Nocturnal Hypoxemia Causes Hyperglycemia in Patients With Obstructive Sleep Apnea and Type 2 Diabetes Mellitus

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ABSTRACT

Background: Our purpose was to investigate the relationship between oxygen saturation (SpO_2) and dynamic interstitial glucose level (IGL) in patients with obstructive sleep apnea (OSA) along with type 2 diabetes mellitus (T2DM), and to investigate the potential mechanisms thereof.

Materials and Methods: A total of 130 patients with OSA and T2DM underwent polysomnography and oral glucose tolerance tests at the Sleep Medicine Center. Using the lowest (L) SpO_2% tested, patients were divided into mild, moderate and severe $LSpO_2$ groups. Polysomnography and continuous glucose monitoring systems were used to analyze the altered pattern of SpO_2 and dynamic IGL in the 3 groups.

Results: $LSpO_2$ during sleep in patients with OSA and T2DM stimulated an increase in IGL. The moderate and severe levels were represented by IGL_{45} and IGL_{30}, respectively. The average nocturnal and peak IGL after $LSpO_2$ in the severe group were significantly higher than in the mild and moderate groups. Stepwise multiple regression analysis showed that the body mass index ($\beta = 0.301$, $P < 0.001$), homeostatic model assessment of insulin resistance ($\beta = 0.260$, $P < 0.001$), apnea-hypopnea index ($\beta = 0.309$, $P < 0.001$), average SpO_2 ($\beta = -0.423$, $P = 0.008$), $LSpO_2$ ($\beta = -0.369$, $P < 0.001$) and microarousal index ($\beta = 0.335$, $P = 0.044$) were probably related to nocturnal IGL in patients with OSA along with T2DM.

Conclusions: Severe and moderate OSA with T2DM is marked by a delayed IGL peak following $LSpO_2$. Nocturnal hypoxemia causes hyperglycemia in patients with OSA along with T2DM.

Key Indexing Terms: Obstructive sleep apnea; Type 2 diabetes mellitus; Polysomnography; Continuous glucose monitoring.
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INTRODUCTION

According to the International Diabetes Federation (2010) estimates, 285 million people worldwide suffer from diabetes, and the number is expected to rise to 438 million in 20 years.[1] Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, resulting in arterial hypoxemia and sleep fragmentation. OSA is the most common sleep-related breathing disorder, affecting an estimated 1.0-5.0% of adult men and 1.0-2.0% of adult women.[2] The condition is predominantly seen in overweight and obese individuals. Prevalence of OSA in obese adults (aged 30-69 years) ranges from an estimated 11-46% in women and 33-77% in men.[3]

A growing body of evidence supports the association between OSA, obesity, insulin resistance, glucose intolerance and the subsequent development of type 2 diabetes mellitus (T2DM).[2,4-7] Elderly and obese men are known to be at a higher risk for the development of OSA as well as T2DM.[3] Cross-sectional estimates from clinical and population studies suggest that up to 40% of patients with OSA have diabetes,[8] but the incidence of new-onset diabetes in patients with OSA is unknown. Similarly, the reported prevalence rates of OSA in diabetic populations range from 23-86%.[9] The interaction of obesity and T2DM with OSA is expected to cause tremendous public health burden. Observational studies suggest that glycemic control is worse in patients with diabetes and OSA.[10,11] In a study of 26 overweight and obese individuals with T2DM, nocturnal glycemia (as assessed by a continuous glucose monitoring sensor [CGMS]) was found to be 38% higher in those with OSA compared with those without the disorder, independent of body mass index (BMI).[12] However, the underlying pathophysiological mechanisms that link OSA to T2DM are still unclear. The mechanisms of hyperglycemia attributed to nocturnal hypoxia and the altered glucose levels in decreased oxygen saturation (SpO_2) are unknown. Additional studies with rigorous assessments of T2DM and OSA are needed.

The objective of our study was to define the prevalence of OSA and OSA with T2DM in Gansu Province,

China. We also investigated the relationship between SpO_2 variation and dynamic interstitial glucose levels (IGL) in OSA with T2DM by performing CGM combined with synchronous polysomnography (PSG), and determined the potential mechanisms of interaction between the 2 conditions.

SUBJECTS AND METHODS

Study Design

In this cross-sectional study, baseline data were divided into mild (lowest [L] SpO_2: 85-90%, $n = 30$), moderate ($LSpO_2$: 80-85%, $n = 49$) and severe ($LSpO_2 < 80\%$, $n = 51$) hypoxemia groups as monitored by PSG (Philips Respironics, Bend, OR). Synchronous PSG and the MiniMed CGMS (Medtronic, Northridge, CA) were used to analyze the relationship between altered SpO_2 and continuous nocturnal IGL in the 3 groups. The data were matched 2 hours after the $LSpO_2$.

