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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Relationship between obstructive sleep apnoea during rapid eye movement sleep and metabolic syndrome parameters in patients with type 2 diabetes mellitus

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Abstract

Purpose Sleep-disordered breathing (SDB) is associated with hypertension, poor glycemic control and dyslipidemia. Usually, apnoea events tend to be more prominent during rapid eye movement (REM) sleep than non-REM (NREM) sleep. We examined which SDB parameters are associated with blood pressure (BP), HbA1c and lipid profile in patients with type 2 diabetes (T2D).

Methods A total of 185 patients with T2D who underwent polysomnography were analysed. Exclusion criteria were: the presence of pulmonary diseases, central sleep apnoea, treated SDB, or REM sleep < 30 min. To predict BP, HbA1c, and lipid profiles, we performed multiple linear regression analyses adjusted for known risk factors. Subsequently, we performed multivariable logistic regression analyses.

Results Patient characteristics (mean ± standard deviation/median) were as follows: age 58.0 ± 11.8 years, body mass index 26.0 kg/m2 (24.1–28.9 kg/m2), systolic BP 134 ± 19 mmHg, mean BP 98 ± 14 mmHg, HbA1c 7.4% (6.8–8.4%), triglyceride 143 mg/dL (97–195 mg/dL), non-high density lipoprotein (non-HDL) cholesterol 143 mg/dL (120–163 mg/dL), REM-apnoea–hypopnea index (AHI) 35.1/h (21.1–53.1/h). The analyses revealed that REM-AHI was independently associated with systolic and mean BP, whereas NREM-AHI was not. A statistically significant association was not observed between REM-AHI and HbA1c or lipid profile.

Conclusion In patients with T2D, REM-AHI was associated with systolic and mean BP. The alteration of BP, associated with SDB during REM sleep, may be an important pathophysiological link between SDB and cardiovascular diseases.

Keywords Diabetes mellitus, type 2 · Sleep apnoea syndromes · Sleep, REM · Hypertension

Introduction

Previous studies reported that about 58 to 86% of type 2 diabetes mellitus (T2D) patients have obstructive sleep apnoea (OSA) [1]. The severity of sleep-disordered breathing (SDB) is related to metabolic syndrome parameters in diabetic patients, such as blood pressure (BP), diabetes mellitus and dyslipidemia [2–4]. Additionally, SDB is associated with cardiovascular events [5].

It has been shown that sympathetic activity is more aroused during rapid eye movement (REM) sleep than non-REM (NREM) sleep [6]. Furthermore, apnoea events during REM sleep are more severe than during NREM sleep [7]. However, currently, it is impossible to distinguish REM from NREM sleep with portable sleep tests. Previous studies assessing Caucasian patients with and without diabetes mellitus have associated REM-apnoea–hypopnea index (AHI) with hypertension [8, 9].

However, to date, there are limited studies assessing the relationship between SDB during REM sleep and metabolic syndrome parameters in T2D patients. Furthermore, to the best of our knowledge, there has been no study on the comprehensive assessment of metabolic syndrome parameters in diabetic patients. The present study aimed to reveal which

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SDB parameters had a higher correlation with metabolic syndrome parameters in Japanese T2D patients.

Methods

Patients

The present report was a single centre, cross-sectional study. We enrolled 528 T2D patients who underwent polysomnography in our hospital between May 2005 and June 2013. The diagnosis of diabetes was made according to the criteria released by the Japan Diabetes Society [10]. Patients treated with hypoglycaemic agents, with no history of type 1 or other types of diabetes, were also regarded as T2D patients. Exclusion criteria were as follows: patients missing essential data of polysomnography for analysis, insufficient information on T2D due to follow-up by other clinic, patients with diabetes other than T2D, pulmonary diseases and treated SDB, patients with REM sleeping hours shorter than 30 min when undergoing polysomnography, cases who underwent diagnostic polysomnography and CPAP titration in one night, a total sleep time < 60 min, presence of hypothyroidism, diagnosis of chronic kidney diseases (eGFR < 30 or on haemodialysis), past medical history of heart failure and atrial fibrillation, and recent history of cerebral vascular accidents.

Due to the unacknowledged nature of the data, the informed consent was obtained through an opt-out policy. The institutional review board of Toranomon Hospital approved the study protocol.

