行政院國家科學委員會專題研究計畫　成果報告

阻塞性睡眠障礙與第二型糖尿病之相關性研究

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OBJECTIVE

In the recent years, obstructive sleep disorder or obstructive sleep apnea (OSA) is suggested to be associated with the vascular disease (ex: hypertension, atherosclerosis) and the metabolic syndrome (ex: insulin resistance, obesity) respectively. It has been shown that there exists some extent of correlation among all of the diseases mentioned above. Insulin resistance, which is characterized by hyperinsulinemia, glucose intolerance, hypertension and dyslipidemia, is well established as a risk factor for vascular disease. Furthermore, there were some evidences showing that insulin resistance predisposes to cardiovascular risk. Hence in the present study, we will investigate the relationship between OSA and metabolic syndrome including type 2 diabetes.

METHODS

Subjects

The present study was based on 606 subjects who continuously attended to metabolic or sleep clinics with a chief complaint of sleep disturbance and were impressed as SDB, including the subtype of sleep apnea, i.e. upper airway resistance syndrome.

All the subjects had a clinical interview and evaluation for internal medicine, neurological and psychological major problems, at which time they were requested for detailed information on demographic, lifestyle, and behavior risk factors. Besides of completing a written informed consent, a validated sleep questionnaire and Epworth Sleepiness Scale, body mass index, neck circumference, hip and waist width measurements were obtained.

Before data calculating and analysis we had excluded any major diagnosed cardiovascular or cerebrovascular diseases, such as coronary artery diseases, heart disease, arrhythmia, congestive heart failure, chronic obstructive lung disease, stroke, and chronic renal failure.

Sleep Studies

The overnight sleep studies were conducted at the Sleep Center of Chung Shan Medical University Hospital, Taichung, Taiwan. All persons were requested to arrive at the sleep laboratory between 8:00 pm and 9:00 pm and underwent one night polysomnography. After the assessment of life style habitues by questionnaire, technician affixed polysomnography leads to each participant and performed calibrations. An 18-channel polysomnographic recording system (model 78, Grass Instruments, Quincy, Mass.) was used to assess sleep state and respiratory and cardiac variables. The recordings of electroencephalography (C3/A2, C4/A1), electrooculography, and submental electromyography to assess sleep state. These signals were used to determine the sleep stage for each 30-second interval of the polysomnographic record, according to conventional criteria. Oxyhemoglobin saturation (pulse oximetry), nasal and oral airflow (thermister), nasal pressure (nasal cannulae and pressure sensor), rib cage and abdominal respiratory motion were all measured to assess episodes of sleep-disordered breathing. Sleep staging and sleep-disordered breathing were subsequently scored using standard techniques but with all apneas and hypopneas inductance plethysmography, inclusive of a mandatory minimum 4% oxygen desaturation. Sleep stages and respiratory events were

assessed by trained technicians and reviewed by an expert sleep specialist.

Cessation of airflow for at least 10 seconds was defined as an episode of apnea.

A discernible reduction in the sum amplitude of the rib-cage plus the abdominal excursions on respiratory inductance plethysmography that lasted at least 10 seconds and that was associated with a reduction in the oxyhemoglobin saturation of at least 4 percent was defined as an episode of hypopnea. The respiratory distress index (RDI) was defined as the average number of episodes of apnea and hypopnea per hour of objectively measures sleep and was the summary measurement of the occurrence of SDB.

The American Academy of Sleep Medicine arousal criteria were used. In brief, arousals were defined as a sudden rise in EEG frequency to alpha or theta activity lasting at least 3 seconds but less than 15 seconds preceded by at least 10 seconds of sleep.

Sleep-Quality Variables

Entirely, eleven Sleep-Quality Variables to measure sleep quality were calculated: Total sleep time; the percentage of total sleep time spent in Stage 1 (Stage I%), Stage 2 (Stage II%), Stage 3 (Stage III%), Stage 4 (Stage IV%), and Stage rapid eye movement (REM) sleeps (Stage REM%); RDI; the arousal index; desaturation index, lowest oxygen saturation (LOS, %) and duration of O2 saturation less than 90%.