Setting and Subjects

All participants, both outpatients and inpatients, were consecutively enrolled from the Sleep Medicine Center in Gansu Province, China, and treated at Gansu Provincial Hospital from February 2011-February 2013. The study protocol was approved by the Regional Ethics Committee of the hospital, and all the patients provided written (signed) informed consent. Only patients with T2DM and OSA, who had stable daytime glucose levels were included in the study. Patients were admitted at 8.00 am for a sleepiness scale assessment and to collect general clinical data, followed by CGMS. The SpO_2 and biochemical parameters were evaluated after overnight PSG monitoring from 9:00 pm-8:00 am. The diagnostic criteria of OSA and T2DM are given later.

Definitions

Apnea was defined as $\geq$90% reduction in baseline nasal airflow lasting at least 10 seconds. Hypopnea was defined as a 50-90% decrease in the pre-event baseline of nasal airflow lasting $\geq$10 seconds accompanied by at least a 3.0% decrease in SpO_2 or an arousal or both. OSA was defined by an apnea-hypopnea index (AHI) $\geq$ 5 events/h. Scoring rules were in accordance with the *American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events* (2007).[13] Hypoxemia was defined by an $LSpO_2 < 90\%$. Mild, moderate and severe hypoxemia was defined by an $LSpO_2$ of 85-90%, 80-85%, and $\leq$80%, respectively.[14]

T2DM was defined according to the guidelines of the American Diabetes Association and the World Health Organization. The current standard criteria for the diagnosis of T2DM are as follows: (1) hemoglobin A1c (HbA1c) $\geq$ 6.5%, (2) fasting plasma glucose (FPG) $\geq$ 126 mg/dL, (3) 2-h PG $\geq$ 200 mg/dL in an oral glucose tolerance test (OGTT) or (4) random PG $\geq$ 200 mg/dL in a patient with classic symptoms of hyperglycemia.[15]

The time of the first $LSpO_2$ was found using PSG. In total, 2 hours of CGMS data were intercepted and the values of IGL every 15 minutes (totally 8 points) were abstracted (IGL_x; $x = 15, 30, 45, 60, 75, 90, 105$ and 120 minutes). The peak IGL after $LSpO_2$ was defined as the first highest IGL after $LSpO_2$ during sleep. Nocturnal sleep duration was defined as the interval from the time the patient fell asleep to the time when the patient woke up according to the PSG. The average IGL during sleep was calculated according to every IGL point value downloaded from the CGMS results during nocturnal sleep time.

Anthropometry and Laboratory Measurements

Following PSG monitoring, the general clinical demographics including age, sex, smoking habits, alcohol consumption, duration of snoring, history of T2DM, history of antidiabetic treatment, complications including hypertension (HT), coronary heart disease, cerebral infarction, diabetic retinopathy (DR), diabetic nephropathy and diabetic peripheral neuropathy were collected. Systolic blood pressure, diastolic blood pressure, body height and weight, neck circumference and waist and hip circumference were measured. The BMI was calculated as the ratio of weight (kg) and height squared (m^2), and the waist-to-hip ratio (WHR) was calculated as the ratio of waist-to-hip circumference.

Epworth Sleepiness Scale[16] and Pittsburgh Sleep Quality Index[17] were used for subjective assessment of sleep efficiency and latency.

Venous blood samples were used to measure glycosylated HbA1c, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs) and fasting insulin (FINS) FPG. Blood samples were collected from subjects fasting from 8:00 pm until 8:00 am the next day. Instantaneous IGLs were monitored using guardian real-time CGMS (Medtronic, Northridge, CA) synchronizing with overnight PSG tests from 9:00 pm-8:00 am every 2 hours. Insulin resistance was derived using the homeostasis model assessment method and was calculated using the following formula: homeostatic model assessment of insulin resistance (HOMA-IR) = FINS (μIU/L) $\times$ FPG (mmol/L)/22.5.[18]

PSG was used as the reference standard for sleep and breathing registration and performed according to the *American Academy of Sleep Medicine Manual for Scoring of Sleep and Associated Events.*[13] All patients were monitored for at least 7 hours during an entire night's sleep. During the day, no drugs or stimulants such as caffeine, alcohol or tea and sedatives or hypnotics (eg, benzodiazepines), which might interfere with data monitoring were allowed. Sleep data were collected and scored using the Alice 5 Diagnostic Sleep System (Philips Respironics, Bend, OR). The

