fragmentation and ESS scores, FPG also was not related to sleep duration (subjects with diabetes: $r = -0.30$, $P = 0.27$; subjects without diabetes: $r = 0.009$, $P = 0.88$). Although the relationships were not significant, both before and after adjustment, the correlations between FPG and sleep duration tended to be stronger in the subjects with diabetes than in those without diabetes.

With regard to the relationship between FPG and average sleep fragmentation, we did not find a significant relationship in the entire subject group ($r = 0.036$, $P = 0.57$). However, a tendency toward a significant relationship in the subjects with diabetes ($r = 0.37$, $P = 0.10$) was found. In the subjects without diabetes, FPG was not related to sleep fragmentation ($r = -0.050$, $P = 0.44$). After adjustment for age, waist circumference, RDI, ESS scores and sleep duration, those results did not differ (subjects with diabetes: $r = 0.38$, $P = 0.10$; subjects without diabetes: $r = -0.057$, $P = 0.34$). Although the relationships were not significant, the correlations between FPG and average sleep fragmentation tended to be stronger in the subjects with than without diabetes. Moreover, in the subjects with diabetes, correlations with FPG and average sleep fragmentation after adjustment tended to be stronger than those with FPG and sleep duration.

Lastly, multiple regression analyses to predict FPG were performed in the entire subject group and in subjects with and without diabetes adjusted for age, waist circumference, RDI, average sleep fragmentation, ESS scores and sleep duration. In the entire subject group, age and waist circumference independently explained FPG [contribution rate (R^2) = 4.5 and 3.5%, respectively; Table 2a]. The rates of the contribution were small, which in part was because the subjects were considered as a single group regardless of the presence of diabetes. We then divided the subjects into two groups (with and without diabetes) to examine whether the effects of the RDI would differ between the two groups. These analyses revealed that in the subjects with diabetes, only RDI independently explained FPG ($R^2 = 19.9\%$; Table 2b). In contrast, age and waist circumference, but not RDI, independently explained FPG in the subjects without diabetes ($R^2 = 7.1$ and 3.5%, respectively; Table 2a,b). When considering subjects with IFG and those with normal fasting glucose, only age independently explained FPG ($R^2 = 6.3\%$, both). Those results did not differ when we replaced sleep fragmentation by sleep duration in the analysis (Table 2a,b).

Furthermore, we performed an additional analysis replacing waist circumference by BMI. Pearson correlation coefficients tests showed that there was no significant relationship between FPG and BMI in the subjects with diabetes ($r = -0.037$, $P = 0.88$), while there was a significant relationship between FPG and BMI in subjects without diabetes ($r = 0.15$, $P = 0.019$). Multiple regression analyses showed that after adjustment for age, BMI, RDI, average sleep fragmentation, ESS scores and sleep duration, only the RDI independently explained FPG in the subjects with diabetes ($R^2 = 19.9\%$), a result similar to that with the use of waist circumference. In the subjects without diabetes, age and BMI (alternative to waist circumference) independently explained FPG ($R^2 = 8.2$ and 2.9%, respectively).

Association between diabetes and sleepiness

As to relationships between FPG and sleepiness and between RDI and sleepiness in the subjects with and without diabetes, as well as in all subjects taken together, no significant relationships were found. Only sleep duration was significantly related to sleepiness in subjects with and without diabetes (subjects with diabetes: $r = -0.67$, $P < 0.001$; subjects without diabetes: $r = -0.17$, $P = 0.0067$). Multiple regression analyses adjusted for age, waist circumference, RDI, average sleep fragmentation, sleep duration and FPG showed that in the subjects with diabetes, only sleep duration independently contributed to sleepiness ($R^2 = 44.9\%$), while in the subjects without diabetes, although sleep duration also independently contributed to sleepiness, the contribution rate was much lower ($R^2 = 3.0\%$) than in those with diabetes.

DISCUSSION

Among the 275 male workers who underwent a health examination in an urban company in Japan, the prevalence of diabetes was 7.6%, which is the same as in the general population in that age group in Japan as reported in 2008 (Ministry of Health, Labor and Welfare, 2008). The prevalence of OSA in patients with diabetes is high in Japan as well as in Western countries. In this study, RDI and sleep duration were significantly related to FPG, as has already been reported (Aronsohn *et al.*, 2010). However, after adjustment for the confounders of age, waist circumference, average sleep fragmentation, sleepiness and sleep duration, RDI was significantly related to FPG only in subjects with diabetes. Sleep fragmentation was more closely correlated with FPG than sleep duration in patients with diabetes, but without significance ($P = 0.10$).

In this study, OSA was highly prevalent in subjects with diabetes, which is compatible with findings of recent Western studies (77 and 86%; Aronsohn *et al.*, 2010; Foster *et al.*, 2009) and a Japanese study (78%; Kashine *et al.*, 2010); however, subjects in the Japanese study were not from the general population. Although the mean BMI (25.9 kg m^{-2}) in subjects with diabetes in the present study was lower in comparison with subjects in the Western studies (33.8 and 36.5 kg m^{-2}; Aronsohn *et al.*, 2010; Foster *et al.*, 2009) and in the Japanese study (28.3 kg m^{-2}; Kashine *et al.*, 2010), a low BMI is characteristic of persons with diabetes in Asia (Chan *et al.*, 2009). This finding is similar to those showing that the prevalence of OSA is as high in Asian populations as in Western populations even though Asian subjects with OSA have a lower BMI than Western subjects. The mean BMI in our study was

Table 2 (a) Relationships with FPG; (b) stepwise multiple regression analyses to predict FPG

	r	P-*value*	*95% CI*
(a)			
In the entire subject group			
Age (years)	0.23	<0.001	0.11–0.34
Waist circumference (cm)	0.20	<0.001	0.084–0.32
RDI (h^{-1})	0.19	0.0019	0.072–0.31
Average sleep fragmentation (%)	0.036	0.57	−0.086 to 0.16
ESS scores	0.043	0.49	−0.079 to 0.16
Sleep duration (h)	−0.13	0.041	−0.25 to 0.005
In the subjects with diabetes			
Age (years)	−0.23	0.32	−0.60 to 0.22
Waist circumference (cm)	0.016	0.95	−0.42 to 0.45
RDI (h^{-1})	0.45	0.042	0.017–0.74
Average sleep fragmentation (%)	0.37	0.10	−0.075 to 0.69
ESS scores	−0.10	0.66	−0.51 to 0.35
Sleep duration (h)	−0.24	0.30	−0.61 to 0.22
In the subjects without diabetes			
Age (years)	0.28	<0.001	0.16–0.39
Waist circumference (cm)	0.21	0.0011	0.083–0.32
RDI (h^{-1})	0.14	0.030	0.013–0.26
Average sleep fragmentation (%)	−0.050	0.44	−0.17 to 0.076
ESS scores	0.066	0.30	−0.060 to 0.19
Sleep duration (h)	0.005	0.93	−0.12 to 0.13

