Comparison of the Risk Factors for Obstructive Sleep Apnoea between Type 1 and Type 2 Diabetes Patients: A Cross-Sectional Study Using the Diabetes Study from the Center of Tokyo Women's Medical University (DIACET) 2014

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Original

Comparison of the Risk Factors for Obstructive Sleep Apnoea between Type 1 and Type 2 Diabetes Patients: A Cross-Sectional Study Using the Diabetes Study from the Center of Tokyo Women's Medical University (DIACET) 2014

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Background: Past clinical studies have shown the relationship between type 2 diabetes (T2D) and obstructive sleep apnoea (OSA), but little is known about type 1 diabetes (T1D). The purpose of this study is to examine clinical indicators associated with OSA in patients with different subtypes of diabetes.

Methods: Self-administered questionnaires that asked if the patients had been diagnosed with OSA were distributed to patients with T1D and T2D. General and clinical information was confirmed with both questionnaires and medical records.

Result: Among the 1,269 T1D patients and 5,838 T2D patients, 20 T1D patients and 421 T2D patients had received a diagnosis of OSA. OSA patients were more likely to be male, older, and to have a greater BMI and lower LDLC and HDLC. T1D patients with OSA were characterized by a significantly higher prevalence of severe hypoglycemia. On the other hand, T2D patients with OSA had high HbA1c, decreased renal function, high frequency of diabetic neuropathy, and correlated with macrovascular complications.

Conclusion: The prevalence of OSA was significantly higher in T2D patients. It was suggested that OSA-related pathologies might differ between T1D and T2D patients.

Key Words: obstructive sleep apnoea, diabetic complications, macrovascular complications, microvascular complications, diabetes

Introduction

Sleep disturbance associated with sleep apnoea syndrome is a worldwide social problem.[1] There are three types of sleep apnoea: obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and a combination of the two, called mixed type. OSA is at an increased risk of developing diabetes,[2] and patients with type 2 diabetes (T2D) are more likely to have OSA.[3] Diabetes and OSA often develop in the same individuals, suggesting common un-

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derlying mechanisms and bidirectional associations with each other. OSA is also associated with diabetic retinopathy, neuropathy, and nephropathy. In addition, diabetes and OSA share a common risk of atherosclerotic vascular diseases.

Although the seriousness of sleep apnoea in patients with diabetes has been repeatedly emphasized, most of these studies were focused on patients with T2D, and information is lacking regarding the frequency and pathophysiology of OSA in patients with type 1 diabetes (T1D). Therefore, we conducted this study to compare the prevalence of OSA in association with the different types of diabetes. We also investigated the differences in the clinical characteristics in patients with OSA between T1D and T2D.

Materials and Methods

We conducted a single center cross-sectional study as part of the Diabetes Study from the Diabetes Center of Tokyo Women's Medical University (DIACET) from January to December in 2014, which was approved on 16 October 2013 by the Ethical Committee of the Tokyo Women's Medical University (Approval No. 2481-R) and written informed consent was obtained from each subject. In DIACET, a self-administered questionnaire consisting of several clinical questions was distributed to patients with diabetes who visited the Diabetes Center of Tokyo Women's Medical University Hospital.

In the current study, we used the data from DIACET 2014, in which 7,964 patients, including 3,404 females, 4,560 males, and 1,421 patients with T1D, 6,266 patients with T2D participated and 277 patients with other type of diabetes. Among those who responded to this questionnaire, patients undergoing haemodialysis, those with psychiatric conditions, and those under 15 years of age were excluded. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

1. DIACET 2014

In DIACET 2014, we asked the participants whether they had been diagnosed with OSA in specific examinations. We also asked patients about medication for hypertension and dyslipidaemia, the frequency of severe hypoglycaemia, past and current history of smoking and drinking, history of clinical visits for cardiac diseases, cerebrovascular disease, or gangrene, and symptoms due to diabetic autonomic neuropathy. Severe hypoglycaemia was defined as episodes with hypoglycaemia accompanied by a consciousness disturbance that required assistance from others.