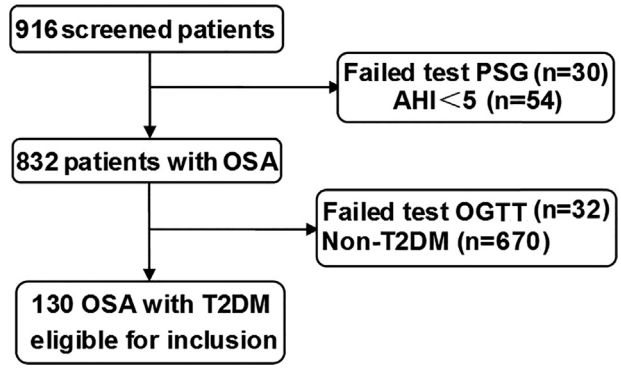

FIGURE 1. Flow chart outlining screening criteria of participants: initially, 84 patients were excluded because of a failed PSG or apnea-hypopnea index < 5 in PSG; 32 and 670 of those patients missed the oral glucose tolerance test (OGTT) or were non–type 2 diabetics (T2DM), respectively. The remaining 130 patients with obstructive sleep apnea (OSA) and T2DM were included in the current analysis.

measurements included an electroencephalogram (F4-M1, C4-M1, O2-M1, F3-M2, C3-M2 and O1-M2), bilateral electro-oculography, electrocardiography, electromyography (submental and anterior tibialis) l oral airflow (transducer and nasal cannula), rib cage and abdominal movements and measurements obtained from an arterial SpO_2 sensor on the left index finger. The subjects' sleep pattern at the Sleep Center was scheduled to match their habitual sleep schedule.

Statistical Analyses

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). The results are presented as the mean ± standard deviation or the proportion (%). The Kolmogorov-Smirnov test was used to determine the normal distribution of data. Skewed variables were transformed using natural logarithms before statistical analyses. Differences in clinical variables among mild, moderate and severe hypoxemia groups were assessed using analysis of variance followed by Tukey's posthoc test or the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. The average IGL_x in the 3 groups was calculated and the increased IGL after $LSpO_2$ was determined by comparison. Pearson correlation coefficients were calculated to determine the relationship between average IGL during sleep and sleep apnea–related variables. Stepwise multiple regression analysis was used to identify factors that contributed to average IGL during sleep. A value of $P < 0.05$ was considered the threshold of statistical significance.

RESULTS

Patient Screening

A total of 916 patients were screened for participation in this study, excluding those with diseases that might lead to hypoxia, such as severe cardiovascular or respiratory disease, central nervous system disease and mental disorders. Of these patients, 84 were excluded for failing the PSG ($n = 30$) or AHI < 5 ($n = 54$), and 702 were dropped because of missing OGTT ($n = 32$) or non-T2DM ($n = 670$). Finally, 130 (15.6%) patients with OSA and T2DM were included in the current analysis (Figure 1). All subjects were newly diagnosed with both OSA and T2DM.

Clinical Demographics and Biochemical Profile

Clinical demographics and biochemical characteristics of the 130 patients with OSA and T2DM based on nocturnal $LSpO_2$ (mild, moderate and severe hypoxemia groups) levels during sleep are listed in Table 1. Compared with the mild hypoxemia group, prolonged snoring ($P = 0.034$, 0.029) and T2DM ($P = 0.047$, 0.038), higher FPG ($P = 0.024$, 0.017) and FINS ($P = 0.011$, 0.009) and more serious insulin resistance (HOMA-IR, $P = 0.001$, 0.001) were found in the moderate and severe groups, respectively. Comorbid conditions, such as HT ($\chi^2 = 5.060$, $P = 0.018$), coronary heart disease ($\chi^2 = 3.230$, $P = 0.045$), CI ($\chi^2 = 3.579$, $P = 0.033$) and DR ($\chi^2 = 4.074$, $P = 0.038$), were more prevalent in the severe group than in the mild group. There were no significant differences among groups regarding sex, age, smoking, BMI, neck circumference, WHR, systolic blood pressure, diastolic blood pressure, TC, LDL-C, HDL-C, TG, HbA1c, DR or diabetic peripheral neuropathy ($P > 0.05$) (Table 1).

Differences in Sleep-Related Parameters

The differences in PSG values of subjects in different groups are shown in Table 2. Compared with the mild hypoxemia group, higher mixed apnea index (MAI) ($P = 0.035$, 0.021) and AHI ($P = 0.018$, 0.010) were found in the moderate and severe groups, respectively. Compared with the mild and

TABLE 1. Clinical demographics and biochemical profile.

