Association between severity of obstructive sleep apnea and glycated hemoglobin level in Japanese individuals with and without diabetes

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Abstract. Aim of this study was to examine the association between the severity of obstructive sleep apnea (OSA) and dysglycemia in Japanese individuals with and without type 2 diabetes (T2DM). We enrolled 115 individuals diagnosed with OSA with an apnea hypopnea-index (AHI) ≥ 20 in whom continuous positive airway pressure (CPAP) therapy was introduced (N = 115, 44 with T2DM, age 62 ± 11 years, BMI 27.0 ± 4.4 kg/m² and AHI median 36.1; interquartile range 27.2–48.1). During admission, the severity of OSA was evaluated by polysomnography, and its association with glycated hemoglobin (HbA1c) level was examined. Continuous glucose monitoring (CGM) was also conducted during the admission in 94 individuals. Apnea-hypopnea index (AHI), non-rapid eye movement (REM) AHI, minimum peripheral capillary oxygen saturation (SpO₂) and percentage of sleep time (%TST) with SpO₂ < 90% were significantly associated with HbA1c level in total and non-diabetic individuals (all p < 0.05) but not in those with T2DM, the majority of whom were treated with anti-diabetic medications. The associations of the non-REM AHI and %TST with SpO₂ < 90% with HbA1c level remained significant after adjustment for age, sex and BMI in non-diabetic and T2DM subjects treated with dietary therapy only. Mean glucose level, but not SD or coefficient of variation of glucose, assessed by CGM was significantly associated with AHI and non-REM AHI in non-diabetic subjects after adjustment for age, sex and BMI. In conclusion, the severity of OSA was associated with increased HbA1c level independently of BMI in Japanese individuals, especially in those without diabetes.

Key words: Obstructive sleep apnea, Type 2 diabetes, Apnea-hypopnea index, Oxygen saturation, Continuous glucose monitoring

OBESITY is associated with both type 2 diabetes (T2DM) and obstructive sleep apnea (OSA) [1-3]. It has been reported that approximately 25–80% of patients with T2DM are complicated by OSA, while approximately 15–30% of patients with OSA are complicated by T2DM [1-3]. OSA is a treatable chronic sleep disorder characterized by recurrent episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway. Recent studies have shown that OSA is not only comorbid with T2DM, but also associated with worsening or development of T2DM [1-3]. OSA leads to intermittent hypoxia and hypercapnia, increased oxidative stress, low grade inflammation, sympathetic activation, hypothalamus-pituitary-adrenal axis stimulation, sleep fragmentation and chronic sleep loss, all of which contribute to insulin resistance and beta cell dysfunction, hallmarks of T2DM.

However, the association between OSA and T2DM has been reported mainly in the Caucasian population in which most patients with T2DM are obese, defined as BMI ≥30, and few reports have been reported in the Japanese population, which is less obese compared with Caucasians [4, 5]. Therefore, in this study we examined the association between the severity of OSA and glyca-
Methods

Subjects

This study was approved by the Institutional Review Board (IRB) of Keio University School of Medicine (reference number: 20120177, UMIN000009301).

A total of 115 consecutive Japanese individuals who were admitted to Keio University Hospital for the diagnosis of OSA based on the results of polysomnography (PSG) (apnea-hypopnea index; AHI ≥ 20 events/hour) in whom CPAP therapy was introduced were enrolled in this study. Written informed consent was obtained from each individual. Of those, there were 44 patients with T2DM and 71 without diabetes (Table 1). Eight patients with T2DM were treated with lifestyle modification only and 28 were treated with oral hypoglycemic agents and/or glucagon-like peptide-1 (GLP-1) receptor agonists. Eight patients were treated with insulin. There were no patients with severe renal and/or liver failure.

Protocol

All patients stayed in the hospital for 3 days. Blood sampling in addition to anthropometric measurements was conducted on admission. Smoking habits and alcohol intake were assessed through questionnaires to the patients. Alcohol intake ≥20 g and ≥10 g per day were defined as regular alcohol intake in men and women, respectively. The patients underwent PSG during the first night, and continuous positive airway pressure (CPAP) therapy was introduced during the second night in those with AHI ≥ 20 derived from PSG. During admission,
Continuous glucose monitoring (CGM) was also performed in 94 individuals (34 with and 60 without T2DM). The hospital diet (ideal body weight (kg) × 25–30 kcal/day) was served during admission. The primary goal of the study was to assess the correlation between the severity of OSA and HbA1c level.