Polysomnography

We performed sleep tests with a digital polygraph (SomnoStar α Sleep System; SensorMedics Corp., Yorba Linda, CA) monitored by sleep technicians. An AHI was determined based on the number of apnoea and hypopnea events per hour during sleeping time. Apnoea was defined as a > 90% reduction of airflow for ≥ 10 s. Hypopnea was described as a > 30% reduction of airflow for ≥ 10 s with desaturation or arousal [11–13]. A REM-AHI was defined as an AHI during REM sleep.

Definitions and data collection

The following information and laboratory data were collected from the medical records: HbA1c, fasting plasma glucose and lipid profile, BP (taken the morning after polysomnography was performed), T2D's duration, height, weight, medications, past medical histories and so on. The glycated haemoglobin (HbA1c) value was assessed as a National Glycohemoglobin Standardisation Program equivalent value. To this end, the following formula was used: HbA1c (%) = 1.02 × HbA1c (Japan Diabetes Society) (%) + 0.25(%) [14]. Finally, lipid profiles were calculated with a commercially available measurement system.

Statistical analysis

Continuous variables were described as mean ± standard deviation or median plus interquartile ranges. The relationship between SDB and cardiovascular disease (CVD) risk factors, such as BP, was assessed by determining dependent and independent variables. Specifically, when assessing the association between SDB and hypertension, the systolic, diastolic and mean BPs were set as independent variables. In the latter analyses, dependent variables included the following: age, sex, body mass index (BMI), use of sleeping pills and smoking history. When assessing hyperglycaemia, HbA1c was set as an independent variable. The dependent variables in this analysis included the following: age, sex, BMI, use of sleeping pills, T2D's duration and use of insulin. Lipid profile assessment, non-high density lipoprotein cholesterol (non-HDL-C), triglyceride (TG) and high density lipoprotein cholesterol (HDL-C) were described as independent variables. In these analyses, dependent variables included the following: age, sex, BMI and the use of sleeping pills and statin.

For dependent variables, we used multiple linear regression analysis. Of note, non-normal distributed numbers were logarithmically transformed. Specifically, T2D's duration was logarithmically transformed after adding 0.01 to calculate the zero value. Finally, four multivariate models were used after adjusting for multiple dependent variables as follows: (1) model 1 included REM-AHI, (2) model 2 included NREM-AHI, (3) model 3 included both REM-AHI and NREM-AHI, (4) model 4 included AHI. Additionally, we conducted a multivariable logistic regression analyses with target values (systolic BP < 130 mmHg, HbA1c < 7%, non-HDL-C < 150 mg/dL, TG < 150 mg/dL and HDL-C > 40 mg/dL), which were recommended by the Japan Diabetes Society [15]. Furthermore, we examined REM-AHI as categories with stratification into quartiles, calculating odds ratio and 95% confidence intervals. All data were analysed with Dr. SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan), and p values < 0.05 were considered statistically significant.

Results

Of the 528 patients who underwent polysomnography during the research period, 185 were included in analyses (Fig. 1). The clinical characteristics of our cases are described in Table 1. Table 2 shows the results of the multiple linear regression analyses. We observed that REM-AHI was associated with systolic and mean BP ($\beta = 0.18$; $p = 0.18$) while NREM-AHI or AHI was not. In contrast, REM-AHI was not

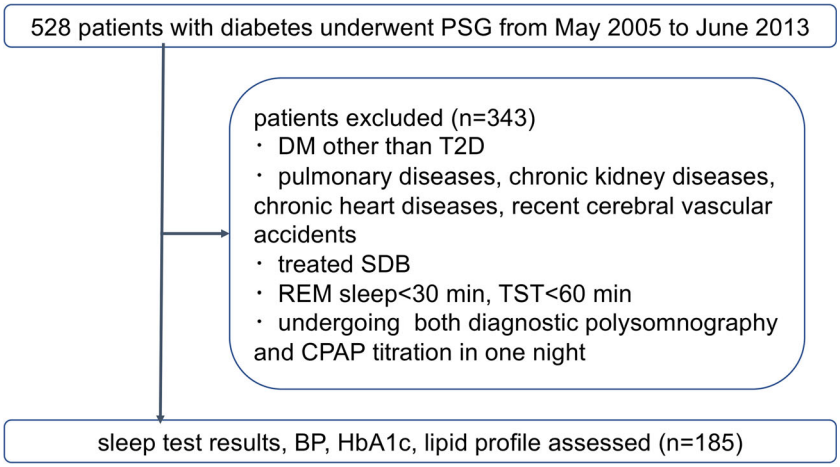

Fig. 1 Patient selection process. DM, diabetes mellitus; T2D, type 2 diabetes; SDB, sleep-disordered breathing; REM, rapid eye movement; TST, total sleep time; CPAP, continuous positive airway pressure; HbA1c, glycated haemoglobin