Variables	Patients with OSA along with T2DM: $LSaO_2$ (%)			*P* Value
	Mild (85-90)	Moderate (80-85)	Severe (<80)	
n	30	49	51	0.074
Sex (Men/Women)	18/12	30/19	37/14	0.056
Age (years)	56.68 ± 12.43	53.38 ± 13.61	54.71 ± 10.82	0.328
Snoring (months)	168.78 ± 74.61	255.96 ± 80.55[a]	240 ± 59.21[a]	0.063
T2DM (months)	91.26 ± 39.89	124.42 ± 54.62[a]	132.22 ± 13.82[a]	0.059
Smokers (%)	53.8	56.4	56.8	0.239
Self-evaluation				
ESS	11.72 ± 1.13	11.22 ± 1.30	11.06 ± 1.03	0.324
PSQI	10.61 ± 1.29	10.69 ± 1.17	11.17 ± 0.97	0.311
Anthropometric measures				
BMI (kg/m^2)	27.35 ± 2.08	28.80 ± 2.44	29.55 ± 2.15	0.236
Neck (cm)	40.63 ± 1.30	40.27 ± 0.96	40.44 ± 1.05	0.127
Waist-to-hip ratio	0.92 ± 0.03	0.92 ± 0.06	0.93 ± 0.06	0.064
Blood pressure (mm Hg)				
SBP	136.73 ± 12.91	139.22 ± 14.14	139.05 ± 14.74	0.014
DBP	86.47 ± 7.03	85.21 ± 10.47	87.22 ± 7.63	0.038
Biochemical indicators				
TC (mmol/L)	4.59 ± 0.77	4.43 ± 1.23	4.54 ± 1.57	0.327
LDL-C (mmol/L)	3.07 ± 0.91	3.13 ± 0.92	3.83 ± 0.97	0.129
HDL-C (mmol/L)	1.31 ± 0.51	1.23 ± 0.22	1.23 ± 0.38	0.071
TG (mmol/L)	2.23 ± 0.48	2.32 ± 1.59	2.60 ± 2.86	0.213
FPG (mmol/L)	6.89 ± 0.53	9.37 ± 1.42[a]	11.87 ± 1.59[a]	<0.001
FINS (μIU/L)	7.07 ± 2.17	14.38 ± 19.05[a]	14.78 ± 5.9[a]	<0.001
HOMA-IR	2.15 ± 0.63	5.83 ± 7.38[a]	6.53 ± 3.19[a]	<0.001
HbA1c (%)	9.01 ± 1.59	10.09 ± 1.98	10.69 ± 2.11	0.027
Comorbidities (%)				
HT	66.1	67.3	76.7[a,△]	<0.001
CHD	24.6	28.8	33.0[a,△]	0.021
CI	12.4	13.2	16.9[a,△]	<0.001
DR	30.4	34.2	38.6[△]	0.099
DN	39.5	39.9	43.0[a,△]	0.041
DPN	10.7	10.1	11.8	0.187

Data are presented as either the mean ± standard deviation or proportions (%) unless stated otherwise. CHD, coronary heart disease; CI, cerebral infarction; DBP, diastolic blood pressure; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; ESS, Epworth Sleepiness Scale; Neck, neck circumference; PSQI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure; waist-to-hip ratio, waist circumference to hip circumference ratio. Statistical analyses: analysis of variance (ANOVA, continuous variables), χ^2 test (categorical variables).

[△]Compared with moderate; $P \leq 0.05$, statistically significant difference.

[a] Compared with mild.

moderate hypoxemia group, lower CT90 ($P = 0.027$, 0.049) and less N3 ($P = 0.039$, 0.045) were observed in the severe group, respectively. There were no significant differences among groups regarding rapid eye movement, N1, N2 and average SpO2 ($P > 0.05$) (Table 2).

Nocturnal Average IGL

The average level of nocturnal IGL during sleep in the severe (235.7 mg/dL) hypoxemia group was significantly higher than in the mild (114.6 mg/dL, $P = 0.022$) and moderate (159.4 mg/dL, $P = 0.038$) groups. Although there was no obvious difference between the mild and moderate groups, the *P* value was still 0.057 (Figure 2A). The average peak nocturnal IGL during sleep after $LSpO_2$ in the severe (276.2 mg/dL) hypoxemia group was significantly higher than in mild (136.8 mg/dL, $P = 0.008$) and moderate (175.4 mg/dL, $P = 0.045$) groups. However, there was no significant difference between the mild and moderate groups ($P = 0.089$) (Figure 2B).

TABLE 2. Differences in sleep-related parameters.

Variables	Patients with OSA along with T2DM: $LSaO_2$ (%)			*P* Value
	Mild (85-90)	Moderate (80-85)	Severe (<80)	
n	30	49	51	0.074
REM (%)	16.4 ± 9.3	11.7 ± 7.6	10.9 ± 5.3	0.251
N1 (%)	8.3 ± 2.1	10.5 ± 3.5	10.4 ± 3.7	0.185
N2 (%)	59.1 ± 7.8	65.6 ± 6.9	69.6 ± 9.8	0.055
N3 (%)	16.2 ± 12.1	12.2 ± 14.3	9.1 ± 13.9[a,b]	0.067
MAI (per hour)	26.8 ± 9.9	35.3 ± 7.2[a]	41.9 ± 20.1[a,b]	0.005
AHI (per hour)	25.9 ± 2.3	33.1 ± 9.4[a]	46.1 ± 19.1[a,b]	0.003
Average SpO_2 (%)	91.4 ± 6.3	89.4 ± 12.1	86.7 ± 12.8	0.296
SLT90 (%)	22.8 ± 13.0	26.3 ± 18.2	39.6 ± 22.1[a,b]	0.065

Data are presented as either the mean ± standard deviation. Average SpO2, average oxygen saturation; N1, percentage of N1; N2, percentage of N2; N3, percentage of N3; REM, percentage of rapid eye movement; SE, sleep efficiency; SLT90, the time percentage of oxygen saturation less than 90%; Statistical analyses: analysis of variance (ANOVA, continuous variables).

