Furthermore, HbA_{1c} is similarly associated with the risk of diabetes as is fasting blood glucose (10). The aim of this multisite cross-sectional study was to evaluate the association between sleep-disordered breathing severity and HbA_{1c} in a large sample of patients without known diabetes investigated for suspected OSA.

RESEARCH DESIGN AND METHODS

Setting
This study was approved by the University of Angers ethics committee, and patients gave their written, informed consent. Between 15 May 2007 and 30 November 2011, HbA_{1c} was measured by the standard high-performance liquid chromatography method in 2,139 patients $\geq$18 years of age who were being investigated for suspected OSA in seven sites from the west of France collaborating in the Institut de Recherche en Santé Respiratoire des Pays de la Loire (IRSR) Sleep Cohort (see Supplementary Table 1 site identification) (11). Participants who had self-reported diabetes

or use of diabetes medication (n = 411) and those with HbA$_{1c}$ values ≥6.5% (n = 129) were excluded from this study. Our final sample size comprised 1,599 patients (475 females, 29.7%). The numbers of patients recruited by each study site were as follows: 618 (38.7%) for site 1, 294 (18.4%) for site 2, 165 (10.3%) for site 3, 171 (10.7%) for site 4, 156 (9.8%) for site 5, 107 (6.8%) for site 6, and 88 (5.5%) for site 7.

Questionnaires and sleep studies

Each patient enrolled in the IRSR Sleep Cohort completed surveys including anthropometric data, smoking habits, medical history of cardiovascular disease (patients were classified as having cardiovascular morbidity if they reported at least one of the following: known and treated hypertension, ischemic heart disease, cardiac arrhythmia, congestive heart failure, and stroke), depression (as defined by ≥7 positive items on the 13-item version of the Pichot depression scale [12] or self-reported use of antidepressant medication), excessive daytime sleepiness (as defined by an Epworth Sleepiness Scale [13] score >10), and complaints of insomnia. Waist circumference (WC) was measured in centimeters with a nonelastic measuring tape. OSA severity was assessed by the apnea-hypopnea index (AHI) measured by overnight polysomnography (n = 563) or overnight respiratory recording (n = 1,036). Overnight polysomnography was performed with continuous recording of the following channels: electroencephalogram, electro-oculogram, chin electromyogram, Sa$_{O_2}$ (finger oximetry), nasal-oral airflow (pressure cannula), electrocardiogram, chest and abdominal wall motion (piezoelectrodes), bilateral tibialis electromyogram, and body position. Overnight respiratory recordings were performed with continuous recording of Sa$_{O_2}$, nasal-oral airflow, chest and abdominal wall motion, and body position. Respiratory events were scored manually according to recommended criteria (14). Apnea was defined as cessation of airflow for ≥10 s. Hypopnea was defined as a ≥50% reduction of airflow or a <50% reduction of airflow accompanied by a ≥3% decrease in Sa$_{O_2}$ or followed by an arousal when OSA was diagnosed by overnight polysomnography.

Statistical analysis

All statistical analyses were performed with SAS software (SAS/STAT Package 2002–2003; SAS Institute Inc., Cary, NC). Characteristics of the study population were determined according to categories of AHI, with standard methods used to calculate mean values and SDs. *P* values for linear trends across AHI categories were calculated by simple linear regression for continuous variables and by the Cochran-Armitage trend test for dichotomous variables.

The primary outcome variable was HbA$_{1c}$. A dichotomous logistic regression procedure was used to model the associations between indices of sleep-disordered breathing and the odds of having an HbA$_{1c}$ value >6.0% rather than an HbA$_{1c}$ value ≤6.0%. This cutoff was applied in a recent well-documented study evaluating HbA$_{1c}$ as an independent predictor of subsequent cardiovascular disease in nondiabetic middle-aged adults (10). Unadjusted and multivariable-adjusted odds ratios (95% CIs) according to sleep-disordered breathing severity for having an HbA$_{1c}$ value >6.0% were calculated. The primary independent variables included the AHI and three different indices of nocturnal hypoxemia (mean Sa$_{O_2}$ during sleep, 3% oxygen desaturation index, and percentage of time with Sa$_{O_2}$ <90%). The following commonly used cutoffs for AHI were used to define categories of disease severity: <5 (no OSA), 5 to <15 (mild OSA), 15 to <30 (moderate OSA), 30 to <50 (severe OSA), and ≥50 (very severe OSA). These cutoffs have been previously applied in a number of studies on OSA and are of clinical value. For other physiologic indices of severity of sleep-disordered breathing, the study sample was grouped into quartiles of the variable. To adjust for potential confounders, the following covariates were entered in the multivariable model: age, sex, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia, total sleep time (TST), and study site. Because TST values were available for only 563 patients, this variable was entered in the model according to discrete modalities (<300 min, ≥300 min, or unavailable). Adjustment for study site was performed with a generalized estimating equation model (15). The independent association between OSA severity and HbA$_{1c}$ was also analyzed by multiple linear regression analysis. A two-tailed *P* value of <0.05 was considered significant.

