Correlation of obstructive sleep apnea hypopnea syndrome with metabolic syndrome in snorers

Qun Zhang\textsuperscript{a}, Xiaofeng Zhang\textsuperscript{a}, Mengmeng Zhao\textsuperscript{a}, Hanpeng Huang\textsuperscript{a}, Ning Ding\textsuperscript{a}, Xilong Zhang\textsuperscript{b,\*}, Hong Wang\textsuperscript{a,*}

\textsuperscript{a}Nanjing Medical University, Nanjing, Jiangsu 210029, China; \textsuperscript{b}Department of Respiratory Medicine, the First Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu 210029, China.

Received 05 November 2012, Revised 24 December 2012, Accepted 12 June 2013, Epub 30 January 2014

Abstract

Though obstructive sleep apnea hypopnea syndrome (OSAHS) and metabolic syndrome (MS) are correlated; the contributing factors for the occurrence of MS in Chinese snorers remain largely undefined. We aimed to investigate the associated pathogenesis of coexistence of OSAHS and MS in Chinese snorers. A total of 144 Chinese habitual snorers were divided into 3 groups, the control group (simple snorers) \( (n = 36) \), the mild OSAHS group \( (n = 52) \) and the moderate-to-severe OSAHS group \( (n = 56) \). The incidence of MS in the moderate-to-severe OSAHS group (26.8%) was significantly higher than that in the control group (8.3%), the mild OSAHS group (11.1%) and all the OSAHS patients (19.45%) (all \( P < 0.05 \)). Homeostatic model assessment (HOMA) index and proinsulin (PI) were negatively correlated with nocturnal meanSpO\textsubscript{2} and miniSpO\textsubscript{2}. Meanwhile, nocturnal SpO\textsubscript{2} were negatively correlated with body mass index, waist and neck circumferences and diastolic blood pressure, but positively correlated with total cholesterol and high-density lipoprotein cholesterol. The study indicated that in Chinese snorers, moderate-to-severe OSAHS was closely associated with MS via nocturnal hypoxemia.

Keywords: hypoxia, insulin resistance, metabolic syndrome, obstructive sleep apnea hypopnea syndrome

INTRODUCTION

It has been reported that there is a high co-prevalence rate of obstructive sleep apnea hypopnea syndrome (OSAHS) and metabolic syndrome (MS)\textsuperscript{[1,2]}\textsuperscript{1}. MS, also called X syndrome, is characterized by impaired glucose metabolism, central obesity, elevated blood pressure and dyslipidemia\textsuperscript{[1]}. Since OSAHS is often accompanied by MS, it has been suggested that the two conditions are causally correlated\textsuperscript{[9]} and even Z syndrome was named for coexisting OSAHS and MS\textsuperscript{[10]}. So far, the associated pathogenesis between OSAHS and MS has not been completely elucidated. Insulin resistance (IR) plays an important role in the pathogenesis of MS and may also be present in patients with OSAHS\textsuperscript{[10]}. To explore pathological factors linking MS to OSAHS, 144 Chinese habitual snorers were investigated by analyzing the correlation of their polysomnography (PSG) and MS-associated metabolic parameters, plasma insulin and proinsulin (PI) and IR as reflected by homeostasis model assessment (HOMA) index, a surrogate index widely used to study the role of insulin sensitivity or resistance\textsuperscript{[11]}.

SUBJECTS AND METHODS

Subjects

From May 2008 to February 2012, 144 Chinese habitual snorers admitted to our sleep center were

\begin{itemize}
  \item 3723731/+86-25-3724440, E-mail: zhangxilong1952@yahoo.com.cn.
\end{itemize}

The authors reported no conflict of interests.

doi: 10.7555/JBR.28.20120120
recruited for this study. The protocol was approved by the local institutional board at the authors’ affiliated institution and written informed consents were obtained from all patients. The subjects received over-night sleep study by PSG. There were 107 males and 37 females with an average age of 51.4 ± 12.3 years. They were grouped into simple snorers (the control group, n = 36) and OSAHS patients. OSAHS patients were divided into the mild OSAHS group (n = 52) and the moderate-to-severe OSAHS group (n = 56) based on their apnea hypopnea index (AHI) during sleep. The prevalence of MS was compared among different groups.

