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Hyperlipidaemia in patients with sleep-related breathing disorders: Prevalence & risk factors

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***Background & objectives*: Several studies have shown a close relationship between obstructive sleep apnoea (OSA) and dyslipidaemia. This study was designed to clarify the relationship of metabolic dysfunctions in sleep related-breathing disorders (SRBD), including OSA and simple snoring. The end point was to determine the prevalence of hyperlipidaemia and hyperuricaemia in SRBD. Factors contributing to hyperlipidaemia and hyperuricaemia in SRBD were also evaluated.**

***Methods*: Outpatients >20 yr old with complaint of habitual snoring were prospectively enrolled. All patients underwent an overnight polysomnography (PSG) in a sleep laboratory and blood assay after overnight fasting. The factors of gender, age, body mass index (BMI), apnoea-hypopnoea index (AHI), and desaturation index (DI) were recorded in the PSG report. A logistic regression analysis was conducted to investigate the relationship between metabolic dysfunctions and these factors.**

***Results*: Of the 275 patients (88.4% male), 236 (85.8%) were diagnosed with OSA (AHI>5/h). The mean (± SD) of age, BMI, AHI, and DI were 44.2 ± 11.4 yr, 27.4 ± 4.0 kg/m^2, 37.9 ± 30.6/h, and 21.2 ± 23.2/h, respectively. The overall prevalence of hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia in this study was 61.1, 55.3, and 25.8 per cent, respectively. Logistic regression analysis revealed that DI was a significant independent factors contributing to hypercholesterolaemia [odds ratio (OR)=1.016, *P*=0.010, 95% confidence interval (CI)=1.004-1.028] and hypertriglyceridaemia (OR=1.021, *P*=0.002, 95% CI=1.008-1.034).**

***Interpretation & conclusions*: The data of the present study support a high prevalence of hyperlipidaemia in SRBD. DI may be a determining factor contributing to hyperlipidaemia in SRDB. Underdiagnosis of hyperlipidaemia in SRBD is a critical problem.**

Key words Dyslipidaemias - obstructive sleep apnoea - sleep-related brathing - snoring

Sleep-related breathing disorders (SRBD), including upper-airway resistance syndrome, snoring, and obstructive sleep apnoea (OSA), are prevalent conditions in younger and older population[1-3]. The major complications of SRBD are hypertension, cardiovascular disease, insulin resistance, and neuropsychiatric impairment[4]. Metabolic dysfunction in OSA patients has been studied[5–11]; however, neither the association between dyslipidaemia and OSA nor the mechanism involved therein has been elucidated. Several studies have shown a close relationship between OSA and an increasing prevalence of dyslipidaemia[11,12], while others suggest that dyslipidaemia is related to other factors such as underlying obesity or type-2 diabetic mellitus[5,8]. Although not confirmed, an association between OSA and increased haematocrit levels and hypothyroidism has also been noted[13,14]. This study was therefore carried out to evaluate the prevalence of hypercholesterolaemia, hypertriglyceridaemia, hyperuricaemia, polycythemia, and hypothyroidism in SRBD patients in Taiwan and to analyze whether there are any associations between these factors and SRBD.

Material & Methods

Patients: From January 1997 to December 2000, 283 consecutives outpatients were enrolled in this prospective study at Chang Gung Memorial Hospital, Taoyuan, Taiwan. Inclusion criteria were that the patients were more than 20 yr of age and had a chief complaint of habitual snoring. Patients with clinical heart failure signs, unstable angina, liver cirrhosis, end-stage renal disease, chronic obstructive pulmonary disease, haematological disease, or diagnosed cancer were excluded. The Research and Ethics Committee of the Chang Gung Memorial Hospital (CGMH) approved the study protocol, and informed consent was obtained from all patients.