[a] Compared with mild.

[b] Compared with moderate; $P \leq 0.05$, statistically significant difference.

Changing Pattern of Nocturnal IGLs at 15-Min Iintervals

No significant differences were seen in the 15 IGL_x values in the mild hypoxemia group, even though IGL_{60} (134.3 mg/dL) tended to increase after $LSpO_2$. Compared with other IGL_x data in the moderate and severe groups, IGL_{45} (208.4 mg/dL) and IGL_{30} (251.2 mg/dL) were the highest time points in moderate and severe groups, respectively (Figure 3A). In a typical severe case, the IGL level increased after approximately 0.5 hours of $LSpO_2$ during sleep matched for the PSG and CGMS IGL curve (Figure 3B).

Correlation and Stepwise Multiple Regression Analysis of Sleep Variables and Nocturnal IGLs

In this study, obesity and sleep-related variables—BMI, neck circumference, WHR, FPG, FINS, HOMA-IR, TC, LDL-C, HDL-C, TG, HbA1c, AHI, longest apnea-hypopnea time, sleep structure, average SpO_2, MAI and $LSpO_2$—were analyzed using Pearson's correlation analysis. A significant correlation was found between the nocturnal average IGL and obesity variables, such as BMI ($r = 0.2646$, $P < 0.001$), HOMA-IR ($r = 0.2627$, $P = 0.007$), HbA1c ($r = 0.2376$, $P = 0.005$) and MAI ($r = 0.6091$, $P = 0.007$). There were significant correlations between nocturnal average IGL during sleep and sleep apnea variables, such as AHI ($r = 0.7338$, $P < 0.001$), average SpO_2 ($r = -0.7531$, $P = 0.011$) and $LSpO_2$ ($r = -0.7895$, $P < 0.001$). In the stepwise multiple regression analysis of variables that showed significance in Pearson's correlation analysis, BMI ($\beta = 0.301$, $P < 0.001$), HOMA-IR ($\beta = 0.260$,), AHI ($\beta = 0.309$, $P < 0.001$), average SpO_2 ($\beta = -0.423$, $P = 0.035$), $LSpO_2$ ($\beta = -0.369$, $P < 0.001$) and MAI ($\beta = 0.335$, $P = 0.044$) were most likely related to nocturnal average IGL during sleep in patients with OSA along with T2DM (Table 3).

DISCUSSION

In the present study, patients afflicted with OSA along with T2DM were divided into mild, moderate and

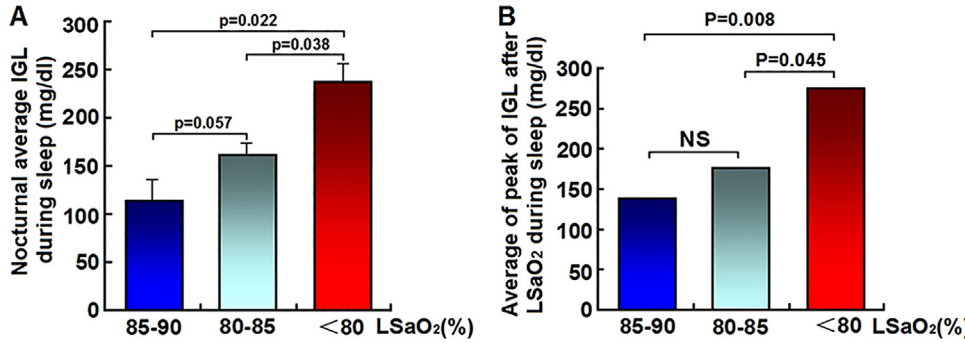

FIGURE 2. A, Differences in the nocturnal average interstitial glucose levels (IGLs) during sleep under a range of oxygen saturation levels ($LSpO_2$). B, Differences among the 3 groups in the average peak nocturnal IGLs under a range of oxygen saturation levels. Blue represents mild hypoxemia defined as $LSpO_2$: 85-90%, green represents moderate hypoxemia defined as $LSpO_2$: 80-85% and red represents severe hypoxemia defined as $LSpO_2 < 80\%$.

