

Obstructive Sleep Apnea Exacerbates Glucose Dysmetabolism and Pancreatic β -Cell Dysfunction in Overweight and Obese Nondiabetic Young Adults

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Purpose: This study aimed to investigate the effects of obstructive sleep apnea (OSA) on the pancreatic β -cells dysfunction and their implications in the glucose dysmetabolism of overweight and obese nondiabetic young adults.

Materials and Methods: The cross-sectional analysis included 422 subjects (261 males/161 females) with the mean age of 27.77 ± 7.51 years and average body mass index (BMI) of 34.84 ± 5.69 kg/m². All subjects underwent polysomnography (PSG), oral glucose tolerance-insulin releasing test (OGTT-IRT) and serum glycosylated hemoglobin A1c (HbA1c) measurement. The glucose metabolism and pancreatic β -cell function in relation to measures of OSA were determined adjustment for important confounders such as age and sex.

Results: OSA subjects accounted for 54.91% in the normal glucose tolerance (NGT) group and 72.11% in the prediabetes (preDM) group ($P = 0.001$). HbA1c was the highest in the preDM subjects with severe OSA. In the NGT subjects, the 1-h glucose level significantly elevated with the OSA severity, and the homeostasis model assessment- β (HOMA- β) was negatively related to nocturnal mean SpO₂ ($P < 0.05$). In the preDM subjects, HOMA- β , early phase insulinogenic index ($\Delta I_{30}/\Delta G_{30}$), total area under the curve of insulin in 180 min (AUC-I₁₈₀), and the oral disposition index (DI_O) were the lowest in the severe OSA group. DI_O was associated with higher oxygen desaturation index (ODI) and lower nocturnal mean SpO₂, and AUC-I₁₈₀ was negatively related to TS90 ($P < 0.05$).

Conclusion: Our study indicated higher prevalence of OSA in overweight and obese nondiabetic young adults, especially preDM subjects. The impaired glucose tolerance was observed early after glucose intake in the NGT subjects. OSA induces compensatory increase in the pancreatic β -cell function in the NGT subjects, while pancreatic β -cell dysfunction is present in the preDM subjects with severe OSA.

Keywords: obstructive sleep apnea, obesity, nondiabetes, glucose tolerance, pancreatic β -cell function

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Introduction

Type 2 diabetes (T2DM) has been a major health problem worldwide and its prevalence increases in the developing Asian countries,¹ particularly China.² Currently, the incidence of T2DM in young adults is dramatically increasing worldwide and is strongly associated with the rise of obesity.^{3,4} Subjects are classified as young-onset T2DM if they were diagnosed with T2DM <45 years.^{3,5} The risk for

the development of micro- and macrovascular complications is much higher in T2DM diagnosed <45 years compared to T2DM diagnosed >45 years.^{4,5} Obstructive sleep apnea (OSA) is a common sleep disorder, affecting 17% of the total population and 40–70% of the obese population.⁶ The prevalence of OSA has increased over the past two decades, and is even higher than 50% in some countries,⁷ due to the increases in the age and body mass index (BMI).⁸ Obesity is the most important risk factor for OSA, and both obesity and OSA are high-risk factors for glucose dysmetabolism.⁹ Despite a large variety of epidemiologic and clinical evidence suggests that OSA is an independent risk factor for T2DM,⁸ whether the association is due to OSA mediated changes in glucose metabolism or simply reflects an association with obesity is not well understood among overweight and obese adults aged <45 years.^{6,10}

Hyperglycemia, a state of prediabetes (preDM), is a high-risk state for diabetes and can be further subdivided into isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and a combination of both (IFG/IGT).^{1,11} American Diabetes Association (ADA) expert panel estimates that 70% of preDM subjects will ultimately develop T2DM.¹² Insulin resistance (IR) and pancreatic β -cell dysfunction are two major risk factors in the pathogenesis of preDM and T2DM.¹³ The β -cell dysfunction with progressive loss of pancreatic β -cell insulin secretion are key defects associated with the transition from a healthy glycemic state to hyperglycemia,¹⁴ which has been observed in high-risk individuals long before the presence of hyperglycemia.¹⁵ The development of diabetic hyperglycemia in young adults seems to be more strongly dependent on β -cell failure than in older patients.⁴ While previous studies have proposed that sleep apnea can increase IR and deteriorate insulin sensitivity, little is known about the OSA-related alterations of pancreatic β -cell secretion function, especially in nondiabetic young adults.^{8,13}

The ADA and American Association of Clinical Endocrinologists (AACE) recommend preDM testing in adults younger than 45 years with BMI greater than or equal to 25 kg/m.^{4,16} Lifestyle modification and pharmacotherapy are important for the prevention and treatment of both preDM and T2DM,^{12,17} but the effect of continuous positive airway pressure (CPAP) therapy on overall glycemic control remains contradictory.¹⁸ Hence, this study was to investigate the glucose dysmetabolism and pancreatic β -cell dysfunction in the normal glucose

tolerance (NGT) and preDM subjects in overweight and obese states from 18 to 45 years. Moreover, the effects of OSA on the pancreatic β -cell dysfunction and their implications in the glucose dysmetabolism were further explored, which may provide evidence about the role of OSA in the management of diabetes among overweight and obese young adults.