Polar examination and group division

Full PSG monitoring was performed with the Compumedics E-series Sleep System (Compumedics Sleep, Abbotsford, Australia) to measure and record overnight PSG parameters such as electroencephalogram, electrocardiogram (ECG), electrooculogram, chin and bilateral anterior tibials electromyogram, chest and abdominal movements by strain gauges, and pulse oxygen saturation (SpO2). All tracings were scored manually according to standard criteria. Apnea was diagnosed when a cessation of airflow was detected for more than 10 seconds, while hypopnea was identified when more than a 50% reduction in airflow and 3% reduction of SpO2 were observed in a patient. The AHI was defined by the combined number of apnea and hypopnea events per hour of sleep, with the minimal criteria for diagnosis of OSAS as AHI ≥ 5. Sleep apnea hypopnea syndrome and its severity were evaluated with an international diagnostic criteria (AHI of 5.0–14.9 as mild, 15.0–29.9 as moderate and ≥ 30 as severe OSAHS)12. An event was defined as obstructive when chest and abdominal respiratory movement was observed during apnea.

Anthropometric measurement

Height was measured, without shoes worn, to the nearest 0.1cm using a height rod that was attached to a Weighing machine (RGz-120-RI, Tin Heng weight instrument history, Wuxi, China) were instructed to stand with their heels, buttocks and shoulders resting lightly against the backing board so that the Frankfort plane(i.e. the line connecting the superior border of the external auditory meatus with the infra-orbital rim) was horizontal and parallel to the floor.

Weight was measured, using a calibrated weighing machine (MS-3400 PIR; MARSDEN, Taiwan), to the nearest 0.1 kg with the participants barefoot and clothed in light clothing. The participants were asked to stand on the centre of the scale without support and to distribute their weight evenly on both feet. Body mass index (BMI) was calculated as weight/height² (kg/m²).

Blood pressure (Bp) was measured after patient had rested in a sitting position for 5 minutes, using models of the sphygomanometer (Jiangsu Yuyue Medical Equipment and Supply Co., Ltd. China) to obtain the systolic Bp (SBP) and diastolic Bp (DBP). Bp measurements were obtained twice, and the average values were used in the data analysis; the time between measurements was 3 minutes.

Examination of metabolic parameters

Venous blood was drawn following 12 hours’ overnight fast for measurement of fasting blood glucose (FBG), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), true insulin and proinsulin at the Central Clinical Laboratory of authors’ affiliated hospital. FBG, TCH, TG, HDL and LDL were detected at the Central Clinical Laboratory of authors’ affiliated hospital. TI was measured using a two-site sandwich enzyme linked immunosorbent assay (ELISA) with the lowest detection limit of 0.82 mIU/L13. Two monoclonal murine antibodies against insulin were employed. The ELISA plate wells were coated by HUI-018, an antibody that binds to an epitope on one side of insulin. The other antibody (OXI-005), which binds to a separate epitope on the other side of insulin, was covalently bound to biotin and then converted to a soluble colored product by addition of substrate peroxide. The developed color was proportional to the amount of insulin in the sample. A calibration curve was constructed based on absorbance values of the sample and insulin concentration was measured by an ELISA-plate photometer (Bio-tek EL900, USA). Proinsulin was measured in a similar manner using another sensitive two-site sandwich ELISA14. The assay was based on 2 monoclonal antibodies, a mouse anti-human C-peptide antibody (PEP-001) and a mouse anti-human insulin antibody (HUI-001). The detection limit in human serum was 0.25 pmol/L. The 4 major proinsulin conversion intermediates reacted in various proportions from 65% to 99%.

The between- and within-assay coefficients of variation for true insulin were 6.8% and 7.8%, respectively and for proinsulin were 6.7% and 7.8%, respectively. The 4 monoclonal antibodies for testing true insulin and proinsulin were kind gifts from Novo Nordisk, Bagsvaerd, Denmark. The ELISA plates were the products of NUNC Co. of Denmark.
To evaluate the extent of IR, HOMA index was used with the calculating formula\(^{15}\): insulin (mIU/L) \times FBG (mmol/L)/22.5.

**Statistical analysis**

FBG, TG, PI and HOMA index showed skewed distribution and were expressed in median (interval of quartile). Analysis of variance and covariance was performed following logarithmic transformation. BP and body indexes were expressed as \(\bar{x} \pm s.d.\). All data were recorded by computer and SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Student’s t-test was used to determine significant differences among groups, which were set at \(P < 0.05\).