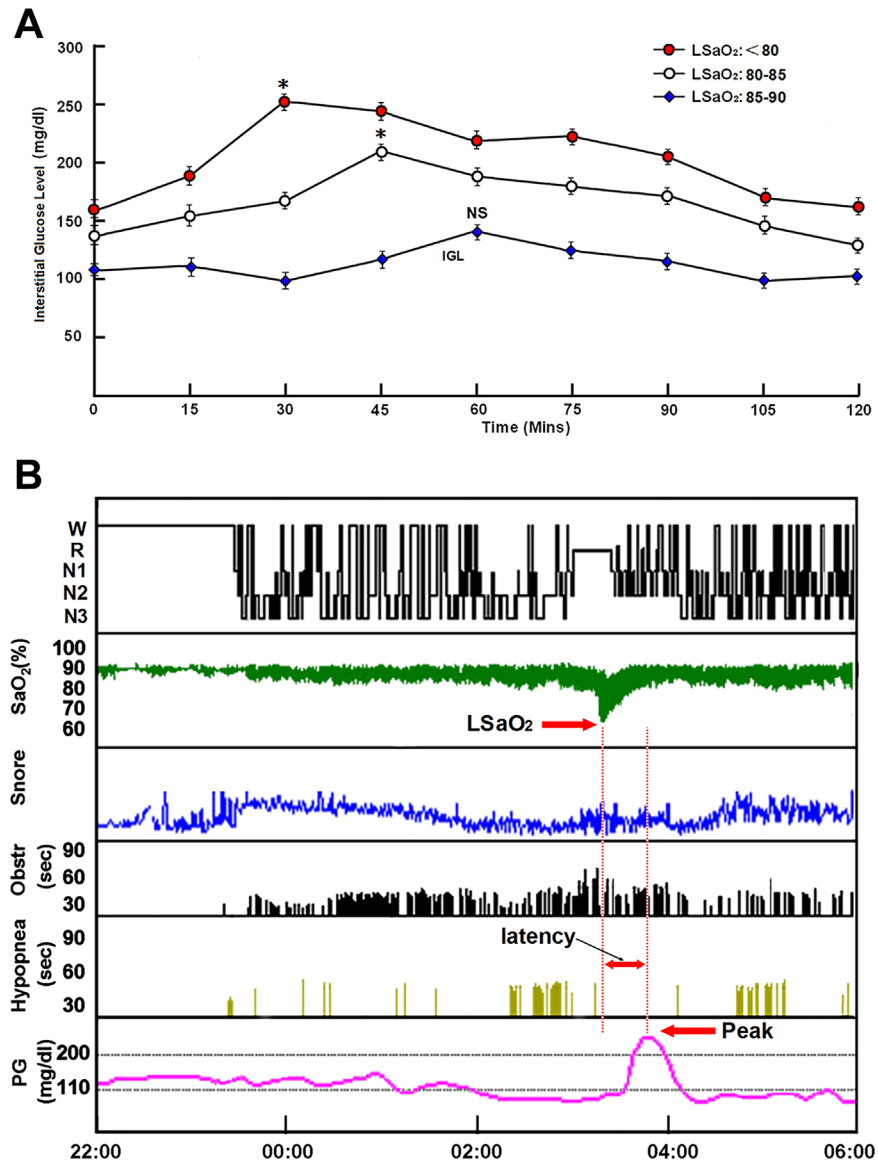

FIGURE 3. A, Nocturnal average IGL_x for 2.0 h in the mild, moderate and severe groups, respectively. Blue represents mild hypoxemia defined as the lowest oxygen saturation ($LSpO_2$): 85-90%, green represents moderate hypoxemia defined as $LSpO_2$: 80-85% and red represents severe hypoxemia defined as $LSpO_2 < 80\%$. B, Overnight IGL of matched polysomnography (PSG) and continuous glucose monitoring system (CGMS) in severe obstructive sleep apnea (OSA) with type 2 diabetes mellitus (T2DM): synchronous PSG and CGMS result from 8:00 pm-8:00 am in a typical patient with OSA along with T2DM belonging to the severe hypoxemia group (*), compared with IGL_x.

severe groups according to $LSpO_2$. The average nocturnal IGL and average peak nocturnal IGL during sleep in the severe hypoxemia group were significantly higher than in the mild and moderate groups. Stepwise multiple regression analysis revealed that BMI, HOMA-IR, AHI, average SpO_2 and $LSpO_2$ were most likely related to the nocturnal IGL in OSA with T2DM. Finally, the altered pattern of severe and moderate OSA with T2DM groups was represented by a delayed peak of IGL appearing after $LSpO_2$.