RESULTS—A dose-response relationship was observed between AHI and percentage of patients with HbA$_{1c}$ >6.0% from 10.8% for AHI <5 to 34.2% for

AHI ≥50 (Table 1). Patients with elevated AHI were also more likely to be older and male and to have higher BMI, WC, and fasting glucose and more frequent cardiovascular morbidities. In contrast, no link was observed between AHI categories and smoking habits, Epworth Sleepiness Scale score, TST, and rates of depression and insomnia. As shown in Table 2, a positive and significant linear trend was observed for the odds of HbA$_{1c}$ >6.0% with increasing AHI. Although the strength of the association was attenuated with multivariable adjustment, the linear trend in the odds of HbA$_{1c}$ >6.0% with increasing AHI remained highly significant after adjustments for age, sex, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia, TST, and study site (Table 2). We further investigated the associations between three different indices of nocturnal hypoxemia and HbA$_{1c}$. As shown in Table 3, increasing hypoxemia during sleep was independently associated with the odds of HbA$_{1c}$ >6.0%. A positive and significant linear trend in the odds of HbA$_{1c}$ >6.0% with decreasing mean Sa$_{O_2}$ and increasing 3% oxygen desaturation index and time spent with Sa$_{O_2}$ <90% was observed after adjustment for age, sex, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia, TST, and study site (Table 3). Multiple linear regression analysis confirmed an independent association between HbA$_{1c}$ and OSA severity as assessed by AHI or nocturnal hypoxemia indices (see Supplementary Table 2).

CONCLUSIONS—A recent well-documented study indicated that nondiabetic adults with HbA$_{1c}$ values of 6.0 to less than 6.5% are at high risk for development of diabetes, coronary heart disease, and ischemic stroke after adjustment for confounding variables and independent of baseline fasting blood glucose (10). In this large cross-sectional study, we have demonstrated that patients without known diabetes presenting moderate to very severe OSA are at higher risk for HbA$_{1c}$ exceeding 6.0% after adjustment for confounding factors.

Previous studies investigating the relationship between OSA severity and HbA$_{1c}$ in patients with diabetes have shown conflicting results (16,17). A previous study examined the correlation between sleep-disordered breathing and HbA$_{1c}$ in 31 nondiabetic men with newly