Blood Sampling and Biochemical Variables

Venous blood was collected between 6:00 and 7:00 am before the subject had any diet. Fasting glucose was measured after an overnight fast in whole blood using glucose-oxidase-based assay (*****YSI 2300, Analytial Technologies, Farnborough, UK). Fasting cholesterol, triglyceride (Bayer Corporation, Tarrytown, NY, USA), and HDL cholesterol (Sigma Diabnostics, St. Louis, MO, USA) concentrations were measured after an overnight fast using an immunocolourimetric assay on an ADVIA® 1650 chemistry system (Bayer Corporation, Tarrytown, NY, USA). Low density lipoprotein (LDL) cholesterol was derived using the Friedwald equation. Serum levels of high-sensitivity C-reactive protein (hsCRP) were measured with a latex particle-enhanced immunoturbidimetric assay. Serum CRP was assayed with a high-sensitivity assay, For 81% of he samples, the aassay performed had a lower limit of 0.1 and an upper limit o 90 mg/L (Immulite High Sensitivity CRP, Immulite 2000 Analyzer); the remaining 29% were assayed with a lower detectable limit of 0.15 mg/L (BNII nephelometer [N High Sensitivity CRP, Dade Behring Inc]). Serum Uric acid concentration was measured using standard techniques.

The components of metabolic syndrome were set according to the definition of the National Cholesterol Education Program's Adult Treatment Panel III (ATP III, 2001), which was relatively more useful for clinical practice. The items included 1) fasting plasma glucose ≥ 6.1 mmol/L, 2) hypertension: blood pressure ≥ 135/85 mm Hg, 3) HDL cholesterol < 1.0 mmol/L (male), < 1.3 mmol/L (female), 4) triglycerides ≥ 1.7 mmol/L and 5) central obesity: waist circumference > 102/90 cm (male), >88/80 cm (female).

Analysis and Statistics

Data are expressed as the mean ± standard error. The inter-group differences of variables were examined by ANOVA. A value of $p \leq 0.05$ was considered statistically significant without adjustment for multiple comparisons. A log transformation was used if variables were not normally distributed. SPSS (version 12) software was used to perform all analysis.

RESULTS

Total 606 subjects were recruited for the study. Among them 226 were diagnosed as metabolic syndrome, while 22 of 226 were type 2 diabetic patients. The demographic characteristics are shown in table 1. According to the components of metabolic syndrome involved, they are categorized into 6 groups. Age, BMI, neck and waistline circumference all increased gradually by the increased numbers of metabolic syndrome components. Blood pressure, including systolic, diastolic and mean pressure in the evening or morning revealed the same trend. Glucose, triglycerides, cholesterol, LDL, Uric acid, hs-CRP or Log hs-CRP levels also increased gradually as mentioned above, while HDL decreased in an opposite manner. These data are all statistically significant, indicated that these subjects are a good sample of metabolic syndrome for further analysis.

The data for sleep quality are shown in Table 2. Total sleep time of each group is more than 240 minutes, which is long enough for sleep quality analysis. Time percentage for stage III+IV decreased by the increased metabolic syndrome components, except those with 5 ones. RDI, an indicator of obstructive sleep apnea syndrome, strikingly increased gradually by the increased numbers of metabolic syndrome components. Like hs-CRP, when components of metabolic syndrome are used as a function, RDI increases linearly (Fig.1, Fig.2). Arousal index, desaturation index and duration of Sa02 less than 90% also show the trend. In addition, the lowest oxygen saturation was 88.8±6.2 % for those without any component, and decreased gradually to 74.2±15.6 % for those with 5 components.

Further sleep analysis for a subgroup of 22 type 2 diabetic patients, RDI did not show significant difference according to BMI, HbA1c, cholesterol, LDL, and HDL levels (data not shown). A slight increased RDI by the increased diastolic BP was observed (Fig.3).