Nocturnal Hypoxemia Causes Hyperglycemia in OSA With T2DM

According to an epidemiological survey, OSA is closely related to glucose metabolic disorders and diabetes, which are highly prevalent, especially in obese people.[8] Up to 83% of patients with T2DM suffer from unrecognized OSA, and the increased severity of OSA is associated with worsening glucose control. Other OSA studies demonstrated that IR and T2DM incidence was much higher in patients without OSA. In 1,387 patients

TABLE 3. Stepwise multiple regression analysis of sleep apnea variables and nocturnal average IGL.

Variables	Nocturnal average IGL			
	Correlation coefficient (*r*)	*P* Value	Regression coefficient (*β*)	*P* Value
BMI	0.2646	<0.001	0.301	<0.001
HOMA-IR	0.2627	0.007	0.260	0.008
AHI	0.7338	<0.001	0.309	<0.001
HbA1c	0.2376	0.005	0.018	0.832
Average SpO_2	−0.7531	0.011	−0.423	0.035
$LSpO_2$	−0.7895	<0.001	−0.369	<0.001
MAI	0.6091	0.007	0.335	0.044

Data are provided as correlation coefficient (*r*) using Pearson's correlation analysis and as regression coefficient (*β*) using stepwise multiple regression analysis. *P* Value indicates statistically significant difference.

from a Wisconsin series of studies,[19] it was found that AHI and the average night SpO_2 were associated with elevated fasting glucose levels. A sleep heart-health study found that SpO_2 was associated with a significant increase in fasting and OGTT 2.0-h blood glucose levels, and OSA severity was associated with the degree of insulin resistance.[20,21] OSA was characterized by inflammation, intermittent hypoxia, recurrent sleep arousals and sleep fragmentation, increased airway resistance causing sympathetic stimulation and systemic oxidative stress. It suggests that nocturnal intermittent hypoxia played a key role in nocturnal hyperglycemia in our patients. Sympathetic stimulation results in the release of stress hormones and catecholamines, which are known to decrease insulin sensitivity and reduce glucose tolerance. In addition, altered corticotrotropic and somatotropic functions increase circulating adipocytokines, which alter glucose metabolism.[22] In OSA, there is excessive release of catecholamines and cortisol during sleep, causing a disorder similar to Cushing's disease. The nocturnal elevation in cortisol and catecholamine secretions can also spillover into the day (spillover effect) resulting in fasting hyperglycemia. In such cases, 2.0-h OGTT is essential if postprandial blood glucose levels are normal. In fact, fasting hyperglycemia raises the suspicion of sleep disordered breathing—OSA. Daytime sleepiness in patients with OSA is reflected in the development of obesity resulting from a lack of physical activity. Patients are too tired and sleepy to participate in physical activities. In addition, exercise against a background of hypoxemia and elevated catecholamines can precipitate cardiovascular events.

OSA-related variables such as AHI, average SpO_2 and $LSpO_2$ were shown to be independently related to nocturnal IGL in patients with OSA along with T2DM in stepwise multiple regression analysis. A study reported that apnea-hypopnea duration and nocturnal hypoxemia duration with oxyhemoglobin saturation <90% were longer in the elderly group compared with those in the young and adult groups.[23] Multiple regression analyses of 275 men who underwent cross-sectional health examinations in Japan revealed that the respiratory disturbance index was independently related to FPG levels only in diabetic subjects. In patients with diabetes, after adjustment for age, waist circumference and other factors, sleep fragmentation had a greater correlation with FPG than sleep duration, but without any significance ($P = 0.10$). Owing to the extremely high prevalence of OSA in patients with diabetes, sufficient sleep duration and OSA treatment, which ameliorates sleep fragmentation, might improve FPG levels.[1] Another cohort study demonstrated that severe undiagnosed OSA and nocturnal hypoxemia were independently associated with the development of diabetes. The burden of undiagnosed OSA and undiagnosed diabetes is likely to decrease if patients are assessed for both disorders.[24]

This study supports the need to assess correction of hypoxemia as a management strategy for glycemic control.

Lowest SPO_2 During Sleep in OSA With T2DM

CGMS is an accurate method to assess nocturnal glucose fluctuations and glucose stability. CGMS in the present study revealed an altered pattern in severe (IGL_{30}) and moderate (IGL_{45}) OSA with T2DM with a delayed peak of IGL following $LSpO_2$. Several studies have shown that blood glucose levels in patients with T2DM change greatly during the entire day. For example, high blood glucose levels during the day decrease greatly from 1:00-6:00 am.[25] Several studies have shown differences in blood glucose level according to circadian changes in OSA with T2DM when compared with the general patients with T2DM who have significantly higher glucose levels.[26] Patients with OSA along with T2DM with severe nocturnal hypoxemia manifest increased glucose levels. Intermittent hypoxemia leads to altered blood sugar levels at night. The sympathetic nervous system, systemic oxidative stress and inflammation cause a significant rise in blood glucose levels. Different latency periods are needed under various degrees of hypoxia, which leads to the release of stress hormones and catecholamines. Therefore, the altered OSA pattern in T2DM is reflected by a delayed peak of IGL following the LSpO2.