	Model 1		Model 2	
	β	R^2 (%)	β	R^2 (%)
(b)				
In the entire subject group				
Age (years)	0.20	4.5	0.20	4.5
Waist circumference (cm)	0.17	3.5	0.17	3.5
RDI (h^{-1})	NA	NA	NA	NA
Average sleep fragmentation (%)	NA	NA	–	–
ESS scores	NA	NA	NA	NA
Sleep duration (h)	–	–	NA	NA
Cumulative R^2		8.0		8.0
In the subjects with diabetes				
Age (years)	NA	NA	NA	NA
Waist circumference (cm)	NA	NA	NA	NA
RDI (h^{-1})	0.45	19.9	0.45	19.9
Average sleep fragmentation (%)	NA	NA	–	–
ESS scores	NA	NA	NA	NA
Sleep duration (h)	–	–	NA	NA
Cumulative R^2		19.9		19.9
In the subjects without diabetes				
Age (years)	0.26	7.1	0.26	7.1
Waist circumference (cm)	0.17	3.5	0.17	3.5
RDI (h^{-1})	NA	NA	NA	NA
Average sleep fragmentation (%)	NA	NA	–	–
ESS scores	NA	NA	NA	NA
Sleep duration (h)	–	–	NA	NA
Cumulative R^2		10.6		10.6

CI, confidence interval; ESS, Epworth Sleepiness Scale; FPG, fasting plasma glucose; RDI, respiratory disturbance index; β, standard regression coefficient; r, correlation coefficient; R^2, contribution rate; NA, not applicable.
Model 1 was adjusted for age, waist circumference, RDI, average sleep fragmentation and ESS scores.
Model 2 was adjusted for age, waist circumference, RDI, ESS scores and sleep duration.

comparable to that in normal Japanese males. Also the prevalence of diabetes and IFG in Japanese males in their 40 s was reported to be 7.6 and 11.0%, respectively, in 2007 (Ministry of Health, Labor and Welfare, 2008), similar to findings of this study (7.6 and 12%, respectively). Therefore, our data that reflect the current background in Japan might be applicable to Western populations, although further studies are required to confirm this.

The proportion of OSA among our subjects, especially of mild OSA, was higher than that previously reported (Young *et al.*, 1993). We suspect as one reason that we defined hypopnoea as a more than 50% reduction in the amplitude of nasal pressure or respiratory effort associated with a more than 3% reduction in oxyhaemoglobin saturation, while Young *et al.* (1993) defined hypopnoea as a discernible reduction in respiratory airflow accompanied by a decrease of 4% or more in oxyhaemoglobin saturation. In addition, to detect hypopnoea, we used a nasal pressure sensor, while Young *et al.* (1993) used a thermo sensor. The American Academy of Sleep Medicine (1999) reported that a pressure sensor was much more effective and sensitive than a thermo sensor to detect hypopnoea, especially slight hypopnoea. In addition, the sampling time of the percutaneous arterial saturation was 1 s in our study. The sampling time, which means constant intervals to convert the amplitude of analogue signals to numbers, might have become shorter and more accurate in the 2000s than in the 1990s owing to advances in technology. However, Young *et al.* (1993) did not describe the sampling time in their methods. Also, our findings might have been influenced by the fact that we could make assessments under usual circumstances, where more than half of the subjects took alcohol before sleep (Nakayama-Ashida *et al.*, 2008).

Some relationship between diabetes and OSA was indicated by the following findings: (i) subjects with diabetes had a higher prevalence of OSA than those without diabetes ($P = 0.037$); (ii) there was a significant relationship between FPG and RDI ($P = 0.042$); and (iii) multiple regression analyses showed a significant association between FPG and RDI only in persons with diabetes. Diabetes has been linked to OSA in many studies. However, obesity, which is a common condition predisposing persons to both OSA and diabetes, is a main confounder, and causality remains to be determined (Tasali *et al.*, 2009). Among our study subjects with diabetes, waist circumference and BMI were not independently related to FPG, but RDI was. Cross-sectional analyses in an American cohort (Punjabi *et al.*, 2004) and an Australian cohort (Marshall *et al.*, 2009) also showed a significant relationship between diabetes and OSA. However, the Australian study showed that after adjustments for patient characteristics, the association was not significant. Thus, the independent relationship between OSA and diabetes needs further study.

As it was said that short sleep duration induced poor glucose metabolism (Spiegel *et al.*, 2009), in our study, a significant relationship between FPG and sleep duration was noted when the entire subject group was considered, although that relationship disappeared when subjects were divided according to having and not having diabetes. One reason might be the small number of subjects in each group after the division. The use of the actigraph might be another reason. Most previous epidemiological studies examined the relationships between diabetes and sleep duration as assessed by subjective self-reported measures (Tasali *et al.*, 2009). Objective actigraph-measured sleep duration is more accurate than self-reported sleep duration (Van Den Berg *et al.*, 2008). Moreover, total sleep time and sleep efficiency do not always significantly differ from those determined by PSG data and the combined data from actigraphy and subjective reports (Kushida *et al.*, 2005). Thus, our study design differed from that of previous studies on this issue, and sleep duration could have been assessed more accurately.

Associations between FPG and sleep fragmentation were reported (Knutson *et al.*, 2011). In this study, we found only a tendency toward a significant relationship between FPG and sleep fragmentation in the subjects with diabetes. One reason might be the small number of subjects, another might be that we used average sleep fragmentation for 7 days, and the PM was attached to the subjects for two of the 7 days. Sleep fragmentation on the days that PM recordings were made might have been overestimated as the PM might have disturbed sleep. In addition, in subjects with OSA, sleep fragmentation might fluctuate widely day by day, and determining sleep fragmentation might be more difficult than in those without OSA. Although sleep fragmentation might significantly affect FPG in subjects with OSA as well as the recent report (Knutson *et al.*, 2011), further studies are needed.