CONCLUSION

The strong correlation between OSA and metabolic syndrome (including a subgroup of type 2 diabetes) has been confirmed in this study. Increased hs-CRP correlated significantly with severity with RDI suggested systemic inflammation involved in OSA, which might be a pathogenesis for cardiovascular disease. Blood pressure also correlated well with RDI, with the increased components of metabolic syndrome. The effect is also seen in type 2 diabetic patients. However, beside BP, there were no correlations among HbA1c, lipid profiles and RDI in type 2 diabetes.

It's of significance that from this study, we could realize the relationship between OSA and metabolic syndrome including type 2 diabetes, and might open a new therapeutic development for these patients, especially for those with severe insulin resistance, uncontrolled hypertension or other chronic complications.

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Table 1. Demographic characteristic of subjects with different number of components for metabolic syndrome (1)

	0 （n=103）	**1 （n=147）**	**2 （n=130）**	**3 （n=107）**	**4 （n=89）**	**5 （n=30）**
Female percentage,%	56%	45%	35%	40%	28%	60%
Age, *yrs*	37.9 ± 12.3	45.± 16.6	48.9 ± 14.9	50.8 ± 14.4	54.5 ± 12.2	50.9± 10.8
BMI, *kg/m²*	21.5±2.6	22.9±3.6	24.2±3.54	26.3±4.8	27.6±4.1	28.2±4.07
Neck circumference, *cm*	34.1 ± 3.3	36.2 ± 6.3	37.2 ± 3.2	38.4 ± 5.1	39.5± 4.3	38.8±3.5
Waistline circumference[1], *cm*	75.3 ± 6.9	81.5 ±9.6	88 ± 9.7	93.1 ± 13.5	97.3 ± 9.4	97.3±8
Buttock circumference[2], *cm*	92.9 ± 4.9	94.8 ± 6.6	96.6 ± 6.9	101.6 ± 15	101.9 ± 9.3	105.7 ± 9.1
ESS	6.8±4.4	6.9±3.9	6.5±4.3	6.9±4.7	8.1±4.2	6.8±4.7
Evening BP, *mmHg*						
Systolic	113.4 ± 13	123 ± 16.6	129 ± 18	132.7 ± 23	138.8 ± 19.7	136.6 ± 17.8
Diastolic	74.1 ± 11.1	81.1 ± 11.8	85.2 ± 12.3	87.7 ± 13.7	90.3 ± 13	86.9 ± 11.1
Mean	87.2 ± 10.3	95.1 ± 12.4	99.8 ± 13.2	102.8 ± 15.9	106.5 ± 12.9	103.4 ± 12.2
Morning BP, *mmHg*						
Systolic	108.9 ± 9.2	122.6 ± 15.6	131.3 ± 20.6	136 ± 23.6	145.1 ± 23.4	143 ± 11.7
Diastolic	72.6 ± 7.7	83.1 ± 12.4	88.9 ± 12.9	92.3 ±14.3	93.3 ± 12.4	92.4 ± 9.7
Mean	84.7 ± 7	96.2 ± 12.2	103 ± 14.1	106.8 ± 15.9	110.6 ± 14.3	109.3 ± 8.2

Table 1. Demographic characteristic of subjects with different number of components for metabolic syndrome (2)