Symptoms due to autonomic neuropathy consisted of the following 12 symptoms: constipation, diarrhoea, faecal incontinence, orthostatic hypotension, sexual impotence, hyperhidrosis, anhidrosis, frequency urination, dysuria, belching, heartburn, and a dull feeling in the stomach. If more than three of these symptoms were present, we diagnosed the patient with autonomic neuropathy.

2. Other information related to diabetes

General and clinical information, such as age, sex, the duration of diabetes, body weight, body-mass index (BMI), HbA1c, estimated glomerular filtration rate (eGFR), serum lipid profiles, and the stages of microvascular complications (neuropathy, retinopathy, and nephropathy) were confirmed by reviewing the medical records.

The presence and stage of diabetic retinopathy was identified by ophthalmologic examination by ophthalmologists according to the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales.[4] We classified patients into the following three groups according to the stage of diabetic retinopathy: 1) no apparent retinopathy, 2) background retinopathy, and 3) pre-proliferative or proliferative retinopathy. The stage of diabetic nephropathy was evaluated by the urinary albumin/creatinine ratio (ACR) and eGFR as follows: stage 1 (ACR < 30 mg/g and eGFR ≥ 30 mL/min/1.73 m^2); stage 2 (ACR 30-299 mg/g and eGFR ≥ 30 mL/min/1.73 m^2); stage 3 (ACR≥ 300 mg/g and eGFR ≥ 30 mL/min/1.73 m^2); and stage 4 (eGFR < 30 mL/min/1.73 m^2, regardless of ACR level).[5] The stages of chronic kidney disease (CKD) were classified into the following four groups according to eGFR: stage 1 (≥ 90 mL/min/1.73 m^2); stage 2 (60-89 mL/min/1.73 m^2); stage 3 (30-59 mL/min/1.73 m^2); and stage 4 (<30 mL/min/1.73 m^2). Macrovascular complications were defined when a pa-

Table 1 Clinical background.

	Type 1 DM (n=1,269)	Type 2 DM (n=5,838)	p
OSA (n) (%)	20 (1.6)	421 (7.2)	<0.0001*
Age (years)	45±14	66±12	<0.0001
Male (n) (%)	425 (33.4)	3,679 (58.3)	<0.0001*
Duration of diabetes (years)	20.9±11.8	17.8±11.2	<0.0001
BMI (kg/m^2)	22.9±3.3	24.5±4.3	<0.0001
HbA1c (%)	8.1±1.3	7.7±1.3	<0.0001
eGFR (ml/min/1.73 m^2)	78.1±24.9	58.2±21.5	<0.0001
Cr (mg/dl)	0.73±0.41	0.89±0.52	<0.0001
ACR (mg/gCr)	6 (4.2-11.0)	12 (6-46)	0.0009
Triglyceride (mg/dl)	81.0 (60-115)	126 (91-175)	<0.0001
LDLC (mg/dl)	107.6±24.1	108.5±25.3	0.4583
HDLC (mg/dl)	78.6±19.9	59.0±16.5	<0.0001
Cholesterol-lowering drugs (%)	20	49	<0.0001*
Antihypertensive drugs (%)	28	61	<0.0001*
Severe hypoglycaemia (%)	47	11	<0.0001*
Smoking (%)	14	12	0.0116*
Neuropathy (%)	15	19	0.0004*
Retinopathy none/background/proliferative (%)	72/14/14	70/17/13	0.0071*
Nephropathy stage 1/2/3-5 (%)	87/9/4	69/22/9	<0.0001*
CKD stage1/2/3/4-5 (%)	29/47/21/3	9/34/50/7	<0.0001*
Ischemic heart disease (%)	2.1	12.7	<0.0001*
Cerebrovascular disease (%)	1.3	5.0	<0.0001*
Diabetic gangrene (%)	0.3	1.3	0.0007*

Student's t-test, *χ^2 or Fisher's exact probability test, mean ± SD, median (interquartile range).
OSA, obstructive sleep apnoea; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; CKD, chronic kidney disease.

tient suffers from one or more of ischemic heart disease, cerebrovascular disease and diabetic gangrene.