Previously, we reported the effects of the presence of hypertension on the relationship between OSA and sleepiness. We showed that sleepiness was related to the severity of OSA in hypertensive subjects but not in non-hypertensive subjects, although sleepiness was related to short sleep duration in both groups (Harada *et al.*, 2011). Thus, we thought that the effects of sleepiness would differ between subjects with and without diabetes. Then we assessed the effects of the presence of diabetes on the relationship between OSA and sleepiness. Barceló *et al.* (2008) reported that sleepiness in OSA was associated with higher FPG and insulin resistance and might be a risk factor for diabetes. However, in this study, we did not find such an association. Perhaps this was because the ESS scores used in our study were subjective assessments of sleepiness and might differ from objective measurements. In addition, our study subjects in this study had short sleep durations, which might have significant effects on the relationships between sleepiness and FPG. Although only sleep duration was independently related to sleepiness in both study groups, the influence of short sleep duration on sleepiness was much greater in the subjects with diabetes ($R^2 = 44.9\%$) than in those without diabetes ($R^2 = 3.0\%$). Therefore, ensuring sufficient

sleep duration could ameliorate sleepiness in subjects with diabetes.

The present study has some limitations. First, this is a cross-sectional study and it was difficult to completely exclude the influence of confounders such as age, obesity, medication, etc. Second, the number of subjects was small, and further studies with a larger number of subjects are needed to clarify this issue. Third, we did not perform PSG, partly because we wanted to assess sleep under usual lifestyle conditions. However, the non-attached type 3 monitoring was reported to be reliable under the specific conditions in which our study was conducted (Collop *et al.*, 2007). In addition, as to the reliability of the PM used in this study, Cunnington *et al.* (2003) stated AHI measured by PSG and by the PM highly correlated ($r = 0.94$), and also stated the median difference (AHI by PSG–AHI by the PM) was -0.5 events h^{-1} (95% confidence intervals -4.4 to 5.4, $P = 0.83$). Further, they indicated that the same PM as we used could correctly evaluate OSA that had been defined by PSG with a sensitivity of 96% and specificity of 83% (Cunnington *et al.*, 2009). In addition, as we previously reported, inter-scorer and night-to-night reliability of RDI were excellent (interclass correlation coefficient of 0.98 and 0.95, respectively; Nakayama-Ashida *et al.*, 2008). Also, laboratory tests on blood samples of the study subjects were performed yearly in accordance with the rules of the company. Therefore, subjects were advised yearly not to eat and drink anything after 20:00 hours except water and, of course, they were given the same instructions when this study was performed. Although the blood studies were performed after a longer than 12-h fast, we did not assess the exact time when the last meal or drink was consumed. Therefore, some subjects might have taken food or drink after 20:00 hours. We did not measure haemoglobin A1c values and we could not examine insulin resistance as we did not measure fasting insulin. Also, actigraphy seemed to have some limitations as it could not identify specific sleep stages like rapid eye movement sleep, although we did not consider this a problem because we only assessed awake time and sleep time during the night. We did not administer the Multiple Sleep Latency Test to estimate sleepiness objectively. ESS scores used in our study reflected subjective sleepiness and might differ from objectively measured sleepiness. Lastly, our participants did not include women because there were few female employees in the company.

In conclusion, OSA and sleep duration were related to FPG, and RDI was independently related to FPG in the subjects with diabetes. From results of this study, in addition to those of other studies (Aronsohn *et al.*, 2010; Punjabi *et al.*, 2004; Spiegel *et al.*, 2009), patients with diabetes should be examined for the presence of OSA. If OSA is present, it should be treated intensively, which will possibly have a favourable effect on plasma glucose control. Although the association between FPG and sleep duration in this study was weak, patients with diabetes should be advised to get sufficient sleep with less sleep fragmentation through the treatment of OSA.

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CONFLICTS OF INTEREST

No authors have indicated any financial conflicts of interest.

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CASE REPORT

Impact of nasal continuous positive airway pressure for congenital adrenal hyperplasia with obstructive sleep apnea and bruxism

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Abstract
Introduction Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders in humans. The most frequent CAH variant is 21-hydroxylase deficiency. Patients with 21-hydroxylasedeficiency require long-term glucocorticoid replacement treatment. Although sleep disturbance is frequently observed under glucocorticoid replacement treatment, a case of obstructive sleep apnea (OSA) in patients with CAH has not been reported.
Case report A 43-year-old man with CAH who complained about sleep disturbance and sleep bruxism was diagnosed as obstructive sleep apnea (OSA) by polysomnography (PSG). Following the introduction of nasal continuous positive airway pressure (nCPAP), his sleep disturbance with symptoms also improved; in addition, he was able to reduce the dose of glucocorticoid replacementtherapy without any adverse consequences on his sleep pattern.
Conclusions Physicians who treat a patient with CAH should know the possibility in the existence of OSA in their patients. Because symptoms with OSA in CAH patient may increase the dosage of long-term glucocorticoid treatment for the patient, which may induce several adverse effects including body weight gain on the patient.

Keywords congenital adrenal hyperplasia · obstructive sleep apnea · nasal continuous positive airway pressure · glucocorticoid replacement therapy

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Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders in humans, with an estimated worldwide incidence of 1 in 15,000 live births [1]. The most frequent CAH variant, accounting for 95% of all affected patients, is 21-hydroxylase deficiency. This deficiency is caused by inactivating mutations in the *CYP21* gene, presenting as impaired cortisol synthesis and increased corticotrophin secretion. The resulting adrenal stimulation leads to increased production of androgens. In healthy individuals, it is well known that there is a marked circadian rhythm in cortisol release with the lowest levels occurring shortly after midnight and rising between 0200 and 0300 h, and peaking around 0600 to 0800 h (after waking). Patients with 21-hydroxylase deficiency require long-term glucocorticoid treatment to inhibit excessive secretion of corticotoropin-releasing hormone and corticotropin by the hypothalamus and pituitary, respectively, and to reduce elevated levels of adrenal sex steroids [2]. Glucocorticoid replacement therapy in adults has to be adjusted according to individual goals; there is no perfect regimen [3]. The dosage of glucocorticoid replacement therapy must be carefully adjusted to mimic this circadian rhythm. Inadequate levels of glucocorticoid replacement

