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Correlations of OSA Severity and Carotid Intima-Media Thickness in Patients with Type 2 Diabetes

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Abstract

Aim: To determine whether carotid intima-media thickness (C-IMT) was elevated in diabetic patients with Obstructive Sleep Apnea (OSA), and correlations of OSA severity with IMT and other clinical characteristics.

Materials and methods: The study subjects were composed of 36 diabetic patients with OSA (group A), and 34 patients without OSA (group B). In both groups, blood lipids, fasting blood glucose, glycated hemoglobin, Epworth Sleepiness Scale, C-IMT and carotid resistance index (C-RI) were assessed, and results of sleep study were collected to investigate possible correlations with IMT and other clinical characteristics.

Results: We found a statistically significant higher IMT value (0.93 ± 0.14 vs 0.83 ± 0.16, *P*=0.007), C-RI (0.72 ± 0.05 vs 0.68 ± 0.05, *P*=0.001), and waist circumference (95.00 ± 11.24 vs 88.74 ± 8.34, *P*=0.010) in diabetic patients with OSA. Carotid IMT was associated with waist circumference, BMI, LDL-C, AHI (*r*=0.415, *P*<0.001), ODI (*r*=0.474, *P*<0.001), $LSaO_2$, and C-RI. AHI was associated with waist circumference, BMI, IMT, ODI, LSaO2, and C-RI (*P*<0.05).

Conclusion: Our study showed that in a group of diabetes, IMT was elevated in those with OSA, and OSA severity positively related to IMT values, indicating that in diabetic patients, OSA severity can be associated with atherosclerosis risk.

Keywords

Obstructive sleep apnea (OSA), Diabetes type 2 (T2DM), Carotid intima media thickness (C-IMT)

Introduction

Diabetes mellitus (DM) [1,2] and Obstructive sleep apnea (OSA) [3,4] are growing health challenges in developed and developing countries. In the diabetic population, macrovascular complications are the main leading cause of morbidity and mortality, and cardiovascular disease (CVD) risk is 2- to 8-fold higher than non-diabetic ones [5,6]. The prevalence of OSA is between 2%-14% [7] in the general population, and even up to 27% in diabetic patients [8]. OSA is often the result of inspiratory flow limitation and obstruction resulting in snoring and recurrent apnoeic episodes during sleep. Previous studies have indicated that OSA is independently linked with cardiovascular diseases and metabolic conditions like insulin resistance and type 2 DM, and also impact on glycaemic control among DM patients independent of the effect of obesity [9-12].

It was well recognized that carotid intima media thickness (IMT), a reliable marker of risk for CAD and cardiovascular events[13], is elevated in diabetic patients[14,15]. However, little is known about changes of IMT in patients suffering from both diabetes and OSA.

The aim of this study was to investigate whether there is an increase in intima-media thickness in diabetic patients with OSA, and the relationship between OSA severity and IMT values of the same patients.

Materials and Methods

Data collection started from September 1st, 2012 to December 31st, 2013. All the patients with type 2 diabetes (diagnosed by 1999 World Health Organization criteria), age between 33 and 77, were enrolled from the inpatient department of Endocrinology in our hospital in Shanghai. The study group was composed of 36 patients with newly diagnosed OSA (group A); controls were 34 patients without OSA (group B), which was confirmed by sleep monitoring using a portable sleep recorder (ALICE LE, USA) after a 1-night in-hospital sleep study. All the patients in group A were on Oral Antidiabetic Drugs (OAD). In group B, 2 patients were on the combination therapy of insulin and OAD; and the rest ones on OAD.

Patients with history of diabetic ketoacidosis or other acute diabetic complications in recent 1 months, severe heart failure, chronic renal failure, lung disease, hypothyroidism, or had the history of infection in central nervous system, stroke, cerebral hemorrhage or other clinical evidences of central nervous damages were excluded.

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Table 1: Comparison of medication use between two groups.

	Group A	Group B	χ^2	*P*
Number of patients	36	34	-	-
The use of insulin (%)	0(0)	2(5.9)	2.180	0.140
OAD(%)	36(100)	34(100)	-	-
Antihypertensive medications (%)	25(69.4)	20(58.8)	0.463	0.496
β- Blockers (%)	3(8.3)	2(5.9)	0.158	0.691
ACEI/ARB (%)	16(44.4)	11(32.4)	1.079	0.299
CCB (%)	8(22.2)	10(29.4)	0.473	0.492
Lipid-lowering medications (%)	4(11.1)	2(5.9)	0.610	0.435

OAD: Oral Antidiabetic Drugs; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin II Receptor Blockers; CCB: Calcium Channel Blockers

χ^2 test was used to test for significant differences. All values were >0.05.