Measurements

HbA1c level was measured by HPLC. OSA was diagnosed by overnight PSG (for ≥6 h) at our hospital, apnea was defined as the termination of respiratory airflow for ≥10 s, and hypopnea was defined as a ≥50% decrease in oxygen saturation. AHI was defined as the number of instances of apnea and hypopnea per 1 h (while sleeping). CPAP therapy was introduced in patients with OSA, defined as AHI ≥ 20. Rapid eye movement (REM) AHI, non-REM AHI, minimum peripheral capillary oxygen saturation (SpO2), mean SpO2, total sleep time (TST), percentage of total sleep time (%TST) with SpO2 < 90% and REM/TST were also evaluated using PSG. CGM was performed using a CGMS Gold (Medtronic Minimed, Northridge, CA, USA). Patients checked their capillary blood glucose with a Medisafe Fit Pro blood glucose meter (Terumo Corporation, Tokyo, Japan) at least 4 times a day (premeal and bedtime) and entered the readings into the CGM monitor for calibration. After downloading the CGM data, mean glucose and standard deviation (SD) as well as coefficient of variation (CV) of glucose levels were evaluated during a 24 h period between day 2 and day 3. Fasting capillary blood glucose (FBG) was calculated as the mean of day 2 and day 3 measurements.

Statistical analysis

Normally distributed data were presented as mean ± SD. Non-normally distributed data were presented as median (interquartile range; IQR), and log-transformed values were used for analyses. Comparisons between the two groups were examined with Student’s t test or Fisher’s exact test. Simple and multiple regression analyses were performed to assess the association between two variables with Pearson’s correlation coefficient. These analyses were performed using the Statistical Package for the Social Sciences (version 23.0; SPSS, Chicago, IL, USA). Values of p < 0.05 were considered statistically significant.

Results

Comparison between patients with and without T2DM

Characteristics of patients with and without T2DM are shown in Table 1. BMI and HbA1c level were significantly higher in patients with T2DM compared with non-diabetic patients (both p < 0.05). FBG and mean, SD and CV of glucose readings during CGM were also significantly higher in those with T2DM (all p < 0.05). Indices of OSA were not significantly different between patients with and without T2DM (all p > 0.05), while BMI was significantly associated with the severity of OSA; i.e., REM AHI, mean SpO2, minimum SpO2 and %TST with SpO2 < 90% in total subjects (r = 0.242, –0.319, –0.193 and 0.244, respectively, all p < 0.05). There was no significant association between the severity of OSA and smoking status or alcohol intake (all p > 0.05).

Association between severity of OSA and HbA1c level

HbA1c level was significantly higher in those with severe OSA (i.e., AHI ≥ 30, N = 82) compared with those without (6.2%, IQR 5.7–6.7 vs. 5.8%, IQR 5.4–6.4, p = 0.04). In total subjects, AHI, non-REM AHI and %TST with SpO2 < 90% were significantly positively correlated and mean SpO2 was negatively correlated with HbA1c level (all p < 0.05, Table 2). These correlations remained significant in non-diabetic subjects (all p < 0.05, Table 2), whereas no significant correlation was observed between the severity of OSA and HbA1c level in patients with T2DM (Table 2).

Although these significant correlations between the severity of OSA and HbA1c level in total subjects were attenuated after adjustment for age, sex and BMI (p = 0.07, 0.55 and 0.09 for AHI, mean SpO2, and %TST with SpO2 < 90%, respectively), the correlation between non-REM AHI and HbA1c level remained significant even after these adjustments (β = 0.197, p = 0.04).

Since the treatment with anti-diabetic medications affects HbA1c levels, we further conducted the analyses in the subgroup which consisted of non-diabetic subjects and T2DM subjects treated with dietary therapy only (NDM + T2DM-Diet, N = 79). In this group, AHI, non-REM AHI, minimum SpO2, mean SpO2, and %TST with SpO2 < 90% were significantly associated with HbA1c level and the associations of non-REM AHI and %TST with SpO2 < 90% with HbA1c level remained significant after adjustment for age, sex and BMI (β = 0.263, p = 0.03 and β = 0.260, p = 0.03, respectively, Fig. 1 and Table 2).
Association between severity of OSA and glycemic indices assessed by CGM

Mean, SD and CV of glucose values during CGM were all significantly correlated with HbA1c level ($r$ = 0.780, 0.517 and 0.339, respectively, all $p < 0.01$). AHI and non-REM AHI were significantly associated with mean and SD, but not CV of glucose during CGM in total subjects ($r$ = 0.248, 0.214 and 0.167, $p = 0.02$, 0.04