Table 1 Polysomnogram analysis of the effect of introducing CPAP on OSA

	Before CPAP	After CPAP
Sleep duration (min)	478	431.5
Awakenings/h	17.1	9.9
Micro-arousals/h	9.3	6.5
Arousal index/h	26.4	16.4
Sleep onset (min)	3	4
Sleep efficacy (%)	86.8	86.1
Stage I (%)	6.5	12.6
Stage II (%)	66.1	63.5
SWS (%)	9	0.7
REM (%)	18.4	23.2
AHI/h	26.2	1.8
Obstructive apnea/h	2	0
Mixed apnea/h	0	0
Central apnea/h	0.1	1.5
Hypopnea/h	24.1	0.3
Minimum SpO_2 (%)	80	89

Descriptive statistics were calculated and for measurements of duration of sleep bruxism before and after nCPAP and compared by unpaired *t* tests. Values are ± standard deviation

CPAP Continuous positive airway pressure, *SWS* Slow wave sleep, *REM* Rapid eye movement, *AHI* Apnea hypopnea index, *SpO_2* Percutaneous oxygen saturation

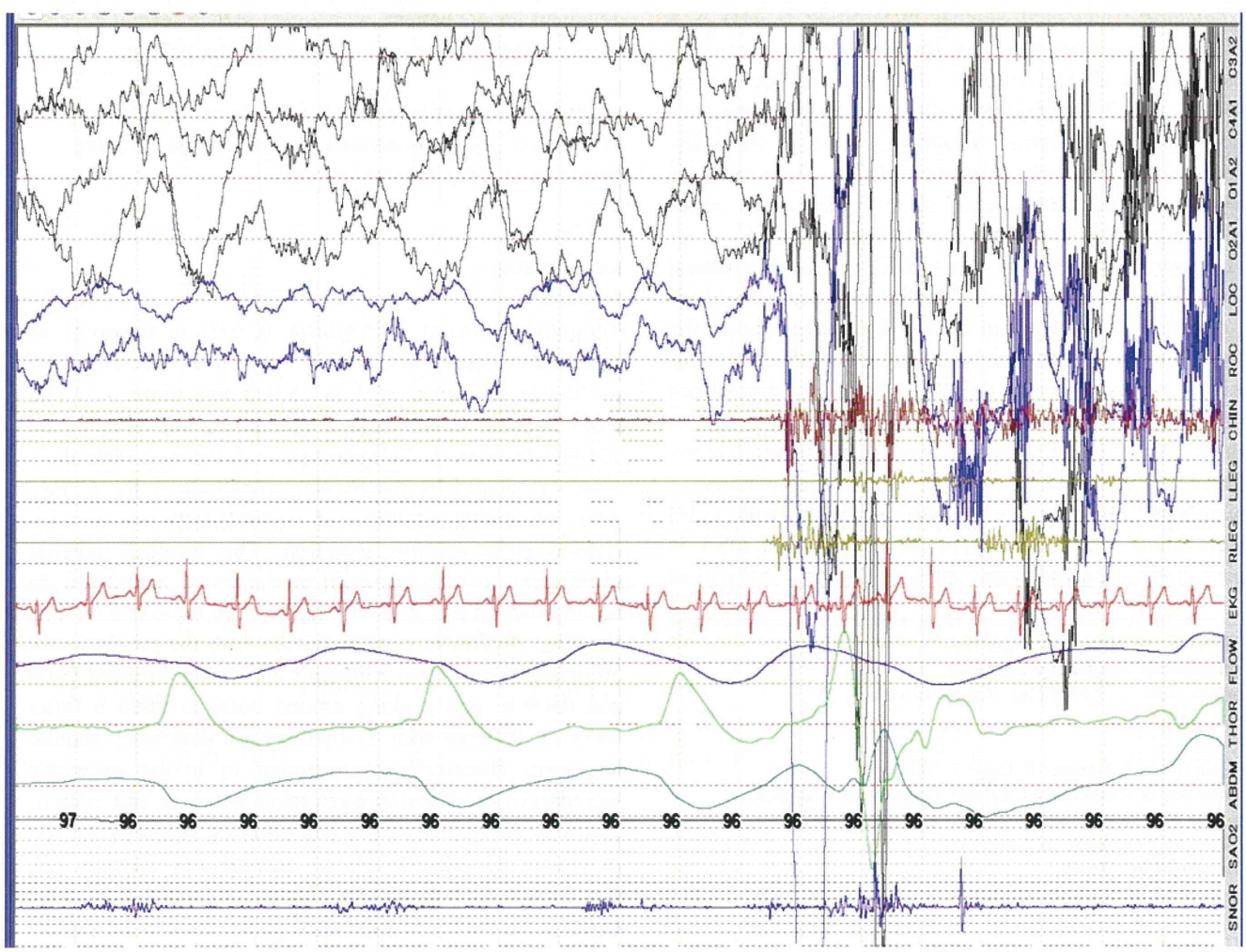

Fig. 1 A 30-s epoch of a diagnostic polysomnogram. Sleep bruxism was present with preceding micro-arousal. Depicted derivations include (from *top* to *bottom*) four electroencephalographic derivations; left and right electrooculogram; chin and both extremities electromyograms; electrocardiogram; thermal sensor; combined, thoracic, and abdominal movements by piezoelectric belts; oxygen saturation; snore

therapy may lead to many adverse effects such as sleep disturbance, elevated body mass index (BMI), glucose tolerance, osteoporosis and increased cardiovascular risk [4–7]. Increase in BMI is a main risk factor for obstructive sleep apnea (OSA) [8], which often induces sleep disturbance. We report here the first case of a CAH patient who complained of sleep disturbance and was diagnosed to have OSA and bruxism via polysomnography (PSG), and for whom nCPAP was prescribed.

Case presentation

The patient was a 43-year-old man who had been diagnosed with CAH when he was 4 years old. After the diagnosis, glucocorticoid replacement therapy was started. He suffered from diabetes mellitus, osteoporosis, hyperlipidemia and lumbar hernia; there was no family history of congenital metabolic disorder. His growth was arrested when he was 12 years old. Mutations of the CYP21 gene were detected in 2001. In 2005, when the patient was 39 years old, he complained of daytime fatigue, sleep disturbances such as insomnia with daytime sleepiness, lack of sensation taking a good sleep the feeling that he was unable to have a "good sleep", and sleep bruxism. At that time, his height and weight were 152.6 cm and 55.0 kg, respectively, and his BMI was 23.6 kg/m^2.

The overnight monitoring of his oxygen saturation by pulse oximetry was investigated. The oxygen desaturation index (ODI), defined as the number of 3% oxygen desaturations per hour of sleep, was 10/h, which indicated diagnosis of mild to moderate OSA. Oral appliance therapy was prescribed and his ODI improved to 0.57/h. However, the patient continued to complain of sleep disturbance.