**RESULTS**

**Incidences of MS in different groups**

Coexisting MS was found in 21/108 (19.4%) of all OSAHS patients. The incidence of MS in the moderate-to-severe OSAHS groups (15/56, 26.8%) was significantly higher than that of the control group (3/36, 8.3%) (\(\chi^2 = 5.217, P = 0.034\)) and the mild OSAHS group (6/52, 11.1%) (\(\chi^2 = 4.002, P = 0.045\)). The incidence of MS in the mild OSAHS group was slightly higher than that of the control group, but no statistical difference was found (\(\chi^2 = 0.243, P = 0.622\)).

**Clinical characteristics of the subjects**

The demographic and baseline characteristics of the study subjects are shown in Table 1. Gender and age distribution was comparable among the groups (\(P > 0.05\)). Table 1 reveals that there was a statistical difference in BMI, WC, NC, diastolic BP (DBP), TCH, HDL and HOMA index among the groups, while there was no statistical significance in systolic BP (SBP), LDL, uric acid, TG, FBG and PI.

**Spearman correlation analysis of HOMA index, PI, PSG parameters and other variables**

Spearman correlation analysis (Table 2) indicated that HOMA index and PI were negatively correlated with nocturnal miniSpO\(_2\) and meanSpO\(_2\), but posi-
Table 2 Spearman correlation of HOMA index and proinsulin with patient characteristics.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>HOMA</th>
<th>PI (pmol/L)</th>
<th>AHI</th>
<th>LSaO2</th>
<th>AsaO2</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA</td>
<td></td>
<td>0.716</td>
<td>0.114</td>
<td>-0.289</td>
<td>-0.341</td>
<td>-0.628</td>
</tr>
<tr>
<td>PI (pmol/L)</td>
<td>0.716</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI</td>
<td>0.114</td>
<td>0.151</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MiniSpO2 (%)</td>
<td>-0.289</td>
<td>-0.341</td>
<td>-0.628</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeanSpO2 (%)</td>
<td>-0.237</td>
<td>-0.234</td>
<td>-0.490</td>
<td>0.694</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.237</td>
<td>0.319</td>
<td>0.202</td>
<td>-0.151</td>
<td>-0.167</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.057</td>
<td>-0.159</td>
<td>-0.159</td>
<td>0.007</td>
<td>-0.139</td>
<td>-0.365</td>
</tr>
<tr>
<td>BMI</td>
<td>0.417</td>
<td>0.426</td>
<td>0.394</td>
<td>-0.382</td>
<td>-0.291</td>
<td>0.329</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>0.344</td>
<td>0.372</td>
<td>0.354</td>
<td>-0.419</td>
<td>-0.435</td>
<td>0.271</td>
</tr>
<tr>
<td>NC (cm)</td>
<td>0.255</td>
<td>0.364</td>
<td>0.427</td>
<td>-0.389</td>
<td>-0.391</td>
<td>0.182</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.219</td>
<td>0.099</td>
<td>0.076</td>
<td>-0.194</td>
<td>-0.131</td>
<td>0.084</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.281</td>
<td>0.244</td>
<td>0.216</td>
<td>-0.341</td>
<td>-0.121</td>
<td>0.167</td>
</tr>
<tr>
<td>FBG (mmol/L)</td>
<td>0.478</td>
<td>0.581</td>
<td>0.005</td>
<td>-0.035</td>
<td>0.034</td>
<td>0.336</td>
</tr>
<tr>
<td>TCH (mmol/L)</td>
<td>-0.051</td>
<td>-0.104</td>
<td>-0.207</td>
<td>0.290</td>
<td>0.248</td>
<td>0.025</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>0.431</td>
<td>0.451</td>
<td>0.137</td>
<td>-0.107</td>
<td>0.005</td>
<td>0.141</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>-0.397</td>
<td>-0.437</td>
<td>-0.258</td>
<td>0.411</td>
<td>0.431</td>
<td>0.075</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>0.149</td>
<td>0.061</td>
<td>-0.102</td>
<td>0.030</td>
<td>-0.011</td>
<td>0.074</td>
</tr>
<tr>
<td>UA (mmol/L)</td>
<td>0.024</td>
<td>0.122</td>
<td>0.141</td>
<td>-0.038</td>
<td>-0.104</td>
<td>0.161</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01, AHI: apnea hypopnea index; BMI: body mass index; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein cholesterol; HR: heart rate; HOMA: homeostasis model assessment index; LDL: low-density lipoprotein cholesterol; MeanSpO2: mean pulse oxygen saturation; MiniSpO2: minimal pulse oxygen saturation; NC: neck circumference; PI: proinsulin; SBP: systolic blood pressure; TCH: total cholesterol; TG: triglyceride; UA: uric acid; WC: waist circumference.