Sleep study: Standard overnight polysomnography (PSG) (Nicolet UltraSom System, Madison, WI, USA) was performed to document sleep parameters and architecture in each patient in a sleep laboratory, between 22:00 and 06:00-08:00 h. Variables recorded in the quiet and darkened room included two channels of electroencephalogram (EEG) (C3/A2, C4/A1); bilateral electro-oculogram; chin and left and right anterior tibial electromyogram; electrocardiogram; airflow, measured by nasal and buccal thermistors; chest and abdominal wall movement by inductive respiratory plethismography bands; snoring with a neck microphone; and arterial oxygen saturation (SpO_2) by pulse oximetry. Video recording assessed the behaviour of all patients. All measurements were collected on a computerized sleep system (Ultrasom.; Nicolet, Middleton, TX, USA). Apnoea was defined as more than 90 per cent dropping of baseline airflow with continued chest wall and abdominal wall movement for a minimum of 10 sec, regardless of whether or not there was an associated oxygen desaturation or sleep fragmentation; baseline is defined as the mean amplitude of the three largest breaths in the two minutes preceding the onset of the event[15,16]. The definition of hypopnoea was a 50 per cent or greater reduction in airflow for a minimum of 10 seconds, associated with an equal to or greater more than a 4 per cent drop in SpO_2 or an EEG alpha wave arousal[15,16]. The definition of desaturation episode was equal or more than a 4 per cent drop in SpO_2, which was induced by apnoea or hypopnoea events. Apnoea hypopnoea index (AHI) was the number of apnoea plus hypopnoea events per hour of total sleep time, and desaturation index (DI) was the number of desaturation episodes per hour of total sleep time. OSA was defined according to American Academy of Sleep Medicine criteria[16]. Patients with an AHI score lower than five per hour was classified as a simple snorer. Gender, age, body weight, body height, and DI were recorded simultaneously with PSG. Body mass index (BMI) was defined as weight (kg) divided by height $(m)^2$.

Metabolic survey: Patients were asked to consume nothing during the PSG study. At the end of the study, patients were shifted to a sitting position, and blood sample was drawn from the upper limb by venipuncture between 06:00 and 08:00 h. Cholesterol, triglyceride (TG), uric acid, and TSH were analyzed via the colorimetry method (Hitachi 717, Hitachi Ltd., Tokyo, Japan). Haematocrit (Hct) was examined via the automated cell count method (SYSMEX NE-8000, Toa Medical Electronics Co., Ltd., Kobe, Japan). Patients with a history of hypercholesterolaemia, hypertriglyceridaemia, or hyperuricaemia who had been currently under treatment by diet or medication-as well as patients with fasting cholesterol >200 mg/dl, triglyceride >150 mg/dl, and uric acid >8 mg/dl were defined as having hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia, respectively. Polycythemia was defined as Hct >52 per cent in males and Hct >48 per cent in females. Hypothyroidism was defined as a TSH level greater than 5.5 IU/ml.

Statistical analysis: The categorical data included OSA or simple snorers, gender, hypercholesterolaemia, hypertriglyceridaemia, hyperuricaemia, polycythaemia, and hyperthyroidism. The numerical data included age, BMI, AHI, and DI. Chi-square test was used to compare the categorical data between OSA and simple snorers, and odds ratios (ORs) were computed for these factors. To compare the numerical data between OSA and simple snorers, a two-sample t-test was used. To exclude the confounding factors, a logistic regression analysis was performed to analyze the effects of gender, age, BMI, DI, and AHI on hypercholesterolaemia, hypertriglyceridaemia, and hyperuricemia. All tests were two-tailed, and a $P<0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 283 patients were enrolled in this study, but eight patients who did not perform the PSG were excluded from the final analyses. Of the 275 patients, 88.4 per cent were male, and 236 patients were diagnosed with OSA. The mean age, BMI, AHI, and DI in all patients were 44.2 ± 11.4 yr, 27.3 ± 4.0 kg/m^2, 37.9 ± 30.6/h, and 21.2 ± 23.2/h, respectively. In all, 168 (61.1%), 152 (55.3%), and 71 (25.8%) patients, respectively, had hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia (Table I); 203 (74%) patients had hyperlipidaemia, but only seven of them were diagnosed and under control before enrolling in our study. In the OSA group, the mean age, BMI, AHI, and DI were 44.6 ± 11.4 yr, 27.7 ± 4.0 kg/m^2, 43.8 ± 29.0/h, and 23.9 ± 22.9/h, respectively, whereas in the simple snorer group, those figures were 41.7 ± 10.9 yr, 25.3 ± 3.4 kg/m^2, 2.3 ± 1.5/h, and 3.5 ± 16.3/h, respectively. The OSA group was predominantly male ($P<0.001$), and had larger BMI ($P<0.001$), DI ($P<0.001$), and higher hypertriglyceridaemia ($P<0.05$) prevalence than did simple snorer group.