Four years passed. His sleep disturbance continued. He gained approximately 2 kg within 1 month when he

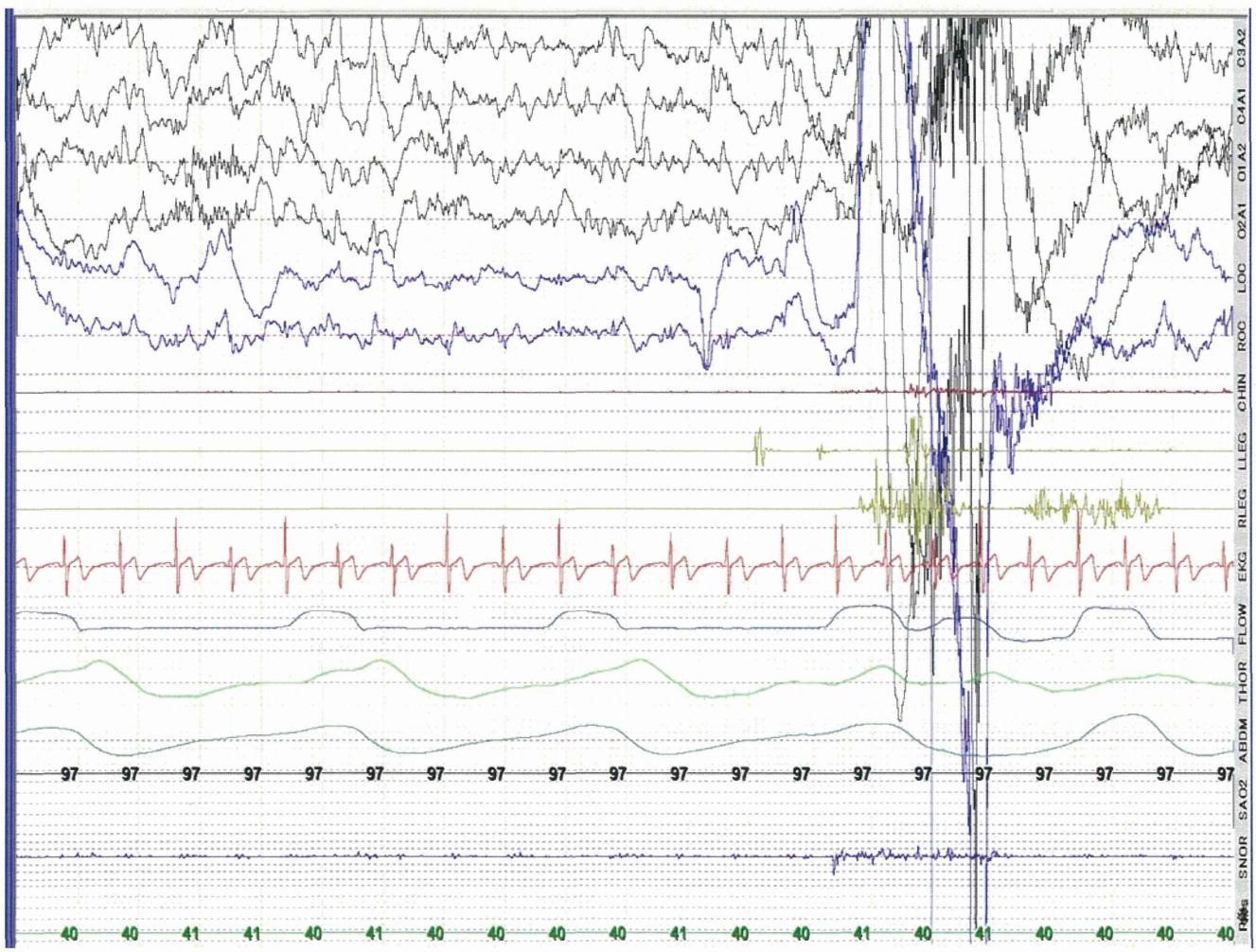

Fig. 2 A 30-s epoch of a therapeutic polysomnogram, with continuous airway pressure set. The duration and amplitude of sleep bruxism was improved. Depicted derivations include (from *top* to *bottom*) four electroencephalographic derivations; left and right electrooculogram; chin and both extremities electromyograms; electrocardiogram; CPAP flow; thoracic and abdominal movements by piezoelectric belts; oxygen saturation; snore; CPAP pressure

received oral 5.0 mg hydrocortisone at 1200, 1500, and 1800 hours, and oral 0.375 mg dexamethasone at 2200 hours as glucocorticoid replacement therapy. His BMI increased from 23.6 to 24.6 kg/m^2. His blood test analysed at 0800 hours revealed that adrenocorticotropic hormone (ACTH) and eosinophil levels were 11 (reference value: 7–56) pg/ml and 300 (reference value: 96–480)/μl, respectively. The Epworth Sleepiness Scale (ESS) score was 12 (reference value ≦10) points.

PSG (Somnostar Pro System, Fukuda Denshi, Tokyo, Japan) was performed without the oral appliance and the apnea and hypopnea index (AHI) was 26.2/h (Table 1 and Fig. 1). Apnea was defined as the cessation of airflow ≧10 s and hypopnea was defined as a >50% decrease in a valid measure of airflow in association with oxygen desaturation of >3% or an arousal. Nasal continuous positive airway pressure (nCPAP) therapy was prescribed and his AHI improved to 1.8/h (Table 1). Bruxism was measured by activation on an electromyogram, together with sounds of bruxism that could be heard by the attendant sleep technician. A comparison between the PSGs recording without nCPAP and with showed an improvement of in mean durations of bruxism from 13.4±7.1 to 9.7±6.0 s ($p<0.05$ 1 Figs. 1 and 2); however, the number of bruxism events was not changed significantly, from 40 to 37.

About 10 days following the introduction of nCPAP, the dose of dexamethasone was reduced from 0.375 to 0.25 mg because his insomnia and daytime sleepiness improved. He subsequently continued nCPAP and the level of glucocorticoid replacement therapy was reduced, resulting to improvements in symptoms of sleep disturbance without exacerbation of the other symptoms.

Discussion

This study describes a CAH patient with moderate OSA, whose symptoms were thought to be symptoms of CAH, which were relieved by nCPAP treatment and which enabled the dose of glucocorticoids to be reduced. To our knowledge, this case represents the first report of OSA in a CAH patient with glucocorticoid replacement treatment.