3. Statistical analysis

Statistical analysis was performed using JMP version 12.0 (OSA Institute Inc., USA). Differences in the continuous variables between groups were tested with an unpaired Student's t-test if the values were normally distributed or with the Mann-Whitney U test if the values were not normally distributed. Pearson's correlation test and the R^2 (adjusted coefficient of determination) were used to analyse the relationships between OSA and the other clinical parameters. Univariate and multiple logistic regression analyses were performed to determine the clinical factors associated with sleep apnoea. The level of statistical significance was set at $p < 0.05$.

Results

1. Clinical characteristics of the subjects by the type of diabetes (Table 1)

Among the 7,964 patients who participated in DIACET 2014, 7,107 patients who answered the question of whether they had a diagnosis of sleep apnoea were studied. There were 1,269 patients with T1D and 5,838 patients with T2D. The clinical characteristics of the patients with T1D and T2D are listed in **Table 1**. In patients with T1D, the mean age was lower, the duration of diabetes was longer, the BMI and ACR were lower, and the HbA1c and eGFR were higher than those in patients with T2D. Regarding the serum lipid profiles, patients with T1D had lower triglyceride and higher high-density lipoprotein cholesterol (HDLC) levels than those in patients with T2D; there was no significant difference in the low-density lipoprotein cholesterol (LDLC) levels in patients with T1D and T2D. In patients with T1D, the

Table 2 Comparison of the clinical background of patients with and without OSA by the type of diabetes.

	Type 1 DM			Type 2 DM			p*
	OSA (+) (n=20)	OSA (-) (n=1,249)	p	OSA (+) (N=421)	OSA (-) (N=5,417)	p	
Age (years)	56±3	45±1	0.0005	63±0.6	66±0.2	0.0002	0.0058
Male (n) (%)	15 (75)	410 (32.8)	0.0001*	350 (83.1)	3,329 (61.5)	<0.0001*	0.3697*
Duration of diabetes (years)	23.3±2.6	20.9±0.3	0.3721	17.0±0.6	17.9±0.2	0.1612	0.0122
BMI (kg/m^2)	24.7±0.7	22.8±0.1	0.0130	27.6±0.2	24.2±0.1	<0.0001	0.0143
HbA1c (%)	7.5±0.3	8.1±0.1	0.0644	7.9±0.1	7.7±0.1	0.0018	0.2525
eGFR (ml/min/1.73 m^2)	62.7±6.2	78.4±0.8	0.0118	52.3±1.1	58.6±0.3	<0.0001	0.0504
Cr (mg/dL)	0.80±0.10	0.73±0.01	0.5126	1.1±0.1	0.9±0.1	<0.0001	0.2154
ACR (mg/gCr)	3.8 (2.9-9.8)	6.0 (4.1-10.8)	0.6563	17.6 (7.1-86.8)	11.5 (6.0-45.0)	0.0203	0.4417
Triglyceride (mg/dL)	92 (80-133)	81 (59-115)	0.1057	151 (108-211)	125 (90-172)	<0.0001	0.1101
LDLC (mg/dL)	92.7±5.7	107.9±0.7	0.0086	102.0±1.3	109.0±0.4	<0.0001	0.1417
HDLC (mg/dL)	66.4±4.7	78.8±0.6	0.0087	52.6±0.9	59.4±0.2	<0.0001	0.0002
Cholesterol-lowering drugs (%)	35	20	0.1271*	55	49	0.0106*	0.0739*
Antihypertensive drugs (%)	45	28	0.1058*	75	61	<0.0001*	0.0054*
Severe hypoglycaemia (%)	70	47	0.0425*	12	12	0.9124*	<0.0001*
Smoking (%)	15	14	0.9330*	14	14	0.8604*	1.0000*
Neuropathy (%)	30	15	0.0818*	26	18	0.0002*	0.6869*
Retinopathy none/background/proliferative (%)	85/0/15	72/14/14	0.1945*	68/19/13	70/17/13	0.6373*	0.0156*
Nephropathy stage 1/2/3-5 (%)	86/14/0	87/9/4	0.6535*	63/25/12	70/21/9	0.1231*	0.2843*
CKD stage 1/2/3/4-5 (%)	0/50/43/7	30/48/20/2	0.0158*	55/22/2/21	65/18/5/12	0.0006*	0.6660*
Ischemic heart disease (%)	10	2	0.0706*	25.4	11.8	<0.0001*	0.0876*
Cerebrovascular disease (%)	0	1.3	0.4744*	10.2	5.0	<0.0001*	0.0403*
Diabetic gangrene (%)	0	0.3	0.7213*	5.0	1.3	<0.0001*	0.1575*