The Fig. shows the prevalence of hyperlipidaemia in different desaturation index groups. Patients were divided into three groups according to DI: DI<5/h (LDI), 5/h<DI<30/h (MDI), and 30/h<DI (HDI).

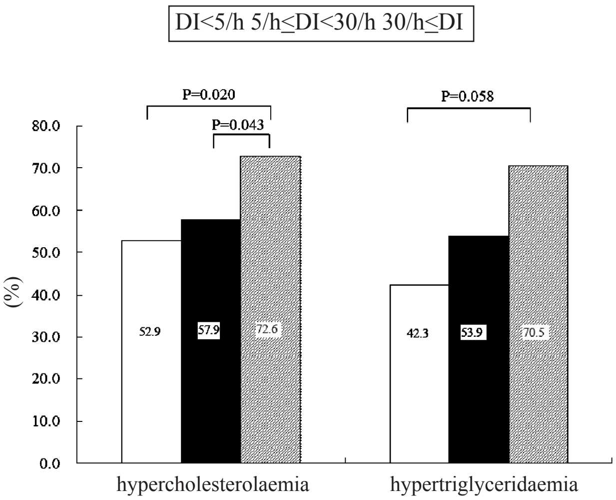

Fig. Prevalence of hyperlipidaemia in different desaturation index categories. *P* value is adjusted for gender, age, AHI and BMI. (DI, desaturation index; AHI, apnoea/hypopnoea index; BMI, body mass index).

After adjusting for gender, age, AHI, and BMI, the prevalence of hypercholesterolaemia in the HDI group was significantly higher ($P<0.05$) than in the LDI group. In addition, after controlling for confounding otherwise caused by gender, age, AHI and BMI, a logistic regression analysis revealed that DI was the independent risk factor for hypercholesterolaemia (OR=1.016, $P=0.010$, 95% CI=1.004-1.028), hypertriglyceridaemia (OR=1.021, $P=0.002$, 95% CI=1.008-1.034), and hyperuricaemia (OR=1.013, $P=0.036$, 95% CI=1.001-1.026).

An analysis of TSH and T4 data in 88 patients [68 (77.3%) were male and 65 (73.9%) had OSA] revealed no hypothyroidism in any of the 88 patients. Haematocrit levels revealed no polycythaemia in the 238 patients.

Table I. Demographic and metabolic characteristics in the simple snorer and OSA groups

	Overall (n=275)	Simple snorer (n=39)	OSA (n=236)	Odds ratio (95% CI)
Age yr (mean ± SD)	44.2 ± 11.4	41.7 ± 10.9	44.6 ± 11.4	
BMI kg/m^2 (mean ± SD)	27.3 ± 4.0	25.3 ± 3.4	27.7 ± 4.0*	
Gender (male) (%)	88.4	69.2	91.5	1.3 (1.1-1.6)
Hypercholesterolaemia (>200 mg/dl) (%)	61.1	53.8	62.3	1.4 (0.7-2.8)
Hypertriglyceridaemia (>150 mg/dl) (%)	55.3	38.5	58.1	2.3 (1.2-4.6)*
Hyperuricaemia (>8 mg/dl) (%)	25.8	20.5	26.7	1.5 (0.6-3.4)
Polycythaemia	0	0	0	
Hypothyroidism (%)	0	0	0	

CI, Confidence interval; OSA, obstructive sleep apnoea
$^*P<0.05$, OSA versus simple snorer