There has been no report about a CAH patient with OSA. Too high a level of HRT therapy may worsen the severity of OSA by cortisol-induced obesity. Our patient gained 2 kg within 1 month of glucocorticoid therapy. It has been reported many patients with adrenal insufficiency such as CAH have indefinite complaints such as daytime fatigue because of inadequate controlled dosing of glucocorticoid replacement treatment [9, 10]. Therefore, CAH patients who suffer from undiagnosed sleep apnea may be prescribed increasing doses of corticosteroids because of daytime fatigue. The patient in this study was able to reduce his dose of dexamethasone after the introduction of nCPAP treatment. In this way, he might have avoided higher risks of a worsening condition because of elevated BMI due to increased use of corticosteroids in addition to other side effects of corticosteroids, such as diabetes mellitus and osteoporosis.

Our patient also complained sleep bruxism in addition to daytime fatigue and sleep disturbance. The prevalence of sleep bruxism is approximately 8% in the general population. There is no difference in prevalence rates between men and women, but it decreases with age [11]. In an epidemiological study, it has been found that OSA was the highest risk factor for sleep bruxism [12]. Regarding sleep bruxism, the duration improved after nCPAP treatment, although the number of bruxism events did not significantly change. It has been also reported that sleep bruxism is strongly linked to transient arousal episodes [13] and follows an increase in autonomic nervous system [14]. Patients with OSA have a high sympathetic activity when awake, with further increases in sympathetic activity during sleep and these increases are attenuated by treatment with CPAP [15]. In this case, we considered that the attenuated lowered overactivities of sympathetic nerve activity by introducing nCPAP might improve the duration and amplitude of sleep bruxism.

Physicians who treat patients with CAH should be aware of the possibility of OSA in their patients, because symptoms with OSA in CAH patients may lead to increased dosage of long-term glucocorticoid treatment for these patients, which in turn could induce several adverse effects including body weight gain.

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ORIGINAL ARTICLE

Analysis of anatomical and functional determinants of obstructive sleep apnea

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Abstract
Purpose Craniofacial abnormalities have an important role in the occurrence of obstructive sleep apnea (OSA) and may be particularly significant in Asian patients, although obesity and functional abnormalities such as reduced lung volume and increased airway resistance also may be important. We conducted simultaneous analyses of their interrelationships to evaluate the relative contributions of obesity, craniofacial structure, pulmonary function, and airway resistance to the severity of Japanese OSA because there are little data in this area.
Methods A cross-sectional observational study was performed on 134 consecutive Japanese male patients. A sleep study, lateral cephalometry, pulmonary function tests, and impulse oscillometry (IOS) were performed on all patients.
Results Age, body mass index (BMI), position of the hyoid bone, and proximal airway resistance on IOS (R20) were significantly related to the apnea/hypopnea index (AHI) ($p<0.05$) in multiple regression analysis. Subgroup analysis showed that, for moderate-to-severe OSA (AHI≥15 events/h), neck circumference and R20 were predominantly related to AHI, whereas for non-to-mild OSA (AHI<15 events/h), age and expiratory reserve volume were the predominant determinants. In obese subjects (BMI≥25 kg/m^2), alveolar–arterial oxygen tension difference, position of the hyoid bone, and R20 were significantly associated with AHI, whereas age alone was a significant factor in nonobese subjects (BMI<25 kg/m^2).
Conclusions Aside from age and obesity, anatomical and functional abnormalities are significantly related to the severity of Japanese OSA. Predominant determinants of AHI differed depending on the severity of OSA or the magnitude of obesity.

Keywords Obstructive sleep apnea · Obesity · Cephalometry · Pulmonary function · Impulse oscillometry

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway obstruction. The critical pathophysiological feature of OSA is sleep-related narrowing or closure of the upper airway at the level of the pharynx [1, 2]. Anatomical abnormality is an important risk factor for OSA, and most patients with OSA have craniofacial abnormalities such as a small mandible, enlarged tongue, enlarged soft palate, inferior displacement of the hyoid bone, and imbalance between soft tissue volume and bony enclosure size [3–5]. Dempsey et al. [6] analyzed the interactive effects of obesity and craniofacial structure on sleep-disordered breathing and reported that body mass index (BMI) and cephalometric dimensions equally contributed to the elevated apnea/hypopnea index (AHI). However, a recent study showed that craniofacial

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structure and obesity contributed differently to OSA between Caucasian and Asian patients [7]. In addition, Dempsey et al. pointed out some additional factors that might explain elevations in the AHI and speculated that functional abnormalities such as impaired neural control of upper airway muscles and ventilatory instability, which may cause increased airway resistance, might be candidates [6].

It has been shown that pharyngeal patency in OSA patients is lung volume dependent [8, 9], and previous reports indicated a significant correlation between a reduced lung volume and nocturnal obstructive apnea and desaturation [10, 11]. Increased upper airway resistance also was shown to play a role in the pathogenesis of OSA [12, 13] through the association with increased susceptibility of airway narrowing and collapse [2, 14]. Thus, in addition to anatomical abnormalities, functional abnormalities such as reduced lung volume and increased airway resistance have been shown to play important roles in the pathogenesis of OSA.

Obesity, the most important risk factor for OSA, is known to affect craniofacial structures [15], lung volume [16], and airway resistance [17, 18]. However, given the substantial number of nonobese OSA patients in Japan [19], we hypothesized that there would be significant relationships between OSA and anatomical and functional factors as well as obesity, reflecting a multi-factorial pathophysiological feature of OSA. Therefore, in the present study, we simultaneously analyzed the interrelationships among craniofacial structure, pulmonary function, airway resistance, obesity, and OSA to investigate the relative contributions of these factors to the severity of OSA.

Materials and methods

Study subjects

We performed a cross-sectional observational study of 134 consecutive Japanese male patients who visited the Sleep Unit of Kyoto University Hospital between January 2009 and February 2010 for evaluation of OSA. None had been previously diagnosed with or treated for OSA. Patients with pulmonary diseases such as asthma or chronic obstructive pulmonary disease and who were diagnosed as having central sleep apnea were excluded. This study was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee, and informed consent was obtained from all patients. A sleep study, lateral cephalometry, pulmonary function tests, and impulse oscillometry (IOS) were performed on all patients. To establish smoking history, the Brinkman index was calculated by the following formula:

$$\text{Brinkman index} = \text{number of cigarettes smoked per day} \times \text{number of smoking years.}$$

Arterial blood gas analysis, including arterial partial pressure of oxygen (PaO_2) and arterial partial pressure of carbon dioxide ($PaCO_2$), was performed with patients' breathing room air at rest in the supine position at 19:00. Alveolar–arterial oxygen tension difference ($A\text{-}aDO_2$) was calculated according to the standard formula, using the respiratory exchange ratio of 0.8.