Table 1—Characteristics of the study participants according to AHI

	AHI <5	5 ≤AHI <15	15 ≤AHI <30	30 ≤AHI <50	AHI ≥50	P for trend¶
n	203	320	352	417	307	
Age (years)	48.7 ± 13.0	53.6 ± 12.2	56.5 ± 12.7	58.6 ± 11.8	58.2 ± 12.9	<0.0001
Females (%)	46.8	35.3	26.7	25.7	21.5	<0.0001
Current smokers (%)	21.2	21.3	17.1	16.1	22.8	0.39
BMI (kg/m^2)	26.8 ± 5.9	28.3 ± 5.6	29.0 ± 6.5	30.6 ± 5.6	33.7 ± 6.5	<0.0001
WC (cm)	95.2 ± 15.2	100.3 ± 14.4	100.9 ± 14.9	106.4 ± 14.0	115.4 ± 15.4	<0.0001
ESS score	10.2 ± 5.2	10.0 ± 5.1	10.0 ± 4.8	10.3 ± 4.9	10.3 ± 5.0	0.44
Depression (%)†	33.0	27.5	26.7	26.9	29.0	0.22
CV morbidity (%)‡	23.2	34.8	36.1	45.1	51.1	<0.0001
Insomnia (%)	20.7	23.7	24.2	21.1	18.9	0.15
TST (minutes)#	399 ± 85	423 ± 71	409 ± 81	410 ± 73	413 ± 72	0.82
Mean Sa$_{O2}$ (%)	94.8 ± 1.6	94.1 ± 1.7	93.7 ± 1.6	93.0 ± 1.8	91.1 ± 2.8	<0.0001
3% ODI	3.9 ± 10.0	8.9 ± 11.4	17.2 ± 12.6	28.4 ± 12.9	55.6 ± 22.7	<0.0001
Time with Sa$_{O2}$ <90% (%)	1.4 ± 4.8	3.7 ± 10.4	5.2 ± 10.7	11.4 ± 16.4	27.6 ± 22.3	<0.0001
Fasting glucose (mmol/L)	5.2 ± 0.6	5.4 ± 0.6	5.4 ± 0.7	5.5 ± 0.7	5.6 ± 0.7	<0.0001
HbA$_{1c}$ (%)	5.6 ± 0.3	5.6 ± 0.3	5.7 ± 0.3	5.7 ± 0.4	5.8 ± 0.3	<0.0001
HbA$_{1c}$ >6.0% (%)	10.8	15.0	19.0	23.5	34.2	<0.0001

Data are expressed as means ± SD except as indicated. CV, cardiovascular; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index. †Depression was defined by ≥7 positive items on the 13-item version of the Pichot depression scale (12) or self-reported use of antidepressant medication. ‡Patients were classified as having cardiovascular morbidity if they reported at least one of the following: known and treated hypertension, ischemic heart disease, cardiac arrhythmia, congestive heart failure, and stroke. #Data available for 563 patients. ¶Tested by simple linear regression for continuous variables and by the Cochran-Armitage trend test for dichotomous variables.

diagnosed severe OSA (mean AHI 55 ± 26) (18). The authors found a significant correlation between HbA$_{1c}$ levels and apnea-related parameters independent of BMI. The generalizability of previous studies investigating the association between OSA and HbA$_{1c}$ (16–18) may be in question, however, because of a number of methodologic limitations, including limited sample size and lack of adjustment for numerous confounding cofactors that may contribute to glucose metabolism impairment, such as daytime sleepiness (19), depression (20), insomnia (21), smoking habits, and comorbidities. Because daytime sleepiness, depression and insomnia complaints are common in patients with OSA (22), these factors need to be taken into account as potential confounding factors. By including a large sample of patients and numerous confounding covariates, our study has overcome many of these methodologic limitations and provides strong support for an independent cross-sectional association between OSA severity and HbA$_{1c}$. Evidence from a recently published randomized, double-blind, placebo-controlled trial supports the hypothesis of a deleterious effect of OSA on glucose metabolism (23). In 86 patients with moderate to severe OSA, of whom 41 (48%) had no history of diabetes, continuous positive airway presser treatment (vs. sham treatment) for 3 months was associated with a significant decrease in mean HbA$_{1c}$ (23).

The potential mechanisms linking OSA and alterations in glucose metabolism are likely to be multiple. Both chronic intermittent hypoxia and sleep fragmentation could potentially be detrimental to glucose metabolism through intermediate mechanisms, including activation of the sympathetic nervous system, hypothalamic-pituitary axis, and inflammatory pathways (5,24). Support for the hypothesis that hypoxia may be an etiologic factor for impaired glucose metabolism comes from experimental data in humans (6) and animal models (7,25). Intermittent hypoxia resulted in insulin resistance in both genetically obese (25) and lean (7) mice. In healthy subjects, hypoxia acutely induced glucose intolerance and increased plasma epinephrine concentration (6). Our findings that indices of sleep-related hypoxemia are independently related to HbA$_{1c}$ provide additional evidence that nocturnal hypoxia is involved in the relationship between OSA and impaired glucose metabolism.