Table 2  Correlations between HbA1c and severity of OSA

<table>
<thead>
<tr>
<th></th>
<th>Total (N = 115)</th>
<th>NDM (N = 71)</th>
<th>T2DM (N = 44)</th>
<th>NDM + T2DM-Diet (N = 79)</th>
<th>NDM + T2DM-Diet§</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>0.228*</td>
<td>0.247*</td>
<td>0.054</td>
<td>0.280*</td>
<td>0.199</td>
</tr>
<tr>
<td>Non-REM AHI</td>
<td>0.242*</td>
<td>0.253*</td>
<td>0.079</td>
<td>0.337*</td>
<td>0.263*</td>
</tr>
<tr>
<td>REM AHI</td>
<td>0.020</td>
<td>-0.087</td>
<td>0.094</td>
<td>0.010</td>
<td>-</td>
</tr>
<tr>
<td>Minimum SpO$_2$ (%)</td>
<td>-0.107</td>
<td>-0.215</td>
<td>0.026</td>
<td>-0.223*</td>
<td>-0.175</td>
</tr>
<tr>
<td>Mean SpO$_2$ (%)</td>
<td>-0.204*</td>
<td>-0.290*</td>
<td>-0.053</td>
<td>-0.320*</td>
<td>-0.193</td>
</tr>
<tr>
<td>TST with SpO$_2$ &lt; 90% (%)</td>
<td>0.246*</td>
<td>0.269*</td>
<td>0.162</td>
<td>0.336*</td>
<td>0.260*</td>
</tr>
<tr>
<td>TST (min)</td>
<td>-0.036</td>
<td>-0.054</td>
<td>0.224</td>
<td>-0.091</td>
<td>-</td>
</tr>
<tr>
<td>REM/TST (%)</td>
<td>0.027</td>
<td>-0.103</td>
<td>0.289</td>
<td>0.014</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are Pearson’s correlation coefficients. OSA; obstructive sleep apnea, T2DM; type 2 diabetes, NDM; without diabetes, T2DM-Diet; patients with T2DM treated with dietary therapy only, AHI; apnea hypopnea index, REM; rapid eye movement. SpO$_2$; peripheral capillary oxygen saturation, TST; total sleep time. § adjusted for age, sex and BMI. *$p < 0.05$.  

Fig. 1  Association between severity of OSA and HbA1c level in the non-diabetic subjects and subjects with T2DM treated with dietary therapy only (NDM + T2DM-Diet, N = 79). A: apnea-hypopnea index (AHI), B: non-rapid-eye-movement (non-REM) AHI, C: percent of total sleep time (%TST) with oxygen saturation (SpO$_2$) < 90% and D: mean SpO$_2$. See also Table 2.
significantly correlated with mean glucose, but not SD or CV of glucose, between mean glucose and non-REM AHI remained significantly higher in the subjects with severe OSA than those without (113 mg/dL, IQR 113–144, \( p = 0.048 \)). The correlation between mean glucose and non-REM AHI remained significant after adjustment for age, sex and BMI (\( \beta = 0.233, p = 0.03 \)). In non-diabetic subjects, only mean glucose during CGM was significantly correlated with AHI and non-REM AHI \((r = 0.363\) and \(0.378, p = 0.004\) and 0.003, respectively, Table 3). The associations of AHI and non-REM AHI with mean glucose remained significant after adjustment for age, sex and BMI (\( \beta = 0.367, p = 0.006 \) and \( \beta = 0.417, p = 0.003 \), respectively). No significant correlation was observed between the severity of OSA and glycemic indices during CGM in subjects with T2DM (all \( p > 0.05 \), Table 3). In the group of NDM + T2DM-Diet, AHI and non-REM AHI were significantly correlated with mean glucose, but not SD or CV of glucose \((r = 0.257, p = 0.04 \) and \( r = 0.276, p = 0.03 \), respectively), although these correlations were attenuated after adjustment for age, sex and BMI (both \( p = 0.2 \)). Even when the CGM data was divided into daytime and nighttime, respectively, neither SD nor CV of glucose was significantly associated with the severity of OSA in each period of time (data not shown).

### Discussion

In this study, we reported that the severity of OSA; \( i.e., AHI, \) non-REM AHI, mean \( \text{SpO}_2 \) and \%TST with \( \text{SpO}_2 < 90\% \) were associated with HbA1c level in the Japanese population, independently of BMI. These associations were mostly derived from the non-diabetic individuals but not the subjects with T2DM.