Materials and Methods

Study Sample

This study was a cross-sectional analysis performed between September 2009 and December 2017 at the Sleep Disorders Center of Ruijin Hospital, Shanghai Jiao Tong University. Our study sample included overweight and obese subjects aged 18 to 45 years. We excluded subjects without standard oral glucose tolerance test – insulin releasing test (OGTT-IRT) and clinical examinations. The demographic characteristics, smoking status, and medical history were recorded for each subject. The BMI was calculated by dividing weight by the squared height (kg/m^2), and we combined the definition of overweight or obesity as $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ according to the World Health Organization criteria.¹⁹ The smokers referred to those regularly consuming 10–20 cigarettes/day for at least 3 years.²⁰ The subjects had no history of sleep disorders other than OSA (e.g. central sleep apnea syndrome, restless leg syndrome, narcolepsy, etc.), previous treatments for OSA (e.g. CPAP, surgery and oral device, etc.), neural-muscular diseases, type 1 diabetes or other endocrine disorders, T2DM treated with glucose-lowering drugs or insulin, liver or pancreatic diseases, alcohol abuse, malignancies, pregnancy, hypoxemic lung diseases, acute and/or chronic infections, autoimmune diseases, and current treatment with anti-inflammatory drugs (such as corticosteroids, non-steroid anti-inflammatory drugs, and immunosuppressive agents, etc.). The postmenopausal women and those with definite or suspected polycystic ovary syndrome (PCOS) based on hyperandrogenemia were also excluded. The study was approved by the Ethics Committee of Ruijin Hospital ([2018] No.107) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Polysomnographic Evaluation

The PSG (Alice 5, Philips Respironics, Pennsylvania, USA) channels included four electroencephalogram

(EEG), submental electromyogram (EMG), two electroculogram (EOG; right and left), and two electrocardiography (ECG) channels, pulse oxygen saturation, oral and nasal airflow, nasal air pressure, thoracic-abdominal respiratory movement, snoring microphone, and body position channels. Only edited records with more than 4 h of good-quality signals were included for further analysis. Apnea was defined as a respiratory event with a drop in the nasal airflow by $\geq 90\%$, and hypopnea as a drop in peak signal excursions by $\geq 30\%$ of pre-event baseline using nasal pressure for at least 10 s with a $\geq 4\%$ oxygen desaturation from pre-event baseline.²¹ Based on the apnea-hypopnea index (AHI), participants were divided into three groups: control group (AHI: < 5), mild-to-moderate OSA group (AHI: 5–29.9) and severe OSA group (AHI: ≥ 30) groups.²² The oxygen desaturation index (ODI) is a measure of the number of times per hour that oxygen saturation decreases per hour, which was defined as the total number of at least 4% oxygen desaturations per total sleep time in hours.^{23,24} The mean oxygenation saturation (mean SpO₂) was defined as the mean pulse oxygen saturation during the sleep period at night. The percentage of sleep duration with SpO₂ $< 90\%$ (TS90) and lowest nocturnal oxygen saturation (LSpO₂) were also determined as previously reported.²²

OGTT-IRT

All the subjects underwent a standard 75-g OGTT-IRT test on the second day after overnight fast. Baseline blood samples were obtained at 0 min. Subsequent blood samples were collected at 30 min, 1 hr, 2 hrs and 3 hrs after taking 75 g of glucose within 5 mins immediately. The OGTT-IRT was designed to assess insulin secretory patterns under physiological conditions while capturing the complex interrelationship between glucose levels and insulin action.^{14,25} Routine glucose-oxidase assay (CX-7 Biochemical Autoanalyzer; Beckman, Brea, California, USA) and electrochemiluminescence immunoassay (Cobas e601 immunoassay analyzer, Roche Diagnostics, Indianapolis, Indiana, USA) were used to measure plasma glucose and serum insulin levels, respectively. Glycosylated hemoglobin A1c (HbA1c) was determined from high-performance liquid chromatography (VARIANT II Hemoglobin Testing System, Bio-Rad Laboratories, Hercules, California, USA). Based on the OGTT, the serum glucose was categorized as follows:^{1,11} (1) normal glucose tolerance (NGT): fasting glucose < 6.1

mmol/L and 2-h glucose < 7.8 mmol/L. (2) impaired fasting glucose (i-IFG): fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L, and 2-h glucose < 7.8 mmol/L. (3) impaired glucose tolerance (i-IGT): fasting glucose < 6.1 mmol/L, and 2-h glucose ≥ 7.8 mmol/L and < 11.1 mmol/L. (4) IFG combined with IGT (IFG/IGT): fasting glucose ≥ 6.1 mmol/L and < 7.0 mmol/L, and 2-h glucose ≥ 7.8 mmol/L and < 11.1 mmol/L. Pre-DM was defined as either i-IFG, i-IGT or IFG/IGT.

For the evaluation of baseline insulin sensitivity, homeostasis model assessment-IR (HOMA-IR) was calculated as fasting insulin \times fasting glucose/22.5. The hyperinsulinemia was defined as fasting insulin ≥ 12.2 μ U/mL, and insulin resistance as HOMA-IR ≥ 2.5 .²⁶ To assess the baseline insulin secretion of pancreatic β cells, homeostasis model assessment- β (HOMA- β) was calculated as fasting insulin $\times 20$ /(fasting glucose $- 3.5$).²⁷ To assess the first-phase (early) insulin secretion after the oral glucose load, 0–30 min insulinogenic index was measured during the OGTT as the difference in the insulin concentration between 30 min and 0 min divided by the difference in the glucose concentration between 30 min and 0 min ($\Delta I_{30}/\Delta G_{30}$).²⁵ The total area under the curve of insulin in 180 min (AUC-I₁₈₀) was calculated the insulin curve by the trapezoidal rule during the OGTT from 0 min to 180 min, expressing the second-phase insulin secretion after the oral glucose load.^{14,28} Lastly, oral disposition index (DI_O) can indicate a compromised ability of β -cells to compensate for peripheral insulin sensitivity,²⁵ which can predict the development of diabetes.²⁷ It was calculated as the product of $10,000/[(\text{fasting insulin} \times \text{fasting glucose}) \times (G \times I)]^{1/2}$ and $\text{AUC-I}_{120}/\text{AUC-G}_{120}$. G and I represent the mean glucose level and mean insulin level at the 4 former time points during the OGTT, respectively. AUC-I₁₂₀ and AUC-G₁₂₀ were calculated with the trapezoidal rule and used in the insulin and glucose curve during the OGTT from 0 min to 120 min.^{25,28} Therefore, pancreatic β -cell function was assessed by HOMA- β , $\Delta I_{30}/\Delta G_{30}$, AUC-I₁₈₀, and DI_O during the OGTT in our study.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (Statistical Product and Service Solutions Inc., USA). Demographic and clinical characteristics of subjects were summarized, and compared between NGT group and pre-DM group. Continuous variables are expressed as mean \pm standard deviation (SD) for data with normal distribution or median with 25–75%