Table 2: Comparison of demographic and clinical characteristics of type 2 diabetic patients with and without OSA.

Characteristic	Group A	Group B	t/χ^2	*P*-value
Age, mean ± SD, years	59.75 ± 12.08	57.32 ± 13.05	0.808	0.422
Men, No. (%)	20(55.6)	14(41.2)	1.447	0.229
Duration of DM, mean ± SD, years	8.60 ± 7.32	5.88 ± 5.23	1.775	0.080
BMI, mean±SD, kg/m^2	26.43 ± 3.93	25.04 ± 3.29	1.595	0.115
Waist circumference	95.00 ± 11.24	88.74 ± 8.34	2.635	0.010
Habitual alcohol drinker, No. (%)	2(5.6)	4(11.8)	0.860	0.354
Current smoker, No. (%)	13(36.1)	9(26.5)	0.754	0.385
Hypertension (%)	27(75.0)	23(67.6)	0.463	0.496
SBP, mean ± SD, mmHg	139.03 ± 15.53	134.41 ± 14.55	1.281	0.204
DBP, mean ± SD, mmHg	83.89 ± 8.63	82.94 ± 7.29	0.495	0.622
FBG, mean ± SD, mmol/L	10.34 ± 4.04	10.48 ± 3.80	-0.150	0.881
HbA1c, mean ± SD, %	9.16 ± 2.30	9.90 ± 1.70	-1.528	0.131
ESS, mean±SD	8.92 ± 3.52	7.21 ± 3.94	1.920	0.059
TG, median (25%-75%), mmol/L	2.03 ± 1.11	2.14 ± 1.58	-0.339	0.736
LDL-C, mean ± SD, mmol/L	3.27 ± 0.99	3.24 ± 1.18	0.138	0.890
HDL-C, mean ± SD, mmol/L	1.24 ± 0.41	1.18 ± 0.39	0.735	0.465
AHI, min-max	7-67	0-5	8.432	<0.001
ODI, min-max	15(0-61)	0-7	7.282	<0.001
$LSaO_2$, mean ± SD	77.31 ± 9.12	84.62 ± 6.14	-3.912	<0.001
C-RI, mean ± SD	0.72 ± 0.05	0.68 ± 0.05	3.501	0.001
C-IMT, mean ± SD, mm	0.93 ± 0.14	0.83 ± 0.16	2.800	0.007

Data are presented as mean values ±SD, minimal–maximal values, or as number and percentage. BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; FBG: Fasting Blood Glucose; HbA1c: HaemoglobinA1c; TG: Triglycerides; HDL-C: High-Density Cholesterol; LDL-C: Low-Density Cholesterol; C-IMT: Common Carotid Intima-Median Thickness; C-RI: Carotid Resistance Index; AHI: Apnea-Hypopnea Index; ODI: Oxygen Desaturations Index; $LSaO_2$: Lowest Arterial Oxygen Saturation

The study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The local Ethics Committee approved the protocol (NO.2013011). Written informed consent was obtained from all participants.

Clinical evaluation

All the subjects received an interview including age, gender, and history of smoking, alcohol consumption, and hypertension. Data of waist circumference, Body Mass Index (BMI), and blood pressure was collected. Hypertension was defined as systolic or diastolic blood pressure ≥140mmHg, or 90mmHg respectively, or self-reported current use of blood pressure lowering medication.

Epworth sleepiness scale

Sleepiness was measured using the Epworth Sleepiness Scale (ESS). The total score was 24, and a score of more than 10 was regarded as excessive daytime sleepiness.

Laboratory methods

Blood samples were obtained by venipuncture after an overnight fast. All the tests were preceded in local laboratory. Fasting Blood Glucose (FBG) , Triglyceride (TG), High-Density Cholesterol (HDL-C), and Low-Density Cholesterol (LDL-C), were measured enzymatically on an automatic analyzer (Cobas 8000 C701 C502 auto chemistry analyzer, Roche, USA), HaemoglobinA1c (HbA1c) was quantified from resolved erythrocytes with high performance liquid chromatography(HPLC) (HLC-723G7 analyzer, TOSOH kabushiki kaisha, Japan).