Student's t-test, *Chi-square or Fisher's exact probability test, p*: the comparison of T1D and T2D with OSA.
OSA, obstructive sleep apnoea; BMI, body mass index; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; CKD, chronic kidney disease.

use of anti-hyperlipidaemic and antihypertensive drugs were much lower than that in patients with T2D (p< 0.0001). Forty-seven percent of patients with T1D experienced severe hypoglycaemia, the prevalence of which was much higher than that of T2D patients (p<0.0001). In those with T2D, the prevalence of diabetic microvascular and macrovascular complications was higher than that in patients with T1D. Among the participants, 20 patients with T1D (1.7%) and 421 patients with T2D (7.2%) reported that they had OSA that had been diagnosed by specific examinations. The prevalence was significantly higher in patients with T2D than in those with T1D, with an odds ratio of 4.85 (95% confidence interval: 3.09-7.63, p<0.001) in the univariate logistic regression analysis.

2. Comparison of the clinical characteristics of patients with and without OSA (Table 2)

Patients with OSA were more likely to be male, had higher BMIs and lower levels of HDLC compared to those in patients without OSA. These findings were similar when comparing either T1D or T2D patients with OSA to patients without OSA. Patients with T1D and OSA were significantly associated with a higher prevalence of a history of severe hypoglycaemia (p=0.0425). In patients with T2D, those with OSA had a higher HbA1c, lower eGFR, higher prevalence of diabetic neuropathy and ischaemic heart disease, diabetic gangrene, compared to those of T2D patients without OSA.

3. Comparison of clinical parameters compared by the presence or absence of SAS for each type of diabetes (Table 2)

T1D patients with OSA were younger (p=0.0058), had a longer duration of diabetes (p=0.0122), and had a lower BMI (p=0.0143) than those of T2D patients with OSA. The rate of antihypertensive drug use was higher in patients with T2D than in patients with T1D. Patients with T1D and OSA experienced more episodes of severe hypoglycaemia than those in patients with T2D and OSA.

Table 3 Linear logistic regression analysis.