Polysomnography

Diagnosis of OSA was confirmed by polysomnography (SomnoStar pro, Cardinal Health, Dublin, OH, USA), which was started at 22:00 and ended at 6:00 the following morning. Surface electrodes were attached using standard techniques to obtain an electrooculogram, electromyogram of the chin, and 12-lead electroencephalograph. Sleep stages were defined according to the criteria of Rechtschaffen and Kales [20]. Ventilation was monitored by inductive plethysmography (Respitrace QDC, Viasys Healthcare, Palm Springs, CA, USA). Airflow was monitored by a nasal air pressure transducer (PTAFlite, Pro-Tech Services Inc., Mukilteo, WA, USA) and supplemented by an oronasal thermal sensor (Sleepmate Technologies, Midlothian, VA, USA). Arterial oxygen saturation (SpO_2) was monitored continuously with a pulse oximeter (Adult Flex System, Nonin Medical, Plymouth, MN, USA).

Apnea was defined as the complete cessation of airflow and hypopnea as a clear decrease in airflow of 30% or more lasting for 10 s or more, accompanied by a decrease in SpO_2 of at least 4% [21]. All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. The lowest SpO_2 during sleep and the percentage of time of SpO_2 90% during sleep also were calculated in each patient. OSA severity was defined by the AHI as follows: non-OSA ($AHI<5$), mild OSA ($5\leq AHI<15$), moderate OSA ($15\leq AHI<30$), and severe OSA ($AHI\geq 30$).

Cephalometry

A lateral cephalogram was obtained for each subject. The cephalograms were taken on image plates (ST-VI, Fuji Medical Systems, Tokyo, Japan) with the subject in the sitting position at a film focus distance of 2 m, with a left to right view. Exposures were made at 75 kV and 320 mA at the end-expiratory phase during quiet breathing through the

nose, and a cephalostat was used to keep the subject's head in a position such that the Frankfort horizontal line was parallel to the floor during exposure. Images of the cephalograms were digitized and input into a computer, previewed and processed for sharp visibility of both the soft tissues and bony structures, and printed out through a computed radiography system (FCR Profect CS, Fuji Medical Systems). A total of 22 variables related to both craniofacial skeletal and soft tissue morphology were measured as angular (degrees), linear (millimeters), or area (square centimeters) by a single observer in a single-blind manner. Images were analyzed using Image J software (US NIH, Bethesda, MD, USA). Every measurement was made by the same observer, who had no knowledge of the clinical status of the patient.

The cephalometric landmarks and reference lines are defined in Table 1 and illustrated anatomically in Fig. 1. The following angles and dimensions were measured: SNA, antero-posterior position of the maxilla in relation to the anterior cranial base (angle between S–N and N–A); SNB, antero-posterior position of the mandible in relation to the anterior cranial base (angle between S–N and N–B); ANB, relative position of the mandible to the maxilla (angle between N–A and N–B); facial axis, vertical position of the mandible in relation to the skull (angle between Pt–Gn and N–Ba); G–VL, antero-posterior position of the chin in relation to the vertebra (linear distance along the perpendicular plane from G to VL); N–Ba, the length of the cranial base (distance between N and Ba); S–N, the length of the anterior cranial base (distance between S and N); ANS–PNS, the length of the hard palate (distance between ANS and PNS); PNS–Ba, bony nasopharynx (distance between PNS and Ba); PNS–P, the length of the soft palate (distance between PNS and P); PNS–V, the length of the pharyngeal airway (distance between PNS and V); MPT, greatest thickness of the soft palate; TGL, the length of the tongue (distance between V and TT); TGH, height of the tongue (linear distance along the perpendicular bisector of the V–TT line to the tongue dorsum); Me–Go, the length of the mandible (distance between Me and Go); MP–H, vertical position of the hyoid bone (linear distance along the perpendicular plane from H to MP); H–VL, antero-posterior position of the hyoid bone (linear distance along the perpendicular plane from H to VL); AW1, upper oropharyngeal airway caliber (narrowest part of the airway between PNS and P); AW2, lower oropharyngeal airway caliber (narrowest part of the airway between P and Go); airway area, dimensions of the oropharynx (area outlined by the inferior border of the nasopharynx, the posterior surface of the soft palate and tongue, the line parallel to the palatal plate through the point V, and the posterior pharyngeal wall); tongue area, dimensions of the tongue (area outlined by the dorsal aspect of the tongue surface and lines that join TT, G, H, and V); and the lower face cage,

Table 1 Definitions of cephalometric landmarks and reference lines

S	Sella, midpoint of the fossa hypophysealis
N	Nasion, anterior point at the frontonasal suture
ANS	Anterior nasal spine, most anterior point of the nasal spine
PNS	Posterior nasal spine, most posterior point of the nasal spine
A	Deepest anterior point in the concavity of the anterior maxilla
B	Deepest anterior point in the concavity of the anterior mandible
Cd	Medial condylar point of the mandible
Cd′	A point that Pg projects onto the perpendicular line to the Cd–A line at the Cd point
Go	Gonion, a mid-plane point at the gonial angle located by bisecting the posterior and inferior borders of the mandible
Me	Menton, most inferior point of the chin bone
Ba	Basion, most posteroinferior point on the clivus
G	Most posterior point on the symphysis of the mandible
Pg	Prognathion, most anterior point on the symphysis of the mandible
P	Lowest point of the soft palate
TT	Most anterior point of the tip of the tongue
H	Most anterosuperior point of the hyoid bone
V	Most antero-inferior point of the epiglottic fold
Pt	Intersection of the posterior pharyngeal wall and most inferior margin of the foramen rotundum
Gn	Gnathion, the most antero-inferior point of body chin
NL	Nasal line, a line through ANS and PNS
MP	Mandibular plane, a plane constructed from Me through Go
VL	A line across C3 and C4