Discussion

Kiely & McNicholas[17] reported the prevalence of hypercholesterolaemia and hypertriglyceridaemia in OSA patients as 46 and 47 per cent, respectively. In our study, the prevalence of hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia in SRBD was 61.1, 55.3 and 25.8 per cent, respectively. A comparison of previously published data from Taiwan reveals a significantly higher prevalence of hypercholesterolaemia and hypertriglyceridaemia in our SRDB patients (Table II)[18,19]. Compared to simple snorers in our study, the ORs (95% CI) of metabolic factors in OSA were high: 1.4 (0.7-2.8) in hypercholesterolaemia, 2.3 (1.2-4.6) in hypertriglyceridaemia, and 1.5 (0.6-3.4) in hyperuricaemia. Although not statistically significant, the prevalence of hyperlipidaemia increased along with the severity of SRDB. In addition to BMI, our study also revealed that DI was an independent risk factor for hyperlipidaemia. These results indicate that SRBD-induced intermittent hypoxia may influence lipid metabolism. Higher BMI and DI may be the risk factors for hyperlipidaemia in such patients.

Some investigators reported the association between OSA and dyslipidaemia. No difference of serum cholesterol and triglyceride between OSA and control group except for HDL dysfunction was noted[20]. In Mayo clinic study, higher prevalence of metabolic syndrome was noted in OSA but the prevalence of hyperlipidaemia was the same[7]. Koro *et al*[9] showed that the prevalence of dyslipidaemia was higher in OSA than non-OSA group. In Sleep Heart Health Study[6], with 5978 participants, significant association between respiratory disturbance index (RDI) and total cholesterol in man, and HDL in women was shown. After controlling the confounding factors, Li and group[20] demonstrated that chronic intermittent hypoxia will induce hypertriglyceridaemia by upregulating the pathway of triglyceride and phospholipids biosynthesis, and hypercholesterolaemia by inhibiting pathways of cholesterol uptake in lean mice liver[21]. In addition, they showed that the degrees of dysregulation of hypercholesterolaemia and lipid peroxidation depend on the severity of the hypoxic stimulus[22]. Although the odds ratio was small, our study showed that DI was independently correlated with hypercholesterolaemia and hypertriglyceridaemia.

Table II. Comparison of prevalence of hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia with published Taiwan data

	Present study	Published Taiwan data[17,18]	*P* value
Hypercholesterolaemia (%)	61.1	10.7	<0.001
Hypertriglyceridaemia (%)	55.3	9.6	<0.001
Hyperuricaemia (%)	25.8	27.2	0.670

One inherent limitation in our study was the lack of generalizability of results to the community at large, given that this was a referral sample. Another limitation was that the cross-sectional nature of the study precluded evaluating causality. It could not be proved that hyperlipidaemia developed after OSA or whether hyperlipidaemia improved after treatment for OSA. A longitudinal study is needed to confirm the sequence of OSA and hyperlipidaemia. The mechanisms behind hypoxia-induced lipid dysfunction in human SRBD patients also require further study.

In our study, 74 per cent of the SRBD patients had hyperlipidaemia, but 196 (96.6%) of these had not been diagnosed prior to our screening. Patients with uncontrolled hyperlipidaemia have higher morbidity and mortality rates from cardiovascular disease[23]. Intermittent hypoxia, which occurs in SRBD patients, increases the antherosclerosis under hyperlipidaemia conditions[10].

The association between sleep apnoea and hypothyroidism is still unclear[13]. Although an association between SRBD and polycythaemia was observed[14], no patients with polycythaemia were noted in the study.

In conclusion, this study reports a high prevalence of hypercholesterolaemia, hypertriglyceridaemia, and hyperuricaemia in SRBD patients in Taiwan. In these patients, BMI and DI were independently correlated with, and may be the risk factors for, hypercholesterolaemia and hypertriglyceridaemia. No hypothyroidism or polycythaemia was noted in the SRBD patients. Underdiagnosis of hyperlipidaemia in SRBD patients remains a critical problem.

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