interquartile range (IQR) for those with abnormal distribution; categorical variables are expressed as percentages (%). Comparisons between NGT and pre-DM groups were done with *t*-test and Wilcoxon/Mann–Whitney test for normally and abnormally distributed continuous variables, respectively. Chi-square test was used to examine the differences among categorical variables. To evaluate the impact of OSA on HbA_{1c}, blood glucose tolerance, IR (HOMA-IR) and β -cell function (HOMA-B, $\Delta I_{30}/\Delta G_{30}$, AUC-I₁₈₀, and DI_O), comparisons were further done in three sub-groups divided based on AHI in NGT group or preDM group. One-way analysis of variance (ANOVA) was used to compare the means of normally distributed homoscedastic data among groups, followed by least significant difference (LSD) test between two groups. While for the quantitative data with heteroscedastic or abnormally distribution, Kruskal-Wallis *H*-test was performed. The partial correlation coefficients were applied to determine the association of PSG parameters with glucose

metabolism and β -cell function after adjusting for age and gender. A value of $P < 0.05$ was considered statistically significant.

Results

Clinical Characteristics and Glucose Metabolic Statuses

A total of 422 subjects (261 males/161 females) were fulfilled the enrollment criteria, and the average age was 27.77 ± 7.51 years. All the subjects were Chinese Han adults with the mean BMI of 34.84 ± 5.69 kg/m². Demographic and clinical characteristics are summarized in Table 1, and were compared between NGT group and pre-DM group. In these subjects, 275 (65.17%) subjects had NGT and 147 (34.83%) had preDM (7 with i-IFG, 114 with i-IGT and 26 with IFG/IGT). The preDM subjects were, on average, 3 years older (26.75 ± 7.05 vs. 29.68 ± 7.98 years, $P < 0.001$) than the NGT subjects. There were no marked differences between NGT group and preDM group in the sex, BMI and

Table 1 Basic Characteristics of Normal Glucose Tolerance and Prediabetes Groups

Variables	Total (n=422)	Glucose Tolerance		
		Normal Glucose Tolerance (n=275)	Prediabetes (n=147)	P value*
Age (years)	27.77 \pm 7.51	26.74 \pm 7.05	29.68 \pm 7.98	<0.001
Male gender, n (%)	261 (61.85)	177 (64.36)	84 (57.14)	0.146
BMI (kg/m ²)	34.84 \pm 5.69	34.64 \pm 5.50	35.22 \pm 6.03	0.318
Neck circumference (cm)	41.96 \pm 4.13	41.80 \pm 4.02	42.28 \pm 4.34	0.319
Smoking status, n (%)	43 (10.19)	29 (10.55)	14 (9.52)	0.741
OSA, n (%)	257 (60.90)	151 (54.91)	106 (72.11)	0.001
Severe OSA, n (%)	109 (25.83)	62 (22.55)	47 (31.97)	0.035
AHI (events/h)	7.70 (2.20–31.98)	6.00 (1.70–27.20)	11.20 (3.90–49.90)	0.001
ODI (events/h)	14.25 (4.73–41.63)	11.55 (3.88–30.15)	23.45 (6.43–62.48)	0.001
Mean SpO ₂ (%)	94.56 \pm 3.89	94.95 \pm 3.29	93.87 \pm 4.71	0.041
LSpO ₂ (%)	78.72 \pm 15.90	80.46 \pm 15.02	75.38 \pm 17.02	0.003
TS90 (%)	0.50 (0.00–6.35)	0.30 (0.00–3.23)	1.90 (0.10–17.00)	<0.001
HbA _{1c} (%)	5.61 \pm 0.59	5.48 \pm 0.51	5.87 \pm 0.65	<0.001
Fasting glucose (mmol/L)	5.17 \pm 0.59	4.99 \pm 0.43	5.50 \pm 0.70	<0.001
2-h glucose (mmol/L)	7.23 \pm 1.82	6.15 \pm 1.03	9.23 \pm 1.17	<0.001
Fasting insulin (mU/mL)	18.83 (12.45–26.30)	18.01 (12.09–25.28)	20.39 (13.63–27.87)	0.048
2-h insulin (mU/mL)	118.50 (68.81–185.15)	105.00 (61.59–157.90)	154.10 (95.21–269.10)	<0.001
HOMA-IR (μ U mol L ⁻²)	4.20 (2.71–6.10)	3.99 (2.62–5.82)	5.05 (3.09–6.93)	0.001
HOMA- β (IU/mol)	231.12 (157.71–340.98)	245.25 (168.33–356.43)	203.90 (136.74–327.85)	0.008
$\Delta I_{30}/\Delta G_{30}$ (IU/mol)	28.54 (17.06–46.53)	34.07 (21.07–53.07)	20.39 (10.42–31.08)	<0.001
AUC-I ₁₈₀ (μ U/mL h)	343.69 (241.47–510.93)	331.33 (236.64–480.28)	359.17 (246.20–560.19)	0.062
DI _O (L ² /mmol ²)	578.14 (434.76–717.85)	655.91 (542.36–806.56)	403.28 (316.25–537.81)	<0.001

Notes: Quantitative data are presented as mean \pm SD or median with inter-quartile range if variables were not normally distributed. *Normal glucose tolerance vs Prediabetes.

Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO₂, mean pulse oxygen saturation; LSpO₂, lowest pulse oxygen saturation; TS90, percent of total sleep time spent below 90% oxygen saturation; HbA_{1c}, glycosylated hemoglobin A_{1c}; HOMA-IR, homeostasis model assessment-insulin resistance; HOMA- β , homeostasis model assessment- β ; $\Delta I_{30}/\Delta G_{30}$, the early phase (0 min–30 min) insulinogenic index; AUC-I₁₈₀, total area under the curve of insulin in 180 minutes; DI_O, oral disposition index.

smoking status. The subjects with preDM had significantly higher AHI, ODI and TS90, while the mean SpO₂ and LSpO₂ were markedly lower than those with NGT ($P < 0.05$, Table 1). The overall prevalence of OSA was 60.9%. Compared with the NGT group, the odds ratio (OR) of OSA was 2.123 (95% CI, 1.379–3.269; $P = 0.001$) in the preDM group. There was also a significantly higher rate of severe OSA in the preDM group than in the NGT group ($P = 0.035$, Table 1). With the increase in the OSA severity, the proportion of NGT subjects declined while the prevalence of preDM increased significantly ($\chi^2 = 12.194$, $P = 0.002$; Figure 1). Then, the glucose metabolic state of preDM subjects was classified into i-IFG, i-IGT and IFG/IGT. The proportions of subjects with i-IFG and IFG/IGT were the highest in the severe OSA group, while the proportion of i-IGT subjects was the highest in the mild-to-moderate OSA group (Figure 2).

Glucose Tolerance

Subjects were subdivided into three subgroups based on AHI in order to further investigate the effects of OSA severity on the NGT and preDM, respectively. Baseline characteristics of included subjects are shown in Table 2. Results showed the advanced age, male gender and larger NC were closely related to the increased severity of OSA. BMI was similar among the three subgroups in both NGT group and preDM group. The serum HbA1c level was the highest in the severe OSA subjects, especially in the preDM group. The oral glucose tolerance curve showed the 30-min glucose and 1-h glucose levels were the highest in the severe OSA subjects with NGT, despite no significant differences in the HbA1c and fasting glucose levels

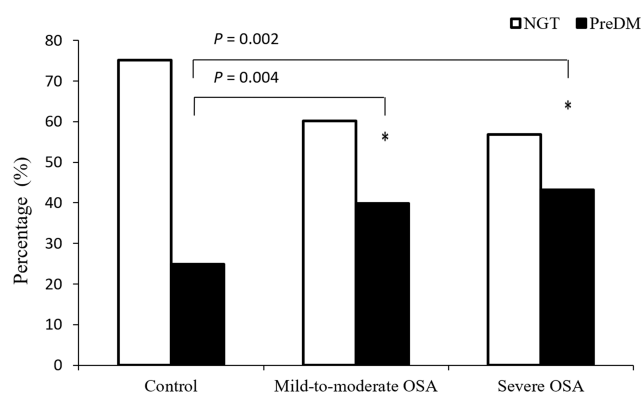


Figure 1 Percentage of subjects with different glucose metabolic statuses in different OSA severity groups. The glucose metabolic status was categorized into normal glucose tolerance (NGT) and prediabetes (pre-DM) according to the results from oral glucose tolerance test. * $P < 0.05$ vs. control group.

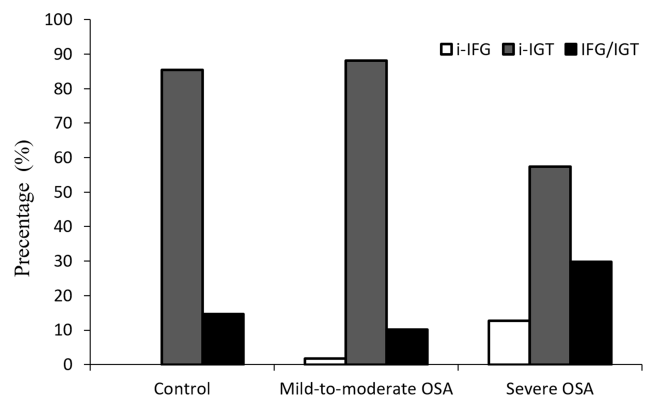


Figure 2 Percentage of subjects with different glucose metabolic statuses in different OSA severity groups among prediabetes subjects. The glucose metabolic status was categorized into isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and combination of both (IFG/IGT) according to the results from oral glucose tolerance test.