The results of logistic analysis are shown in Table 3–5. Univariate logistic regression analysis was performed on HOMA index, proinsulin (group division by interval of quartile) firstly, and then multivariate stepwise logistic regression was undergone with the following parameters as independent variables including sex, age, BMI, WC, NC, HOMA index, proinsulin, SBP, DBP, total cholesterol, TG, HDL, LDL, FBG, and uric acid. Group division was performed based on interval of quartile for all the parameters except age and sex.

Table 3 indicates that the risk for developing moderate-to-severe OSAHS increased by about 93% as HOMA index was elevated by one grade (25%). The comparison between group 4 and group 1 of HOMA index demonstrated that the risk in group 4 increased up to more than 9 folds of that in group 1, as the ratio odds increased to 10.290 (2.767~38.219) (P = 0.001). Table 4 shows that the risk for developing moderate-to-severe OSAHS increased by about 71.6% as proinsulin levels rose by one grade (25%).
Univariate logistic regression analysis suggested that the HOMA index and proinsulin were risk factors of moderate-to-severe OSAHS and the odds ratios (95% confidence interval) were 1.924 (1.301–2.847) \( (P < 0.01) \) and 1.713 (1.172–2.506) \( (P < 0.01) \), respectively. Multivariate stepwise logistic regression analysis (Table 5) shows that two variables, HOMA index and CH finally entered the model, which suggested that HOMA index and moderate-to-severe OSAHS were independently correlated and the odds ratio was 1.989 (1.306–3.031) \( (P < 0.01) \). Interestingly, TCH might be a protective factor against the development of OSAHS as the odds ratio was 0.597 (0.389–0.906) \( (P = 0.016) \).

### DISCUSSION

The diagnosis of OSAHS still relies on PSG. AHI and miniSpO\(_2\) have been considered as important factors in the diagnosis of OSAHS. However, as AHI generally only represents the frequency of the events of apnea and hypopnea but does not reflect the duration of each event of apnea or hypopnea, there are still limitations for AHI in evaluating the whole effect of OSAHS patients and was usually positively correlated with the severity of OSAHS. The causes of IR in OSAHS patients, besides obesity, may include heightened sympathetic activity and increased blood concentration of catecholamine and corticosterone as a result of hypoxia, hypercapnia and arousals following the events of sleep apnea and hypopnea.\(^{[19]}\)

The results of this study confirmed that miniSpO\(_2\) was negatively correlated with BMI, WC and NC. Obesity, especially local obesity represented by increased WC and NC, is related to the narrowing of the lumen of the upper respiratory tract, which can lead to sleep apnea and hypopnea, and result in intermittent hypoxemia and hypercapnia.\(^{[20]}\) A negative correlation between DBP and miniSpO\(_2\) was detected by Spearman correlation analysis. The underlying mechanism was putatively attributed to the activation and sensitization of the peripheral and central receptors by hypoxia/hypopnea.\(^{[21]}\) The result of Spearman correlation analysis displayed a positive relationship between fasting total cholesterol and miniSpO\(_2\). Multivariate stepwise logistic regression analysis on 15 variables revealed that HOMA index and moderate-to-severe OSAHS were independently correlated. This finding showed an independent association between OSAHS and MS or type-2 diabetes.

Owing to the absence of clinical indications, non-snorers seldom came to the sleep laboratory for PSG. Therefore, our database lacked the data from non-snorers. Therefore, the limitation of this study is the lack of non-snorers as control, although we had put simple snorers as control. Further study is needed to exclude the possible influence of snoring by adding a non-snorer group.

It could be concluded from the current study that OSAHS is a risk factor for MS. OSAHS patients with a lower SpO\(_2\) were more susceptible to IR, which could play an important role in the coexistence of OSAHS and MS.

### Acknowledgments

We would like to thank the patients who volunteered for this study and the staff at the Department of
Respirology in the First Affiliated Hospital of Nanjing Medical University.

References