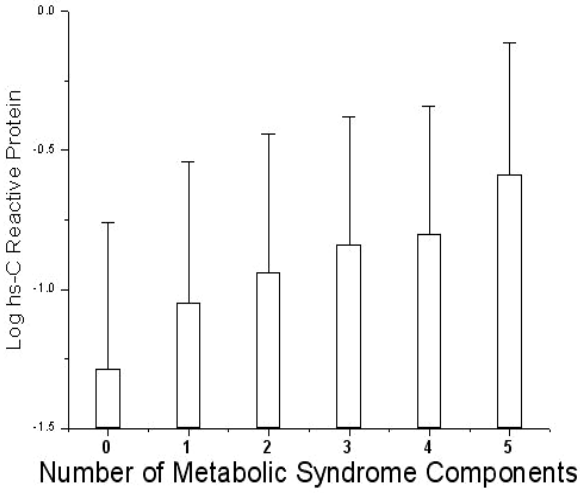
	0 （n=103）	**1 （n=147）**	**2 （n=130）**	**3 （n=107）**	**4 （n=89）**	**5 （n=30）**
Glucose, *mg/dL*	94.6 ± 7.9	97.7 ± 22.4	103.5 ± 21.7	112.4 ± 37	132.1 ± 42.1	145 ± 40
Triglycerides, *mg/dl*	76.4 ± 31.3	97.1 ± 89.4	139.2 ± 164.4	181.7 ± 200.5	213.7 ± 134.6	280.1 ± 252.8
Cholesterol, *mg/dl*	180 ± 39.1	180 ± 33.5	181.6 ± 35.2	192.7 ± 44.3	196.6 ± 35	202.3 ± 50
HDL, *mg/dL*	56.6 ± 10.5	47.7 ± 11.7	45.2 ± 13.2	43 ± 36.2	35.1 ± 8	35.3 ±7.1
LDL, *mg/dL*	112.7 ± 38.1	118.1 ±32	119 ± 30.6	130 ± 45.1	128.7 ± 32.1	133.3 ± 40.5
hs-CRP, *mg/dL*	0.1 ± 0.4	0.2 ± 0.4	0.2 ± 0.7	0.3 ± 0.4	0.3 ± 0.5	0.5 ± 0.6
Log hs-CRP, *mg/dL*	-1.3 ± 0.6	-1.1 ±0.5	-0.9 ± 0.5	-0.8 ± 0.5	-0.8 ± 1.1	-0.6 ± 0.5
Uric Acid, *mg/dl*	5.1 ± 1.5	5.7 ± 1.7	6.0 ± 1.6	6.5 ± 2.1	6.9 ± 1.7	7.0 ± 1.7

Table 2. Sleep quality study for subjects with different number of components for metabolic syndrome (1)

	0 （n=103）	**1 （n=147）**	**2 （n=130）**	**3 （n=107）**	**4 （n=89）**	**5 （n=30）**
Total Sleep Time(TST), *min*	274 ± 54.4	264.1 ± 58.6	245 ± 68.7	270.2 ± 60.4	253.1 ± 64.4	276.3 ± 60.8
Non-REM, *%*						
Stage I,*%*	12.2 ± 7.4	14.8 ± 8.1	17.3 ± 9.9	18.1 ± 12.9	16.4 ± 9.8	12.3 ± 17.1
Stage II, *%*	55.8 ± 16.3	51.6 ± 15.8	46.4 ± 15.3	51.2 ± 15.9	49 ± 14.9	51.6 ±17.9
Stage I+II, *%*	67.9 ± 13.4	66.5 ±14.5	63.1 ± 15.2	69.4 ± 13.9	66.1 ± 14.3	66.9 ± 14.6
Stage III,*%*	4.2 ± 6.1	2.8 ± 4.3	3.5 ± 5.1	2.4 ± 4.2	2.2 ± 4.2	3.8 ± 4.5
Stage IV, *%*	2.0 ± 4.7	1.4 ± 4.3	0.9 ± 3.7	0.9 ± 2.8	0.4 ± 2.1	0.7 ± 3.4
Stage III+IV,*%*	5.6 ± 7.1	4.2 ± 7.2	4.4 ± 7.1	3.1 ± 5.8	2.6 ± 5.1	4.4 ± 6.1
REM, *%*	9.7 ± 5.8	8.6 ± 6.4	7.9 ± 5.8	9.3 ± 7.2	8.6 ± 6	10.2 ± 5.9

Table 2. Sleep quality study for subjects with different number of components for metabolic syndrome (2)