	Type 1 DM		Type 2 DM	
	OR (95% CI)	p	OR (95% CI)	p
Age	1.05 (1.02-1.08)	0.0008	0.99 (0.98-0.99)	0.0002
Male	6.13 (2.36-19.0)	<0.0001	3.09 (2.40-4.04)	<0.0001
Duration of diabetes	1.02 (0.98-1.05)	0.3781	0.99 (1.003-1.007)	0.1587
BMI	1.15 (1.02-1.28)	0.0202	1.15 (1.13-1.17)	<0.0001
HbA1c	0.66 (0.42-0.99)	0.0419	1.12 (1.04-1.20)	0.0025
eGFR	0.97 (0.95-0.99)	0.0106	0.99 (0.98-0.99)	<0.0001
TG	1.00 (0.998-1.004)	0.2768	1.00 (1.002-1.004)	<0.0001
LDLC	0.97 (0.95-0.99)	0.0064	0.99 (0.98-0.99)	<0.0001
HDLC	0.96 (0.93-0.99)	0.0044	0.97 (0.96-0.98)	<0.0001
Cholesterol-lowering drugs	2.13 (0.79-5.26)	0.1271	1.30 (1.06-1.58)	0.0106
Antihypertensive drugs	2.11 (0.85-5.16)	0.1058	1.95 (1.56-2.46)	<0.0001
Severe hypoglycaemia	2.59 (1.03-6.48)	0.0425	1.02 (0.72-1.40)	0.9124
Smoking	1.12 (0.31-4.09)	0.9330	0.95 (0.71-1.30)	0.7527
Neuropathy	2.51 (0.88-6.35)	0.0818	1.56 (1.24-1.96)	0.0002
Retinopathy	0.45 (0.10-1.34)	0.2004	1.10 (0.89-1.37)	0.3677
Nephropathy	1.117 (0.06-6.65)	0.9188	1.37 (1.01-1.85)	0.0440
Ischemic heart disease	5.44 (0.83-20.27)	0.0706	2.56 (2.02-3.23)	<0.0001
Cerebrovascular disease	-	-	2.41 (1.70-3.36)	<0.0001
Diabetic gangrene	-	-	5.18 (3.05-8.59)	<0.0001
Macrovascular complications	3.11 (0.49-11.27)	0.1932	2.79 (2.25-3.45)	<0.0001

OR, odds ratio; CI, confidence interval; TG, triglyceride; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol.

Table 4 Multivariate logistic regression analysis.

	OR	95% CI	p
Type 1 DM (OSA)			
Male	5.40	2.047-16.873	0.0014
Severe hypoglycaemia	2.92	1.132-8.519	0.0338
BMI	1.16	1.26-1.310	0.0147
Age	1.05	1.018-1.085	0.0026
Type 2 DM (OSA)			
Diabetic gangrene	4.074	2.219-7.210	2.66×10^{-6}
Male	3.365	2.547-4.514	8.34×10^{-17}
Ischemic heart disease	2.323	1.738-2.982	6.35×10^{-11}
Cerebrovascular disease	1.981	1.335-2.871	4.50×10^{-4}
BMI	1.168	1.144-1.194	4.29×10^{-46}

Independent variables: age, male, BMI, HbA1c, severe hypoglycaemia, ischemic heart disease, diabetic gangrene, and cerebrovascular disease.
OSA, obstructive sleep apnoea; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Patients with T2D and OSA had more severe retinopathy than that in patients with T1D and OSA, and the T2D patients had significantly more cerebrovascular disease than T1D patients. However, OSA patients with T1D and T2 D did not differ significantly in difference in diabetic nephropathy, CKD, ischaemic heart disease and diabetic gangrene.

4. Correlation of OSA and the clinical parameters (Table 3)

In univariate logistic regression analyses, higher age, male gender, higher BMI, lower eGFR, LDLC, and HDLC were associated with a higher odds ratio of OSA in both patients with T1D and T2D. Severe hypoglycaemia and low HbA1c was significantly associated with OSA only in patients with T1D. High HbA1c, high triglyceride levels, the oral administration of cholesterol-lowering and antihypertensive drugs, neuropathy, the severity of nephropathy, and ischaemic heart disease, cerebrovascular disease and diabetic gangrene, were found to be risk factors for OSA in T2D.

5. Correlation of OSA and the clinical parameters

In the multivariate logistic regression analysis (**Table 4**), male gender, BMI were significantly associated with the risk of OSA in both patients with T1D and T2D. Severe hypoglycaemia, and current age were significantly associated with the risk of OSA in patients with T1D. Diabetic gangrene, ischaemic heart disease, and cerebrovascular disease were found to be associated with the risk of OSA in patients with T2D. As a result of the

Table 5 Multivariate logistic regression analysis of all OSA patients.