Obstructive sleep apnea (OSA) diagnosis

OSA was confirmed by sleep monitoring using a portable sleep recorder (ALICE LE, USA) after a 1-night in-hospital sleep study. Patients' body movements, heart and pulse transit time (PTT) changes were recorded as measures of arousal from sleep. The results of the sleep study were scored automatically, and subsequently reviewed to ensure accuracy of the data. The OSA diagnosis was made on the basis of an apnea/ hypopnea index (AHI) >5 and the severity were quantified as the number of AHI and oxygen desaturations by more than 4% per hour of study (ODI).

Ultrasonography of carotid arteries

The measurements of IMT and carotid resistance index (C-RI) in the extracranial carotid wall were performedusing the high-resolution B mode ultrasound equipment (Sequoia scanner, SIEMENS, Germany). Measurements of IMT were obtained on the anterior and posterior walls of the right and left carotid arteries as follows(16): three measurements on the carotid artery one centimeter proximal to the bifurcation, one measurement in the carotid bulb and two measurements in the first inch of the internal carotid artery. We used the maximum mean of the thickness of each segment for the final analysis. The RI was calculated by subtracting end-diastolic Doppler-shifted frequency from peak-systolic-shifted frequency and dividing this value by peak-systolic-shifted frequency.

Statistical analysis

Data are presented as mean ± SD unless otherwise indicated. All continuous data were tested for normality using Kolmogorov-Smirnov (KS) test. Because of skewness and kurtosis of the distributions, AHI and ODI were logarithmically transformed for statistical analyses. Differences between groups were analyzed by *t* test for independent samples. Coefficients of correlation were calculated using partial correlation analyses when adjusted for age and sex. The Chi^2 test was used for comparison of categorical variables. A *P*-value of less than 0.05 was considered to be significant. The analyses were performed using the Statistical Package for the Social Science (SPSS Version 19.0, IBM).

Results

A number of 70 patients with type 2 DM were recruited into the study and divided into two groups. Group A was composed of 36 patients with OSA, including 20 men and 16 women 33–77 years old (mean age=59.8 years). Frequency of apnea episodes was evaluated by means of polysomnography. Medication use of study participants in two groups are summarized in Table 1. No statistical differences were found in medication use between two groups. Characteristics of the population study, subdivided according to the results of the sleep study, are shown in Table 2. Mean AHI was 23.3(SD ± 14.1). Mild OSA (AHI ≦ 15/h) was diagnosed in 12(33.3%) patients, moderate OSA (AHI=16–30/h) in 15(41.7 %) patients, and severe OSA (AHI>30/h) in 9 (25.0 %) patients. Sleepiness was evaluated with the Epworth scale. In 26 patients (72.2%), the result was normal (0–9 points). Group B was composed of 34 patients without OSA, including 14 men and 20 women 34–77 years old (mean age=57.3 years).

There were no statistically significant differences between the two groups in terms of age, sex, duration of DM, BMI, blood pressure, FBG, HbA1c, levels of blood lipids, and proportion of hypertension, alcohol drinker, and current smoker (Table 2). In group A, waist circumference, AHI, ODI, C-IMT, C-RI increased, and LSaO2 decreased than in group B (*P*<0.05).

After adjusting for sex and age, we searched for correlations between mean IMT and all the anthropometric data, laboratory findings, and results of sleep study, and found that IMT correlated with waist circumference, BMI, LDL-C, AHI, ODI, LSaO2, and C-RI

Table 3: Relationships between IMT and selected parameters in 70 diabetic patients with and without obstructive sleep apnea after adjusting for sex and age

	IMT	
	r	***P***
Waist circumference	0.333	0.005
BMI	0.314	0.009
LDL-C	0.280	0.021
AHI	0.415	<0.001
ODI	0.474	<0.001
$LSaO_2$	-0.295	0.014
C-RI	0.330	0.006

r: correlation coefficient, *P:* level of significance

Table 4: Relationships between AHI and selected parameters in 70 diabetic patients with and without obstructive sleep apnea after adjusting for sex and age

	AHI	
	r	***P***
Waist circumference	0.393	0.001
BMI	0.353	0.003
IMT	0.415	<0.001
ODI	0.959	<0.001
$LSaO_2$	-0.525	<0.001
C-RI	0.443	<0.001

(P<0.05) (Table 3). In the same way, we found AHI was correlated with waist circumference, BMI, IMT, ODI, LSaO2, and C-RI (P<0.05) (Table 4).