	0 n=103	1 n=147	2 n=130	3 n=107	4 n=89	5 n=30
Respiratory Distress Index（RDI）, *events/hr*	13.9 ± 14	24.8 ± 25	30 ± 24.8	35.6 ± 27.2	45.7 ± 30.9	38.9 ± 32.1
Arousal Index, *events/hr*	28.4± 16	35.1 ± 18.7	40.1 ± 19.5	40.9 ± 19.8	48.4 ± 20.5	44.1 ± 23.4
RDI / Arousal ratio （R/A）	0.6 ± 0.7	0.8 ± 0.9	0.7 ± 0.5	0.9 ± 0.7	0.9 ± 0.7	0.8 ± 0.4
Desaturation Index (DsI), *events/hr*	6.0 ± 14.1	14.6 ± 24.8	20.6 ± 23.2	26.0 ± 27	31 ± 26.4	24.5 ± 27.9
Lowest Oxygen Saturation(LOS), *%*	88.8 ± 6.2	86 ± 10	84 ± 9.1	78.7 ± 15.1	77.6 ± 15.1	74.2 ± 15.6
Duration of SaO2<90%, *min*	1.7 ± 3.8	9.8 ± 27	14.7 ± 31.1	26.8± 54.8	35.3 ± 56.5	31.3 ± 51.3



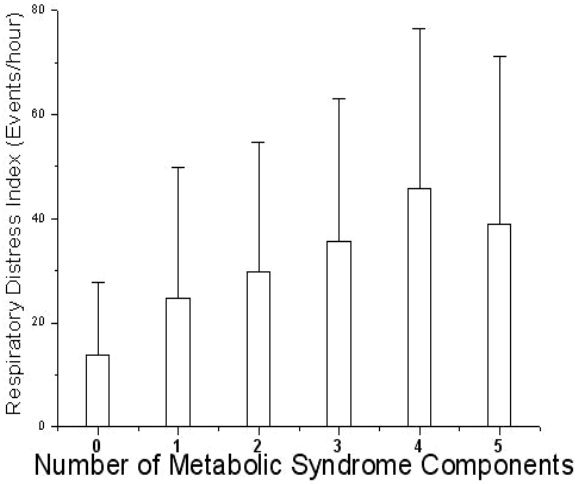


Fig.1. The relation between hs-CRP and different number of components for metabolic syndrome.

Fig.2. The relation between RDI and different number of components for metabolic syndrome.

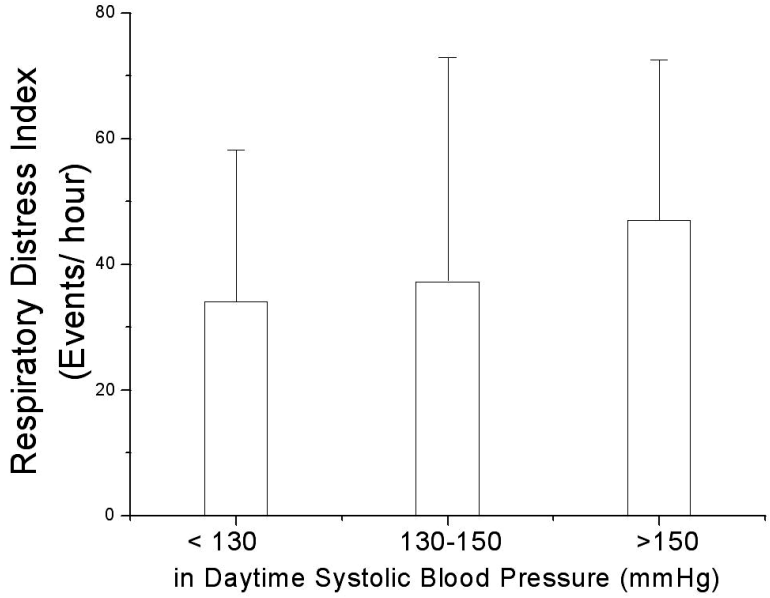


Fig.3 The relation between RDI and daytime systolic blood pressure of type 2 diabetes.