	OR	95% CI	p
DM type	3.14	1.437-6.846	0.0041
Male	2.91	1.912-4.458	<0.0001
BMI	1.14	1.105-1.177	<0.0001
Ischemic heart disease	1.746	1.156-2.637	0.0081
Cerebrovascular disease	2.427	1.347-4.376	0.0032
Diabetic gangrene	5.613	2.455-12.834	<0.0001

Independent variables: DM type, age, male, duration, BMI, HbA1c, smoking, severe hypoglycaemia, neuropathy, retinopathy, ischemic heart disease, diabetic gangrene, and cerebrovascular disease.
OSA, obstructive sleep apnoea; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; BMI, body mass index.

multivariate logistic regression analysis of all patients (**Table 5**), T2D, male, BMI, ischaemic heart disease, cerebrovascular disease and diabetic gangrene were independently associated with OSA.

Discussion

In this study, we identified and compared the clinical characteristics associated with the risk of OSA in Japanese patients with T1D and T2D and found that the prevalence of OSA was significantly lower in patients with T1D than that in patients with T2D. We also found that in patients with T1D, microvascular or macrovascular complications were not associated with OSA. In contrast, a significant association between severe hypoglycaemia and OSA was observed in patients with T1D.

Previous studies from Manin et al[6] (67 patients, 60% male, mean age: 54 ± 10 years; BMI: 25.8 ± 4.7 kg/m^2), Borel et al[7] (37 patients, 68% male, mean age: 43 ± 13 years; BMI: 24.7 ± 3.0 kg/m^2), Banghoej et al[8] (199 patients, 68% male, mean age: 52 ± 15 years; BMI: 25.3 ± 3.3 kg/m^2) have shown that the prevalence of OSA was 40-46% and that of severe OSA was 6-19% in T1D. In our study, the prevalence was much lower. The lower BMI (22.9 ± 3.3 kg/m^2) in our study may be associated with the lower incidence of OSA. Obesity has a strong impact on the onset of OSA, which we also found in this study. In this study, the mean age (45 ± 14 years) and male ratio (33.4%) of subjects were lower compared to previous studies. This character may also, at in part, explain the difference between the current study and past studies.

In addition, the information on OSA in our study was based on the self-assessment of the questionnaire and is most likely underestimated. To diagnose OSA, laboratory-based polysomnography is thought to be the gold standard but is not widely used because of the high cost and the necessity of hospitalization and skilled technical experts. For this reason, polysomnography is usually used for patients who are strongly suspected of having OSA. For OSA screening, questionnaires have often been used, however, using home sleep-monitoring devices is more effective and practical.[9]

We found an independent association between OSA and severe hypoglycaemia in patients with T1D. There was significant difference in HbA1c between patient with and without severe hypoglycaemia (HbA1c 7.9% vs. 8.2%, p=0.0039, data were not shown). OSA in T1D patients was associated with lower HbA1c level. We do not have the exact information of the frequency and duration of severe hypoglycaemia. The mechanism is unknown and cannot be elucidated from the present study, which was not designed to investigate causal relations.

The clinical experience and experimental studies show that hypoglycemia causes neuropathy.[10, 11] Gu's study[12] has suggested that OSA might involve in the duration of neuropathy, and OSA was significantly correlated with neuropathy in T1D. In addition, glossoptosis may be associated with the disturbance of consciousness due to hypoglycaemia, which may cause OSA. In this study, we are unable to find a significant association between OSA and diabetic neuropathy. One of the reasons for this is may be that we assessed diabetic neuropathy with a questionnaire instead of with a physical examination, most likely we did an underestimation of prevalence of neuropathy. Elevated BMI is a risk factor for OSA also in T1D as the same with T2D. Mechanism investigation shows that the resistance of leptin in obesity and diabetes contributes to OSA, which is involved in the neuro-mechanical control of the upper airway.[13, 14]