(Table 2). In the subjects with preDM, HbA1c and fasting glucose levels were significantly higher in the severe OSA group than those in the control and mild-to-moderate OSA groups ($P < 0.001$, Table 2). The preDM subjects with different severities of OSA had higher ODI and TS90 and lower LSpO₂ than the NGT subjects, while the levels of HbA1c, fasting glucose and post-load glucose in preDM subjects were significantly higher ($P < 0.05$, Table 2). Furthermore, the relationship between glucose dysmetabolism and OSA severity was determined using partial correlation analysis after adjusting for age and gender. As shown in Table 3, higher HbA1c level was associated with OSA parameters (AHI, ODI, mean SpO₂, LSpO₂ and TS90 during PSG) in both NGT ($P < 0.05$) and preDM subjects ($P < 0.01$). The partial correlation coefficients were higher in preDM subjects. In the NGT subjects, only 30-min and 1-h glucose levels were positively related to AHI and ODI, while negatively to LSpO₂ ($P < 0.01$, Table 3). In the preDM subjects, fasting glucose level was significantly related to all OSA parameters ($P < 0.05$, Table 3).

Pancreatic β -Cell Function

The majority of these overweight and obese young subjects had hyperinsulinemia and IR, especially in the preDM group, while the HOMA- β , $\Delta I_{30}/\Delta G_{30}$ and DI_O significantly declined in the preDM group than in the NGT group ($P < 0.01$, Table 1). The effect of OSA severity on the pancreatic β -cell dysfunction was further evaluated in both NGT and preDM groups, respectively. As shown in Table 2, insulin secretion parameters during OGTT, such as HOMA- β , $\Delta I_{30}/\Delta G_{30}$, and AUC-I₁₈₀, decreased with the increase of OSA

Table 2 Glucose Tolerance and Pancreatic β -Cell Function Among Subjects with Different Severities of OSA

Variables	Normal Glucose Tolerance			P value	Prediabetes			P value	P value ^a	P value ^b	P value ^c
	Control (n=124)	Mild-to-Moderate OSA (n=89)	Severe OSA (n=62)		Control (n=41)	Mild-to-Moderate OSA (n=59)	Severe OSA (n=47)				
Age (years)	24.35 ± 5.42	26.44 ± 7.02*	31.95 ± 7.30 ^{††}	<0.001	26.15 ± 6.61	28.49 ± 7.68	34.26 ± 7.44 ^{††}	<0.001	0.085	0.096	0.108
Male gender, n (%)	60 (48.39)	62 (69.66)*	55 (88.71) ^{††}	<0.001	15 (36.59)	33 (55.93)	36 (76.60) ^{††}	0.001	0.188	0.088	0.092
BMI (kg/m ²)	34.43 ± 4.12	35.20 ± 5.79	34.25 ± 7.24	0.495	34.56 ± 5.97	34.51 ± 5.45	36.68 ± 6.62	0.133	0.875	0.472	0.075
Neck circumference (cm)	40.87 ± 2.93	42.03 ± 4.48	43.21 ± 4.68*	0.002	39.86±4.18	41.71 ± 3.67*	44.96 ± 3.89 ^{††}	<0.001	0.232	0.683	0.068
Smoking, n (%)	6 (4.84)	9 (10.11)	14 (22.58) ^{††}	0.001	2 (4.88)	3 (5.08)	9 (19.15) ^{††}	0.024	0.992	0.273	0.664
AHI (events/h)	1.55 (0.70–2.60)	11.60 (7.60–17.30)*	58.10 (42.40–77.00) ^{††}	<0.001	1.50 (0.75–3.15)	10.60 (7.10–18.40)*	59.00 (51.00–83.60) ^{††}	<0.001	0.444	0.469	0.334
ODI (events/h)	4.25 (1.63–10.18)	12.90 (7.40–24.20)*	66.10 (45.60–83.45) ^{††}	<0.001	4.50 (3.10–12.10)	17.15 (6.70–32.58)*	71.70 (61.15–89.75) ^{††}	<0.001	0.296	0.123	0.243
Mean SpO ₂ (%)	96.54 ± 1.50	95.61 ± 2.18	91.61 ± 4.18 ^{††}	<0.001	96.68 ± 1.06	95.62 ± 1.86	89.93 ± 5.91 ^{††}	<0.001	0.890	0.861	0.210
LSpO ₂ (%)	88.56 ± 6.61	82.53 ± 8.95*	62.12 ± 17.85 ^{††}	<0.001	87.00 ± 6.68	81.00 ± 9.92*	58.90 ± 17.84 ^{††}	<0.001	0.143	0.329	0.303
TS90 (%)	0.00 (0.00–0.20)	0.30 (0.01–1.45)*	18.95 (4.95–37.13) ^{††}	<0.001	0.05 (0.00–0.35)	0.80 (0.10–2.80)*	25.70 (9.90–43.40) ^{††}	<0.001	0.118	0.199	0.171
HbA _{1c} (%)	5.45 ± 0.60	5.45 ± 0.38	5.62 ± 0.40	0.169	5.78 ± 0.56	5.65 ± 0.62	6.21 ± 0.66 ^{††}	<0.001	0.006	0.027	<0.001
Fasting glucose (mmol/L)	4.94±0.39	5.03 ± 0.46	5.03 ± 0.44	0.231	5.38 ± 0.61	5.29 ± 0.64	5.87 ± 0.72 ^{††}	<0.001	<0.001	0.008	<0.001
30-min glucose (mmol/L)	8.43 ± 1.18	8.67 ± 1.39	9.21 ± 1.38 ^{††}	0.001	9.98 ± 2.01	9.57 ± 1.42	10.15 ± 1.65	0.186	<0.001	<0.001	0.001
1-h glucose (mmol/L)	8.31 ± 1.71	8.92 ± 1.90*	9.53 ± 1.80 ^{††}	<0.001	11.44 ± 2.41	11.17 ± 1.80	11.89 ± 1.97	0.199	<0.001	<0.001	<0.001
2-h glucose (mmol/L)	6.15 ± 1.04	6.18 ± 1.03	6.12 ± 1.03	0.965	9.06 ± 0.97	9.39 ± 1.12	9.18 ± 1.38	0.368	<0.001	<0.001	<0.001