We acknowledge a number of limitations of this study. One potential limitation of this study is that OSA was diagnosed by either polysomnography or respiratory recording. The accuracy of respiratory recording during sleep for the diagnosis of OSA has been demonstrated for a long time (26), and recent randomized studies have concluded that respiratory recordings are not clinically inferior

Table 2—Odds ratios for HbA$_{1c}$ >6% according to AHI categories

AHI categories	Unadjusted odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
AHI <5	1	1
5 ≤AHI <15	1.48 (0.93–2.36)	1.40 (0.84–2.32)
15 ≤AHI <30	1.99 (1.35–3.92)	1.80 (1.19–2.72)
30 ≤AHI <50	2.58 (1.79–3.71)	2.02 (1.31–3.14)
AHI ≥50	4.35 (2.54–7.46)	2.96 (1.58–5.54)
P for linear trend¶	<0.0001	<0.0001

†Odds ratios were adjusted for age, sex, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia, TST, and study site. Because TST values were available for only 563 patients, this variable was entered in the model according to discrete modalities (<300 min, ≥300 min, or unavailable). ¶Tested by the Cochran-Armitage trend test.

Table 3—Adjusted odds ratios* for HbA_1c >6% according to nocturnal SaO_2

Variable	Odds ratio (95% CI)
Mean SaO_2 (%)	
≥95	1
94.0–94.9	1.39 (1.23–1.57)
92.0–93.9	1.57 (1.14–2.16)
<92	1.97 (1.30–2.99)
P for linear trend¶	<0.0001
3% oxygen desaturation index	
≤7	1
7.1–18.0	1.26 (0.93–1.71)
18.1–36.0	1.39 (1.02–1.90)
>36	1.94 (1.41–2.66)
P for linear trend¶	<0.0001
Time with SaO_2 <90% (%)	
<0.1	1
0.1–2.3	1.59 (1.23–2.07)
2.4–13	1.55 (1.12–2.16)
>13	2.54 (1.56–4.44)
P for linear trend¶	<0.0001

*Odds ratios after adjustment for age, sex, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia, TST, and study site. Because TST values were available for only 563 patients, this variable was entered in the model according to discrete modalities (<300 min, ≥300 min, or unavailable). ¶Tested by the Cochran-Armitage trend test.

to standard polysomnography in patients with a high pretest probability for OSA (27,28). We also acknowledge that sleep recording analysis and HbA_1c assays were performed locally in this study; however, adjustment for study site in the regression model did not modify the magnitude of the association between AHI and HbA_1c. Therefore, we do not believe that differences in HbA_1c measurement or sleep recording analysis between sites could have influenced our results. Because of the cross-sectional design of this study, it cannot be determined whether OSA preceded high HbA_1c. A recent prospective study found that high insulin levels preceded observed apneas (29). As acknowledged by that study's authors (29), however, observed apnea reported by the subject is a crude and nonobjective measure of OSA. In a previous study including 205 consecutive patients undergoing polysomnography (30), observed apnea as reported by the participants had positive and negative predictive values for OSA of only 64 and 53%, respectively. Another potential

limitation is that our study was performed in a clinic-based sample. It can be hypothesized that the severity of sleep-disordered breathing and comorbidities may influence the association between OSA and HbA_1c. To the best of our knowledge, no published study has evaluated the association between OSA severity and HbA_1c in the context of a "healthy" checkup in a primary care population. Nevertheless, our findings are in accordance with those of a population-based study demonstrating an independent association between sleep-disordered breathing severity and impaired glucose metabolism in nondiabetic healthy subjects (31). Furthermore, this multisite study can be assumed to describe a "typical" pattern of patients with OSA, because it included a large sample of patients with a wide range of disease severity. Self-reported diabetes as a tool to exclude diabetes may also be subject to bias. An oral glucose tolerance test would probably have revealed diabetes or at least impaired glucose tolerance in some patients of our cohort who self-reported the absence of diabetes (32); however, it would have been very difficult to perform an oral glucose tolerance test in the large sample of this multisite study. Furthermore, we also excluded patients with HbA_1c level ≥6.5%, which is now recognized as a valid cutoff to diagnose diabetes (33). Altogether, our findings and those of previous studies (17,18,34) indicate that the association between OSA severity and impaired glucose metabolism is exerted across the continuum of glucose homeostasis irrespective of the presence of diabetes.

In conclusion, among adults without known diabetes, increasing OSA severity is independently associated with impaired glucose metabolism, as assessed by higher HbA_1c values, which may expose them to higher risks of diabetes and cardiovascular disease.

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