Lévy et al[15] reported that OSA has a strong effect on ischaemic heart disease, and alterations of the cerebral blood flow have been found in OSA.[16] In the current study, BMI, male gender, and a history of ischemic heart disease and cerebrovascular disease were associated with OSA in the patients with T2D, which is in line with previous studies.[16-19] Furthermore, diabetic gangrene was

positively correlated with OSA, suggesting that blood flow in the legs of OSA patients may be reduced. Chronic repetitive nocturnal hypoxia leads to endothelial damage,[20,21] and a positive correlation between the carotid intima media thickness (IMT) and apnoea-hypopnea index is reported,[22] OSA has a strong effect on arteriosclerosis.[15] Also, carotid IMT has a relationship with insulin resistance,[23] which result in endothelial dysfunction and atherogenesis.[24] Even this is still at the stage of hypothesis, but we think the OSA patients with high insulin resistance tend to suffer arteriosclerosis, and cardiovascular disease.

It has been reported that patients with OSA appear to have increased dyslipidaemia,[25] but the mechanism remains unknown. Previous evidence suggests that the hypoxia-inducible factor-1 in the liver activates sterol regulatory element-binding protein-1 (SREBP-1) and stearoyl-coenzyme A desaturase-1 (SCD-1), an important gene of triglyceride and phospholipids biosynthesis controlled by SREBP-1.[26] Although many studies have confirmed the relationship between OSA and concrete lipid indexes, the results varied from one to another. It is demonstrated that LDLC was independently associated with OSA,[27] severity of OSA were associated with higher triglyceride levels and lower HDLC levels,[28] Can et al[29] found total cholesterol, LDLC, triglyceride and apo-B increased in patients with OSA. Nonetheless, in this study, patients with OSA had lower LDLC, higher triglyceride and lower HDLC compared to those of the other patients. The oral administration of cholesterol-lowering drugs such as statin might be the cause of this result, as the patients who were taking these medicines were the most likely have to have a lower LDLC.

This study had some limitations. First, the evaluation of OSA and diabetic complications were performed by using a self-administered questionnaire, restricting the validity of the information that was obtained. We have reviewed medical records and confirmed that patients who have been diagnosed with OSA really have OSA. However, in fact, it is possible that an undiagnosed OSA patient has been missed and the number of cases might be underestimated. Second, this was a single-center study, limiting its generalizability. Nonetheless, the inclusion of a large population with diabetes, consisting of more than 7,000 participants, provided more precise information regarding the association between OSA and diabetes, especially T1D.

Conclusion

In this single-center cross-sectional study, the prevalence of OSA was significantly higher in patients with T2D than that in those with T1D. In patients with T1D, a history of severe hypoglycaemia was associated with an increased risk of OSA. We confirmed a close association between macrovascular diseases and OSA in patients with T2D, which has been shown previously.

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The other authors have no competing interests to declare.