Fasting insulin (mU/mL)	18.43 (13.34–25.03)	19.21 (12.48–26.74)	15.81 (9.94–23.85)	0.386	21.99 (14.72–28.43)	19.29 (13.60–29.48)	19.95 (11.77–25.56)	0.776	0.169	0.406	0.091
2-h insulin (mU/mL)	109.80 (63.30–158.73)	103.60 (57.36–156.95)	109.15 (51.69–161.18)	0.891	172.70 (96.97–297.35)	184.60 (115.20–349.50)	112.40 (84.46–162.90) ^{††}	0.002	<0.001	<0.001	0.329
HOMA-IR ($\mu\text{U mol}\cdot\text{L}^{-2}$)	4.01 (2.84–5.76)	4.13 (2.68–6.17)	3.46 (2.31–5.32)	0.258	5.38 (3.11–6.73)	4.15 (2.98–7.29)	5.49 (3.11–6.94)	0.853	0.053	0.220	0.005
HOMA- β (IU/mol)	263.25 (187.51–359.67)	256.17 (168.73–370.13)	203.77 (123.62–320.03) [*]	0.029	229.14 (174.68–355.13)	228.65 (140.00–330.94)	170.57 (120.00–213.15) ^{††}	0.010	0.286	0.421	0.188
$\Delta\text{I}_{30}/\Delta\text{G}_{30}$ (IU/mol)	37.40 (26.16–57.13)	33.31 (19.93–59.37)	27.53 (16.02–41.00) [*]	0.005	23.02 (12.27–35.67)	21.45 (12.08–37.67)	14.32 (8.50–25.71) [†]	0.054	<0.001	<0.001	<0.001
AUC-I ₁₈₀ ($\mu\text{U mL}\cdot\text{h}$)	351.24 (227.44–514.82)	320.87 (243.76–418.76)	344.16 (220.78–469.11)	0.731	464.36 (280.65–612.75)	406.43 (264.51–679.97)	302.84 (232.77–398.98) ^{††}	0.008	0.084	0.012	0.346
D ₁₀ (L^2/mmol^2)	671.72 (556.54–816.16)	637.33 (527.63–763.06)	627.77 (527.73–770.51)	0.099	463.30 (349.01–559.39)	458.46 (345.60–575.72)	329.40 (284.26–411.86) ^{††}	0.001	<0.001	<0.001	<0.001

Notes: Data are presented as mean \pm SD or median with inter-quartile range if variables were not normally distributed. ^{*} $p < 0.05$ vs. control group; [†] $p < 0.05$ vs. mild-to-moderate OSA group. ^{††} p value[†] for normal glucose tolerance vs prediabetes in control group; P value^{††} for normal glucose tolerance vs. prediabetes in mild-to-moderate OSA group; P value^{†††} for normal glucose tolerance vs prediabetes in severe OSA group.

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO₂, mean pulse oxygen saturation; LSPO₂, lowest pulse oxygen saturation; TS90, percent of total sleep time spent below 90% oxygen saturation; HbA_{1c}, glycosylated hemoglobin A_{1c}; HOMA-IR, homeostasis model assessment–insulin resistance; HOMA- β , homeostasis model assessment– β ; $\Delta\text{I}_{30}/\Delta\text{G}_{30}$, the early phase (0 min–30 min) insulinogenic index; AUC-I₁₈₀, total area under the curve of insulin in 180 minutes; D₁₀, oral disposition index.

Table 3 Correlation of Sleep Apnea Variables with Glucose Metabolic Parameters

Variables	Normal Glucose Tolerance					Prediabetes				
	HbA1c	Fasting Glucose	30-min Glucose	1-h Glucose	2-h Glucose	HbA1c	Fasting Glucose	30-min Glucose	1-h Glucose	2-h Glucose
AHI (r_p , P value)	0.160, 0.016	0.027, 0.653	0.192, 0.001	0.178, 0.003	-0.018, 0.772	0.268, 0.004	0.194, 0.019	-0.013, 0.872	0.021, 0.804	-0.017, 0.835
ODI (r_p , P value)	0.163, 0.019	0.038, 0.556	0.253, <0.001	0.188, 0.003	-0.009, 0.892	0.330, 0.001	0.273, 0.002	0.093, 0.301	0.080, 0.372	0.029, 0.751
Mean SpO ₂ (r_p , P value)	-0.173, 0.044	-0.007, 0.932	-0.146, 0.075	-0.117, 0.155	-0.013, 0.870	-0.543, <0.001	-0.298, 0.006	-0.061, 0.581	-0.066, 0.554	-0.020, 0.858
LSpO ₂ (r_p , P value)	-0.170, 0.014	-0.060, 0.351	-0.226, <0.001	-0.230, <0.001	-0.009, 0.890	-0.350, <0.001	-0.201, 0.023	-0.034, 0.701	0.034, 0.705	0.032, 0.719
TS90 (r_p , P value)	0.179, 0.009	0.079, 0.207	0.119, 0.057	0.138, 0.027	-0.018, 0.776	0.397, <0.001	0.285, 0.001	0.037, 0.666	0.033, 0.704	-0.117, 0.175

Notes: Data are provided as partial correlation coefficient (r_p) using partial correlation analysis after adjustment for age and sex.