Discussion

Obstructive sleep apnea, which is recognized to be correlated with higher risk of cardiovascular events, is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airways obstruction occurring during sleep [7]. The mechanisms that hypoxia and inflammation can cause the damage to the endothelium [17], constantly activate the sympathetic system, and exacerbates oxidative stress [18], may partly explain the relationship between OSA and CVD.

Although OSA seems to be an important cardiovascular risk factor, it is controversial that whether IMT is elevated in OSA patients. Some studies indicated that OSA's pathophysiological consequences (hypoxia, hypercapnia, micro-arousals, sympathetic hyperactivity, oxidative stress, systemic inflammation and hyper-coagulability) were implicated in the development of higher intima-media thickness (IMT) [19-21], while Agnieszka et al. thought IMT does not reflect increased risk of cardiovascular events in patients with isolated OSA [22]. In this study, we found that carotid IMT was increased in diabetic patients with OSA than those without. Besides, IMT was positively associated with AHI and ODI, and inversely associated with $LSaO_2$, indicating that OSA severity can be associated with IMT.

Carotid Resistance Index (C-RI) is calculated from blood flow velocities in vessels during the cardiac cycle by a pulsed-wave Doppler ultrasound, and could represent the stiffness and resistance of carotid vessel. The higher the value, the greater is the impedance to blood flow. Previous studies showed C-RI was closely related to atherosclerosis and CVD [23]. Additionally, our recent study showed that higher C-RI can be risk factors of mild cognitive impairment (MCI) in type 2 diabetic patients [24]. In this present study, AHI was positively related with C-RI, which has not been previously reported in the international literature, to the best of our knowledge. Since OSA is recognized to be a risk factor for developing MCI [25], the potential associations between OSA and C-RI is worthy to be further investigated.

Previously researches have indicated that obstructive sleep apnea, through the effects of intermittent hypoxaemia and sleep fragmentation, could contribute independently to the development of insulin resistance, glucose intolerance, and type 2 diabetes [26]. Type 2 diabetes is prevalent in persons with OSA, although the direction of causality is unknown [27]. Type 2 diabetes might increase predisposition to obstructive sleep apnea, through the development of peripheral neuropathy and abnormalities of ventilatory and upper airway neural control. Previous studies in animal models showed that exposure to hypoxia (sustained or intermittent) can perturb normal glucose homoeostasis, sometimes maybe by increasing fasting insulin concentrations [28,29]. However, no study has been performed on the association of glucose control and OSA severity in diabetes. Our study showed that there were no significant correlations of OSA severity with glucose levels. This result suggested that the occurrence of OSA and its severity may not significantly affect glucose levels in diabetic patients, although it was recognized to be a precursor of abnormalities in glucose metabolism in general population [30].

Our study showed that there was no significant difference in BMI between two groups. However, BMI and waist circumference were positively associated with AHI, after adjusting for age and sex, which was in agreement with previous studies [31,32]. The results indicated that in diabetic populations, visceral obesity can be related with the severity of OSA.

The ESS is a questionnaire widely used to assess the risk of daytime somnolence, which estimates a participant's likelihood to fall asleep in eight different scenarios associated with daily activities [33]. Much attention has been paid to those with a score above 10, which indicating a higher OSA risk. In this present study, we found a relatively higher proportion of normal ESS (72.2%) in patients with OSA, comparing with results of Gorzewska A et al. [22]. Additionally, we didn't find a significant correlation between ESS and AHI, which was in agreement with results of Khan et al. [34]. The results suggested that ESS may not be a sensitivity screening tool for OSA in patients with diabetes. As the high incidence of OSA and it's in diabetes, a more valid screening tool is needed to help investigators find out patients with high OSA risk.

Our population is fairly homogeneous as regards the influence of several cardiovascular risk factors that may affect the results. Sexes, age, dyslipidemia, blood pressure, glucose level, history of smoke and alcohol drink, are all parameters that could influence the IMT, and in our study these elements are well matched between two groups. Waist circumference was the only factor different in two groups. However, the sample size in our study was relatively small, so it remains a possibility that an association between ESS and AHI, and glucose levels and OSA severity among diabetic patients, that our study was underpowered to detect it.

Conclusion

Our work points out that both the occurrence of OSA and OSA severity can be correlated with higher values of IMT, and OSA severity positively related to IMT values, indicating that OSA may exacerbate the damage to the vasculaturer in patients with diabetes, underlining the importance of early diagnosis of the disease in order to slow the progression of atherosclerosis

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