References

1. Zhu BQ, Li XM, Wang D et al: Sleep quality and its impact on glycaemic control in patients with type 2 diabe-

tes mellitus. Int J Nurs Sci 1: 260−265, 2014
2. Ceccato F, Bernkopf E, Scaroni C: Sleep apnea syndrome in endocrine clinics. J Endocrinol Invest 38: 827−834, 2015
3. Lévy P, Bonsignore MR, Eckel J: Sleep, sleep-disordered breathing and metabolic consequences. Eur Respir J 34: 243−260, 2009
4. Wilkinson CP, Ferris FL 3rd, Klein RE et al: Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 110 (9): 1677−1682, 2003
5. Haneda M, Utsunomiya K, Koya D et al: A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. J Diabetes Investig 6: 242−246, 2015
6. Manin G, Pons A, Baltzinger P et al: Obstructive sleep apnoea in people with Type 1 diabetes: prevalence and association with micro- and macrovascular complications. Diabet Med 32 (1): 90−96, 2015
7. Borel AL, Benhamou PY, Baguet JP et al: High prevalence of obstructive sleep apnoea syndrome in a type 1 diabetic adult population: a pilot study. Diabet Med 27: 1328−1329, 2010
8. Banghoej AM, Nerild HH, Kristensen PL et al: Obstructive sleep apnoea is frequent in patients with type 1 diabetes. J Diabetes Complications 31 (1): 156−161, 2017
9. Qing SM, Chen RK, Liu H et al: Comparison of the NoSAS score with four different questionnaires as screening tools for obstructive sleep apnea-hypopnea syndrome. Zhonghua Jie He He Hu Xi Za Zhi 41 (3): 213−219, 2018 (in Chinese)
10. Mohseni S: Hypoglycemic neuropathy. Acta Neuropathol 102: 413−421, 2001
11. Sugimoto K, Murakawa Y, Sima AA: Diabetic neuropathy--a continuing enigma. Diabetes Metab Res Rev 16 (6): 408−433, 2000
12. Gu X, Luo X, Wang X et al: The correlation between obstructive sleep apnea and diabetic neuropathy: a meta-analysis. Prim Care Diabetes 12 (5): 460−466, 2018
13. Polotsky M, Elsayed-Ahmed AS, Pichard L et al: Effects of leptin and obesity on the upper airway function. J Appl Physiol (1985) 112 (10): 1637−1643, 2012
14. Shapiro SD, Chin CH, Kirkness JP et al: Leptin and the control of pharyngeal patency during sleep in severe obesity. J Appl Physiol 116: 1334−1341, 2014
15. Lévy P, Ryan S, Oldenburg O et al: Sleep apnoea and the heart. Eur Respir Rev 22: 333−352, 2013
16. Chen HL, Lin HC, Lu CH et al: Systemic inflammation and alterations to cerebral blood flow in obstructive sleep apnea. J Sleep Res 26 (6): 789−798, 2017
17. Cairns A, Poulos G, Bogan R: Sex differences in sleep apnea predictors and outcomes from home sleep apnea testing. Nat Sci Sleep 8: 197−205, 2016
18. Sharma N, Lee J, Youssef I et al: Obesity, cardiovascular disease and sleep disorders: insights into the rising epidemic. J Sleep Disord Ther 6 (1): 260, 2017
19. Marin JM, Carrizo SJ, Vicente E et al: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 365: 1046−1053, 2005
20. Garvey JF, Taylor CT, McNicholas WT: Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J 33 (5): 1195−1205, 2009
21. Kohler M, Stradling JR: Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol 7 (12): 677−685, 2010
22. Sarioglu N, Demirpolat G, Erel F et al: Which is the ideal marker for early atherosclerosis in obstructive sleep apnea (OSA) - carotid intima-media thickness or mean platelet volume? Med Sci Monit 23: 1674−1681, 2017
23. Purnamasari D, Abdaly MS, Azizi MS et al: Carotid intima-media thickness among normoglycemia and normotension first-degree relatives of type 2 diabetes mellitus. Vasc Health Risk Manag 15: 101−107, 2019
24. Schmidt MI, Duncan BB, Sharrett AR et al: Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 353 (9165): 1649−1652, 1999
25. McNicholas WT, Bonsigore MR: Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 29: 156−178, 2007
26. Drager LF, Jun J, Polotsky VY et al: Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis. Curr Opin Endocrinol Diabetes Obes 17 (2): 161−165, 2010
27. Xu H, Guan J, Yi H et al: Elevated low-density lipoprotein cholesterol is independently associated with obstructive sleep apnea: evidence from a large-scale cross-sectional study. Sleep Breath 20 (2): 627−634, 2016
28. Trzepizur W, Le Vaillant M, Meslier N et al: Independent association between nocturnal intermittent hypoxemia and metabolic dyslipidemia. Chest 143 (6): 1584−1589, 2013
29. Can M, Açikgöz S, Mungan G et al: Serum cardiovascular risk factors in obstructive sleep apnea. Chest 129 (2): 233−237, 2006