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO₂, mean pulse oxygen saturation; LSpO₂, lowest pulse oxygen saturation; TS90, percent of total sleep time spent below 90% oxygen saturation; HbA_{1c}, glycosylated hemoglobin A_{1c}.

severity. In the NGT subjects, only HOMA- β and $\Delta I_{30}/\Delta G_{30}$ were significantly lower in the severe OSA group as compared to the control group ($P < 0.05$, Table 2). In the preDM subjects, HOMA- β , $\Delta I_{30}/\Delta G_{30}$, AUC-I₁₈₀ and DI_O were all the lowest in the severe OSA group, while the 2-h insulin level in the severe OSA group was significantly lower than in the control and mild-to-moderate OSA groups ($P=0.004$ and $P=0.001$, respectively; Table 2). Moreover, patients with severe OSA were found to have markedly higher HOMA-IR and lower DI_O in the preDM group than in the NGT group ($P < 0.01$, Table 2). Partial correlation analysis confirmed that HOMA-IR and HOMA- β were negatively related to mean SpO₂ in NGT patients after adjusting for sex and age ($P < 0.05$, Table 4). In addition, the lower DI_O was significantly associated with higher ODI and lower mean SpO₂ ($P < 0.05$, Table 4), and AUC-I₁₈₀ was negatively related to TS90 ($P < 0.05$, Table 4) in the preDM group.

Discussion

There were three major findings in the present study. First, there was a high OSA prevalence in the overweight and obese nondiabetic young adults. The subjects with preDM tended to have higher AHIs and lower nocturnal SpO₂ than those with NGT. Second, OSA-related hypoxemia exacerbated the obesity-induced glucose dysmetabolism, and especially the disordered glucose tolerance was observed early after glucose post load in the NGT subjects. Third, OSA could induce IR and increased compensatory secretion of the pancreatic β -cells in the NGT subjects, while pancreatic β -cell dysfunction was present in the preDM subjects with severe OSA.

Both obesity and OSA are risk factors for glucose dysmetabolism, and OSA has a higher prevalence among obese adults with diabetes.²⁹ In the Look AHEAD study, 86% of overweight and obese adults with T2DM were diagnosed with OSA.³⁰ Leong et al found the prevalence of OSA was 80.1% in the T2DM patients and 63.1% in the nondiabetic individuals with severely obese.³¹ Similarly, our study showed the overall prevalence of OSA was 60.9% in the overweight and obese nondiabetic young subjects, including 54.91% and 72.11% of subjects with the NGT and preDM groups, respectively. The risk of OSA in the preDM patients increases by more than two folds compared with the NGT subjects, which was consistent with previously reported.³² OSA and glucose dysmetabolism have a bidirectional relationship.⁶ OSA affects the whole process of diabetes development, from preDM to the final

Table 4 Correlation Between Sleep Apnea Variables and Pancreatic β -Cell Function

Variables	Normal Glucose Tolerance					Prediabetes				
	HOMA-IR	HOMA- β	ΔI_{30} / ΔG_{30}	AUC-I ₁₈₀	DI _O	HOMA-IR	HOMA- β	ΔI_{30} / ΔG_{30}	AUC-I ₁₈₀	DI _O
AHI (r_p , P value)	0.004, 0.944	-0.011, 0.862	-0.086, 0.155	0.053, 0.384	0.030, 0.618	0.112, 0.178	-0.083, 0.318	-0.037, 0.662	-0.141, 0.091	-0.113, 0.177
ODI (r_p , P value)	0.062, 0.336	0.045, 0.486	-0.099, 0.120	0.083, 0.196	0.005, 0.937	0.106, 0.239	-0.132, 0.139	-0.105, 0.242	-0.129, 0.150	-0.215, 0.016
Mean SpO ₂ (r_p , P value)	-0.184, 0.025	-0.181, 0.027	0.035, 0.673	-0.118, 0.152	0.146, 0.076	-0.173, 0.116	0.062, 0.573	0.068, 0.538	0.109, 0.325	0.302, 0.005
LSpO ₂ (r_p , P value)	-0.120, 0.060	-0.087, 0.172	0.070, 0.275	-0.116, 0.068	0.045, 0.487	-0.013, 0.880	0.096, 0.279	0.105, 0.240	0.127, 0.152	0.058, 0.515
TS90 (r_p , P value)	0.120, 0.055	0.034, 0.586	-0.114, 0.069	0.032, 0.614	0.001, 0.986	-0.060, 0.487	-0.114, 0.186	-0.508, 0.502	-0.170, 0.048	-0.159, 0.064

Notes: Data are provided as partial correlation coefficient (r_p) using partial correlation analysis with adjustment for age and sex.

Abbreviations: BMI, body mass index; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO₂, mean pulse oxygen saturation; LSpO₂, lowest pulse oxygen saturation; TS90, percent of total sleep time spent below 90% oxygen saturation; HOMA-IR, homeostasis model assessment–insulin resistance; HOMA- β , homeostasis model assessment- β ; $\Delta I_{30}/\Delta G_{30}$, the early phase (0 min–30 min) insulinogenic index; AUC-I₁₈₀, total area under the curve of insulin in 180 minutes; DI_O, oral disposition index.

clinical diabetes.²⁵ Based on our findings, the prevalence of preDM increased significantly with the increase in the OSA severity. Chen et al¹³ found young preDM subjects suffered a worse β -cell dysfunction among i-IFG subjects. Our results also revealed the proportion of i-IGT subjects was higher in the mild-to-moderate OSA group than in the control group, whereas the proportions of i-IFG and IFG/IGT subjects were the highest in the severe OSA group.