An association between the presence or severity of OSA and the worsening or development of T2DM has been reported [6-9]. The severity of OSA has been reported to associate with poor glycemic control in patients with T2DM [7, 9-11]. However, in our study, while we found a significant association between the severity of OSA and HbA1c level in non-diabetic subjects, this association was not significant in subjects with T2DM. The reason for this inconsistency may be the use of anti-diabetic medication in patients with T2DM. Indeed, the majority of patients with T2DM were treated with anti-diabetic medication in our study. Priou \textit{et al.} have reported that greater severity of OSA was associated with increased HbA1c level in untreated but not treated patients with T2DM, and they concluded that OSA may have a limited impact in patients with T2DM receiving anti-diabetic medication [10]. In line with this, in the present study the significant association between the severity of OSA and HbA1c level was observed after excluding the subjects treated with anti-diabetic medication. Moreover, treatment of OSA with continuous positive airway pressure (CPAP) has been shown to have a
limited impact on improvement of glycemic control in patients with T2DM [12-15], although the effect of CPAP therapy on glycemic control depends on adherence to therapy. Thus, although we confirmed that the severity of OSA is associated with HbA1c level in Japanese non-diabetic individuals, the impact of OSA on glycemic control in Japanese patients with T2DM needs further investigation.

In this study, we found that AHI, especially non-REM AHI rather than REM AHI, was significantly associated with HbA1c level in non-diabetic individuals. Whereas upper airway collapse can occur during REM and non-REM sleep, the withdrawal of excitatory noradrenergic and serotonergic input to upper airway motor neurons during REM sleep further reduces pharyngeal muscle activity and substantially increases the propensity for such collapse. Therefore, in patients with OSA, REM sleep is typically associated with an increased frequency of obstructive events that are often prolonged and accompanied by severe oxygen desaturation [16-18]. Grimaldi et al. reported that REM AHI but not non-REM AHI was associated with HbA1c level in patients with T2DM [11]. However, in that study, the proportion of patients with severe OSA; i.e., AHI ≥ 30, was only 30% and the majority had mild to moderate OSA. Sunnetcioglu et al. have reported that non-REM related OSA was more common among patients with severe OSA, whereas REM-related OSA was more common among those with mild-to-moderate OSA [19]. Therefore, since the majority (71%) of our study participants consisted of patients with severe OSA, non-REM AHI might influence glucose tolerance more dominantly compared with REM AHI.

Finally, we also examined the association between the severity of OSA and glycemic index obtained from CGM. CGM is a useful tool to assess glycemic variability as well as mean glucose [20]. Glycemic variability assessed by CGM has been shown to associate with oxidative stress/inflammatory markers, endothelial dysfunction and cognitive dysfunction, and proposed as one of the factors associated with CVD outcomes in patients with and without diabetes [20]. However, to our knowledge, there have been few studies reporting the association between OSA and glycemic variability. In our study, mean glucose was associated with the severity of OSA in non-diabetic subjects, consistent with the results of HbA1c. On the other hand, we did not find any significant correlation between the severity of OSA and CV of glucose, a marker of glycemic variability. Since the association between the severity of OSA and glucose level was observed only in non-diabetic subjects, our sample size might be underpowered to detect a small difference in glycemic variability in non-diabetic subjects. Also, the glycemic profile during the short period of admission might have differed from that in their daily life. On the other hand, using CGM, recent studies have shown that the presence of OSA may increase nocturnal glucose levels, especially during REM sleep [21]. Bialasiewicz et al. have also reported that the presence of OSA in REM sleep reversed the downward trend in glucose level [22]. These findings suggest that the presence of OSA may diminish the downward trend in glucose level during the night, resulting in increased mean glucose level without increasing glycemic variability. The effects of OSA on glycemic variability warrant further investigation.

In addition to the small sample size, limitations of this study include: 1) The majority of the participants were male, although the incidence of OSA is higher in men than in women [23]. Thus, the findings of our study may not be applicable to female subjects. 2) Our study included only subjects with OSA defined as AHI ≥ 20. Thus, our findings may not be applicable to subjects with mild-to-moderate OSA. 3) Although the results were adjusted for age, sex and BMI, other confounding factors such as waist circumference, dietary habits, physical activity and other medications might affect our results. 4) Since our study had a cross-sectional design, the causality of OSA in the development of glucose intolerance in the Japanese population remains uncertain. Prospective studies assessing the effects of treatment of OSA on glucose metabolism in non-diabetic and diabetic populations will be needed to address this question.

In conclusion, the severity of OSA was associated with increased HbA1c level independently of BMI in Japanese individuals, especially in those without diabetes. Appropriate management and treatment of OSA may improve glucose intolerance and the development of T2DM in the Japanese population.

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Conflict of Interest Statement

KF, MH and TB were supported by funds donated by Teijin Home Healthcare Limited (Japan), Fukuda Denshi
(Japan), and Philips Respironics (Japan). However, these companies had no role in the study design, data collection and analysis, or preparation of the manuscript. The other authors declare that there is no conflict of interest regarding the publication of this paper.

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