Table 1 Characteristics of participating patients

n = 185	
Age (years)	58.0 ± 11.8
Men (*n* (%))	161 (87%)
BMI (kg/m^2)	26.0 (24.1–28.9)
HbA1c (%)	7.4 (6.8–8.4)
DM duration (years)	5 (1–12)
Current smoking (*n* (%))	45 (24.3%)
ACE-I/ARB use (*n* (%))	49 (26.5%)
Statin use (*n* (%))	47 (25.4%)
Sleeping pill use (*n* (%))	20 (10.8%)
Insulin use (*n* (%))	14 (7.6%)
Systolic BP (mmHg)	134 ± 19.1
Mean BP (mmHg)	97.5 ± 13.8
Diastolic BP (mmHg)	79.4 ± 12.9
TG (mg/dL)	143 (97–195)
T-Chol (mg/dL)	191 (167–210)
Non-HDL-C (mg/dL)	143 (120–163)
HDL-C (mg/dL)	44 (39–53)
AHI (/h)	29.5 (18.0–45.3)
REM-AHI (/h)	35.1 (21.1–53.1)
Supine-AHI (/h)	39.5 (22.3–55.8)
NREM-AHI (/h)	29.4 (16.3–45.4)
Lowest SaO_2 (%)	80 (72–84.3)
3% ODI	4.25 (0–27.0)
T90SPT (%)	6.6 (1.2–22.2)
Arousal index (events/h)	34.5 (25.6–45.4)
Total sleep time (min)	373 ± 51.2

Values are mean ± SD, median (interquartile range) or percentage (%)

BMI, body mass index; *HbA1c*, glycated haemoglobin; *ACE-I*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BP*, blood pressure; *TG*, triglyceride; *T-Chol*, total cholesterol; *HDL-C*, high density lipoprotein cholesterol; *AHI*, apnoea–hypopnea index; *REM*, rapid eye movement; *NREM*, non-REM; *T90SPT*, percent time spent at SaO_2, 90%

associated with HbA1c or lipid profile. When BP, HbA1c or lipid profile were regarded as binary independent variables, logistic regression analyses revealed no statistically significant association between binary BP, HbA1c or lipid profile and REM-AHI, NREM-AHI or AHI.

Discussion

The current study demonstrated that, in multiple linear regression analyses, REM-AHI was independently associated with systolic and mean BP, while NREM-AHI or AHI was not. Additionally, REM-AHI was not associated with HbA1c, non-HDL-C, TG or HDL-C.

Previous studies reported the association between SDB and hypertension [2, 16]. For instance, Marin et al. showed that OSA's presence was associated with an increased adjusted risk of incident hypertension vs. participants without OSA [2]. Two additional studies associated REM-AHI with hypertension's presence or onset, while NREM-AHI was not [8, 9]. In multiple linear regression analyses, our study showed a statistically significant association between continuous systolic BP or mean BP and REM-AHI (Table 3). On the contrary, the logistic regression analyses indicated no association between the presence of hypertension and REM-AHI. Similarly, no association was revealed between continuous BP and AHI. Such findings may be explained by some factors such as the percentage of patients taking anti-hypertensive drugs, the definition of hypertension and patient characteristics limited to T2D patients.

Several mechanisms may link REM-AHI and BP. However, we believe that the critical mechanism is the difference in sympathetic activity between REM and non-REM sleep. SDB plays a role as a cardiovascular risk factor by boosting sympathetic activity through its effect on BP and heart rate [17, 18]. Of note, sympathetic activity is more aroused during REM than NREM sleep [6]. Additionally,

Table 2 Results of multiple linear regression analysis for systolic BP using AHI or REM/NREM-AHI

	Variables	Ln REM-AHI	Ln NREM-AHI	Ln AHI
Model 1 (Ln REM-AHI)	*B*	4.347	-	-
	P	0.018	-	-
Model 2 (Ln NREM-AHI)	*B*	-	1.41	-
	P	-	0.434	-
Model 3 (Ln REM-AHI + Ln NREM-AHI)	*B*	4.353	− 0.016	-
	p	0.026	0.993	-
Model 4 (Ln AHI)	*B*	-	-	2.782
	p	-	-	0.164

The model was adjusted by age, sex, BMI, sleeping pill use and smoking habit

BP, blood pressure; *AHI*, apnoea–hypopnea index; *REM*, rapid eye movement; *NREM*, non-REM

the hypoglossal nerve's inhibition during REM sleep exacerbates the upper airways' obstruction [19]. Therefore, SDB events during REM sleep may be more critical than those during NREM sleep as a risk factor related to hypertension.