To evaluate glucose metabolism, the majority of previous studies relating OSA have used static measures, such as the HOMA.³³ However, fasting glucose and insulin levels provide limited information about the glucose fluctuations,²⁷ and fail to reflect the degree of β -cells dysfunction.¹² Considering insulin sensitivity and compensatory response of pancreatic β -cell function, OGTT was used to assess the glucose metabolism.^{14,25} In our study, all the subjects received overnight PSG, standard OGTT-IRT and HbA1c measurement to evaluate the relationship between OSA and glucose metabolism. Among the NGT subjects, the 1-h glucose level significantly elevated with the increase in the OSA severity, and it was higher than 8.6 mmol/L in both mild-to-moderate OSA group and severe OSA group (8.92 \pm 1.90 mmol/L and 9.53 \pm 1.80 mmol/L, respectively). This finding is clinically relevant, given that, even in the early stage of glucose homeostasis, disordered tolerance early after glucose post load may be observed and represent an early manifestation of metabolic

dysfunction.³⁴ Indeed, 1-h post-load glucose level of more than 8.6 mmol/L has recently been identified as a better predictor of future T2DM and related complications than the fasting or 2-h glucose level.³⁵ Furthermore, 1-h glucose of \geq 7.4 mmol/L has been found as an independent predictor of progression to preDM in the obese young subjects with NGT.³⁶

The lower oxygen desaturation or intermittent hypoxemia is closely related to the poorer glycemic control.^{29,30} Useful oximetric measures related to OSA include ODI, LSpO₂, mean SpO₂, and TS90.²³ The European Sleep Apnea Database (ESADA) study stated ODI and nocturnal mean SpO₂ were better predictors of HbA1c levels than AHI among 2375 nondiabetic subjects who had undergone PSG.²⁴ Available study also indicated that nocturnal hypoxemia from OSA was associated with poorer glycemic control in the extremely obese subjects.³¹ Our study found HbA1c and 1-h glucose levels were positively related to ODI and TS90, while negatively to LSpO₂ in overweight and obese subjects of NGT group. In the preDM group, higher HbA1c was also independently associated with the OSA-related hypoxia parameters, and their partial correlation coefficients were higher than AHI. HbA1c correlates directly with the mean plasma glucose level in prior 2–3 months, and subjects with higher HbA1c level are more likely to progress from preDM to T2DM over 5 years.^{12,28} The positive relationship between

nocturnal hypoxemia and glycemia implies that it is necessary to assess the correction of OSA-related hypoxemia as a strategy for the glycemic control in obese patients.³¹

Notably, intermittent hypoxia (IH) is a hallmark of OSA.³⁷ Regarding OSA-related exposures, pancreatic β -cells are exquisitely sensitive to hypoxia.⁸ Evidence from animal studies has indicated IH that imitates OSA may lead to pancreatic β -cell injury and worsen the obesity-induced glucose dysmetabolism.^{37,38} We investigated the pancreatic β -cell function in the overweight and obese nondiabetic young adults. The glucose tolerance remained normal in the NGT subjects, however HOMA- β and HOMA-IR were negatively associated with nocturnal mean SpO₂, which was consistent with previous findings.^{32,39} Results showed OSA could exacerbate IR and compensatory increase in the pancreatic β -cell function before the presence of preDM in overweight and obese NGT adults, despite a significant predisposition to IR in obesity subjects.⁴⁰ In preDM subjects, the indicators of pancreatic β cell function, including basal and compensatory secretion, decreased with the increase in the severity of OSA and appeared to be the lowest in the severe OSA group. This could explain that the preDM subjects with OSA had a poorer glucose tolerance. DI_O is the product of measures of insulin sensitivity and first-phase insulin secretion, and it can be used to predict the progression into diabetes over 10 years.^{6,27} In our study, DI_O decreased with the increase in the OSA severity, but it was the lowest in the preDM subjects with severe OSA. Partial correlation analysis also confirmed that DI_O was related to ODI and nocturnal mean SpO₂ in the preDM group. In addition, preDM subjects with severe OSA had the lowest 2-h insulin level in our study, though they still possessed hyperinsulinemia and IR. As such, severe OSA imposes an extreme functional demand on the pancreatic β -cells in the overweight and obese young adults with preDM, which may give rise to impaired secretory capacity and facilitate the exhaustion of β -cells over time.⁴¹

There were several limitations in our study. First, this was a cross-sectional study, and thus we failed to determine the causal relationship between OSA and glucose dysmetabolism. Second, most subjects in this study were recruited from a center from sleep disorders, and disordered breathing during sleep was a predominant symptom, which may limit the generalization of our findings to the whole population. Last but not least, parameters from OGTT-IRT still have limitations in the evaluation of

insulin sensitivity and pancreatic β -cell function despite their correlation with glucose clamp test. Interpretation of these parameters is sometimes sophisticated for the hyperbolic correlation between insulin sensitivity and β -cell secretion.^{8,18} Thus, more prospective clinical studies with larger sample size are needed to confirm the relationship of OSA with glucose dysmetabolism and pancreatic β -cell function in overweight and obese nondiabetic young adults.

Conclusion

In conclusion, our study indicates a higher prevalence of OSA in the overweight and obese nondiabetic young adults, especially the preDM subjects. OSA-related hypoxemia may exacerbate the obesity-induced glucose dysmetabolism, and the impaired glucose tolerance can be observed early after glucose post load in the NGT subjects. There is significant interaction between OSA severity and pancreatic β -cell dysfunction, including basic and compensatory secretion, in both NGT and preDM subjects. OSA may induce the compensatory increase in the pancreatic β -cell function in NGT subjects, while pancreatic β -cell dysfunction is present in the preDM subjects with severe OSA. Further prospective studies are needed to explore the impact of OSA on the pancreatic β -cell function. Meanwhile, clinical trials with CPAP treatment and those in lean subjects with OSA should be included in the future studies to confirm our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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