Interestingly, the severity of hypoxemia is related to the time to reach IGL peak (severe: 30 minutes; moderate: 45 minutes and mild: 60 minutes). The patients with severe hypoxemia have a shorter latency period to IGL peak than mild and moderate groups. Noctural SpO2 decreased to its lowest point in hypoxia, resulting in catecholamine-induced inflammation and oxidative stress.[22,27,28] The increased blood glucose level and insulin resistance may lead to nocturnal hyperglycemia, which stimulates insulin secretion by B cells, with appropriate latency. Serious hypoxemia activates any of the foregoing events, with increased latency to peak IGL levels following shorter LSpO2 (severe: 30 minutes; moderate: 45 minutes and mild: 60 minutes). Activation of these events was attenuated by hypoxemia leading to transient decrease in IGL. Therefore, nocturnal IGL fluctuations in patients with T2DM afflicted with OSA is designated as "glycemic excursion." A lower SpO_2 is associated with shorter latency to peak IGL.

Correlation With Average Nocturnal IGL

It is well known that BMI plays a key role in the pathophysiologic mechanism of OSA, obesity and T2DM. We found similar correlation between BMI and nocturnal IGL in patients with OSA along with T2DM. There is a strong relationship between OSA and obesity —approximately 70% of patients with OSA are obese.[29] Obesity-related subcutaneous and periluminal fat deposits might alter the compliance of upper airway walls and narrow the luminal area, thus increasing the likelihood of airway collapse when exposed to the intraluminal negative pressure caused by inspiration.[30] In addition, sleep privation resulting from OSA-induced stress plays a role in the development of obesity. Sleep-deprived subjects are sleepy during the day and have a tendency to overeat and to eat quickly. Food intake in various forms helps the sleep-deprived subject to overcome daytime sleepiness. Chronic sleep restriction coupled with eating contributes to the development of obesity.[31] Therefore, the problem of obesity in patients with OSA seems to be a vicious cycle that increases the probability of hyperglycemia.

It is well known that there is a positive correlation between HOMA-IR and FPG in patients with T2DM. Similar correlation was shown in nocturnal IGL in patients with OSA along with T2DM. IR denotes the inability of insulin to elicit the usual biological response at circulating concentrations that are effective in normal subjects. In several studies, OSA was found to be independently associated with IR and glucose intolerance.[32,33] More recently, Punjabi and Beamer[6] estimated IR in 118 nondiabetic adults using a frequently sampled intravenous GTT. The authors found that compared with normal individuals, those with mild, moderate and severe OSA showed a 26.7%, 36.5% and 43.7% decrease in insulin sensitivity, respectively, after controlling for age, sex, race and percentage body fat. In most studies, AHI and the frequency as well as the degree of intermittent hypoxia were commonly used indices for OSA severity. On the other hand, a plausible scenario is that the sympathetic overactivity resulting from OSA leads to increased catecholamine release, which produces hyperglycemia and, in turn, hyperinsulinemia, which promotes IR.

The following features suggest that OSA is closely linked to T2DM: (1) strong association with obesity; (2) men; (3) postmenopausal women; (4) systemic effects, such as HT and diabetes and (5) increase in OSA with advancing age, with the peak being 40-49 years for men and 50-59 years for postmenopausal women. Several possible mechanistic pathways might explain how OSA contributes to the development of T2DM. These mechanisms are related to intermittent hypoxia, increased oxidative stress and disturbances associated with concomitant sympathetic activation and sleep fragmentation.[34] Overall, several mechanisms, either alone or in concert, lead to the development of T2DM.

LIMITATIONS

The strengths of the present study include the relatively large number of subjects with a high prevalence of abnormal glucose tolerance and OSA, thereby combining 3 profoundly interrelated medical conditions. Using full PSG to monitor the sleep and breathing parameters, including data pertaining to sleep stages, were extremely helpful in distinguishing sleep and non-sleep OSA. The method used to classify OSA has been confirmed in several studies. Our single-center cross-sectional study had limitations of community and regional representation, without any randomization and with restricted sampling. Finally, our subjects were patients with OSA along with T2DM. Therefore, our results do not represent an accurate assessment of hypoxemia in OSA with T2DM compared with the control.

CONCLUSIONS

Patients with altered pattern of severe and moderate OSA with T2DM are represented by a delayed IGL peak following the $LSpO_2$. BMI, AHI, HOMA-IR, average SpO_2 and $LSpO_2$ are the major risk factors associated with the altered nocturnal IGL in OSA with T2DM. Nocturnal hypoxemia triggers hyperglycemia in these patients. Our study supports the need to correct hypoxemia as a management strategy for glycemic control.

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