A large body of literature suggests an independent association between SDB and glycemic control. Specifically, the previous meta-analysis associated SDB with the development of diabetes [20]. In T2D patients, there is a robust, graded relationship between OSA's severity and HbA1c [21]. Furthermore, in their report, Grimaldi et al. showed an independent association between REM-AHI and increasing levels of HbA1c, contrary to NREM-AHI [22]. Our study, however, did not show a statistically significant association between AHI, REM-AHI or NREM-AHI and HbA1c. We believe that these results may be because, as opposed to Grimaldi et al.'s study, where all patients were under stable glycemic control in the previous 3 months [22], individuals in the present study were not. As a consequence, patients may have been analysed under fluctuating glycemic control. Another study showed a significant association between NREM-AHI and HbA1c level in total and non-diabetic individuals, but not T2D patients [23]. This finding is in agreement with our study, showing no independent association between HbA1c and REM or NREM-AHI in patients with T2D. Patients' characteristics (whether non-diabetic patients were included or not) and SDB's severity might affect the results.

A previous report demonstrated that AHI was associated with HDL-C but not with total cholesterol, TG or LDL-C. Sympathetic activities are thought to be a mechanism linking OSA and lipid profile through some studies focusing on α- and β-adrenoceptor blockers [4]. Another previous article showed the association between NREM-AHI and lipid profile in patients with and without T2D [24]. Importantly, to date, there have been few reports assessing the relationship between REM-AHI and lipid profile. We did not observe an association between AHI, REM-AHI, NREM-AHI and lipid profile. Of note, we believe that our results may have been affected by the fact we included more patients being treated for dyslipidemia than the previous study and by the fact patients with T2D were more likely to suffer from hypertriglyceridemia.

The present study has several limitations. First, we were unable to remove the selection bias thoroughly because this was a single centre, cross-sectional study. Future cohort or intervention studies are needed. Second, the small sample size of our study may limit the associations between SDB and CVD risk factors. Therefore, additional investigations with a

Table 3 Results of multiple linear regression analysis for mean BP using AHI or REM/NREM-AHI

	Variables	Ln REM-AHI	Ln NREM-AHI	Ln AHI
Model 1 (Ln REM-AHI)	B	2.841	-	-
	p	0.033	-	-
Model 2 (Ln NREM-AHI)	B	-	1.339	-
	p	-	0.303	-
Model 3 (Ln REM-AHI + Ln NREM-AHI)	B	2.682	0.46	-
	p	0.058	0.737	-
Model 4 (Ln AHI)	B	-	-	2.192
	p	-	-	0.129

The model was adjusted by age, sex, BMI, sleeping pill use and smoking habit

BP, blood pressure; *AHI*, apnoea–hypopnea index; *REM*, rapid eye movement; *NREM*, non-REM

larger sample size are required. Third, since only T2D patients were selected for the analysis, we are unsure whether or not the results of our study can be applied to the general population. Lastly, we used BP data measured at one time point. Considering BP's fluctuation, using BP data taken at several time points or ambulatory blood pressure monitoring may need to be investigated.

In conclusion, the present study has three strengths. First, we used polysomnography rather than home sleep apnoea testing. Second, it shows an independent association between continuous BP value and REM-AHI, adjusted by multiple risk factors. Third, we demonstrated comprehensive analyses for assessing association between REM-AHI and several cardiovascular risk factors in the same sample. We believe that this study provides further evidence that REM-AHI is associated with systolic and mean BP in T2D patients.

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Data availability The data were collected by the authors in Toranomon Hospital.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The institutional review board of Toranomon Hospital approved the study protocol.

Consent to participate The informed consent was obtained through an opt-out policy.

Consent to publication The informed consent was obtained through an opt-out policy.

Code availability Dr. SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan).

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