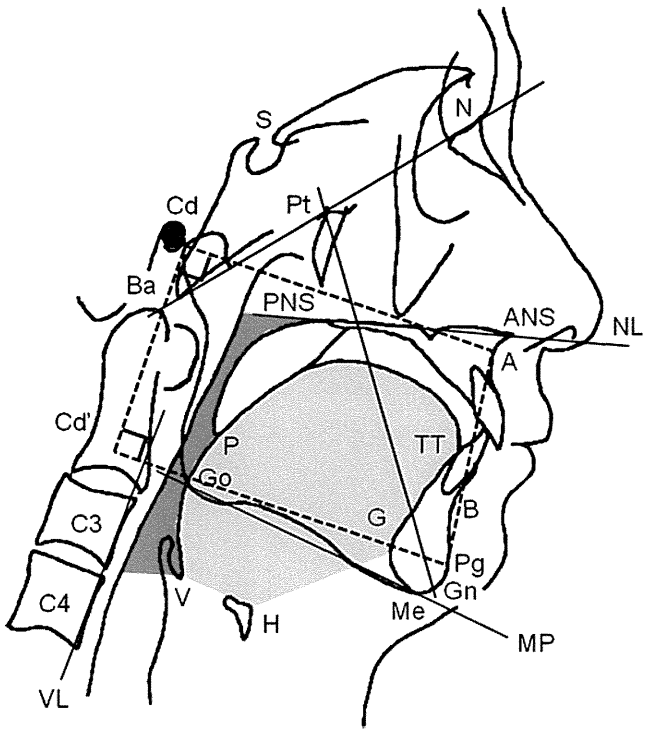

Fig. 1 Cephalometric landmarks and reference lines. For definitions, see Table 1. *Shaded area* indicates cross-sectional area of the tongue. *Dark-stained area* indicates cross-sectional area of the airway. *Lower face cage* was defined as a trapezoid formed by Cd–A–Pg–Cd′ (*dotted lines*)

the maxillomandibular enclosure size of the upper airway (cross-sectional area of the trapezoid enclosed by Cd–A–Pg–Cd′). Upper airway anatomical balance was assessed by the ratio between the tongue area and lower face cage as described in a previous study [5].

Pulmonary function tests

Pulmonary function tests were performed in the sitting position using CHESTAC (Chest M.I. Inc., Tokyo, Japan). Subjects underwent spirometric testing according to the recommended method [22]. Residual volume (RV) and total lung capacity (TLC) were measured by the closed circuit helium method, and diffusing capacity for carbon monoxide (DL_{CO}) was measured using a single-breath technique.

IOS

The assessment of respiratory impedance was performed by IOS (Masterscreen IOS-J, Jaeger, Wurzburg, Germany). IOS is different from the classical forced oscillation technique (FOT) because an impulse rather than a pseudo-random noise signal is applied by the loudspeaker. Data processing is also different between IOS and FOT. But IOS yields respiratory system resistance and reactance values similar to those provided by FOT [23]. Subjects were measured first in the sitting position and then in the supine position, fulfilling standard recommendations [24], as previously reported in detail elsewhere [25, 26]. In short, rectangular mechanical impulses containing the whole frequency spectrum were applied to the respiratory system through a mouthpiece while the patient was breathing quietly. The resulting pressure and flow signals were analyzed for amplitude, and the impedance (Z) represents the total mechanical load of the subject's respiratory system from which the resistance (R) and the reactance (X) of the respiratory system can be derived. The frequency range of the signal was from 5 to 35 Hz. The impedance at 5 Hz (Z5) represents the impedance of the total respiratory system. In the present study, we used respiratory resistance at 5 and 20 Hz (R5 and R20) as indices of total and proximal airway resistance, respectively. In IOS, low frequency oscillations are transmitted to the lung periphery, while those at frequencies ≥20 Hz are thought to be damped out before reaching the peripheral airways [27]. The reactance at 5 Hz (X5) may be determined by homogeneous distribution of ventilation, effective ventilation capacity, and compliance of the lung and chest wall. These indices have been shown to be useful for the evaluation of upper airway patency in OSA [12, 13].

Statistics

All statistical analyses were performed using StatView version 5.0 for Windows (Abacus Concepts, Berkeley, CA, USA). Continuous variables are expressed as means ± standard deviation (SD). Intra-observer agreement for the cephalometric measurements was evaluated by the intra-class correlation coefficient (ICC) [28]. The natural logarithm of the AHI was used as the dependent variable since the absolute values were not distributed normally. Chi-square tests were used to compare dichotomous variables and unpaired Student's t tests were used to compare continuous data between two groups. Relationships between two variables were analyzed by Pearson's correlation coefficient tests. Stepwise multiple regression analyses were performed to identify variables that could best explain AHI. A p value less than 0.05 was considered to indicate statistical significance.

Results

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to AHI in all subjects

Patient characteristics and polysomnographic data are shown in Table 2. The study group of 134 patients comprised 19

Table 2 Clinical characteristics and polysomnographic data on 134 patients

Age (years)	56.5±14.5
BMI (kg/m^2)	26.5±4.2
Neck circumference (cm)	40.2±3.2
Smoking history (current/ex/never)	37/70/27
Brinkman index	528±603
AHI (events/h)	26.0±22.5
Logarithmic AHI	2.8±1.3
Minimum SpO_2 (%)	79.0±10.5
SpO_2 <90% time/TST (%)	14.8±21.4
$PaCO_2$ (kPa)	5.6±0.5
PaO_2 (kPa)	11.4±1.5
A-aDO_2 (kPa)	1.6±1.5

Data presented as mean ± SD

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

Table 3 Stepwise multiple regression analysis to predict AHI (n=134)

	r^2
Age (years)	0.08
BMI (kg/m^2)	0.09
Neck circumference (cm)	–
PaO_2 (kPa)	–
A-aDO_2 (kPa)	–
Tongue area (cm^2)	–
PNS–P (mm)	–
TGL (mm)	–
MP-H (mm)	0.05
ERV (L)	–
%ERV (% pred)	–
R5 (kPa/L/s)	–
Z5[a] (kPa/L/s)	–
R5[a] (kPa/L/s)	–
R20[a] (kPa/L/s)	0.06
Cumulative r^2	0.28

AHI apnea/hypopnea index, *BMI* body mass index, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference, *ERV* expiratory reserve volume

[a] In the supine position

non-OSA, 32 mild OSA, 37 moderate OSA, and 46 severe OSA patients. Regarding cephalometric measurements, intra-observer agreement was excellent (ICC ranged from 0.92 to 0.99) for all variables except for ANB and TGL, which had good intra-observer agreement (ICC=0.82 in ANB and 0.83 in TGL). We investigated the associations between anthropometric variables, arterial blood gas data, cephalometric parameters, pulmonary function, IOS measurements, and AHI. The AHI had a significant positive correlation with age (r=0.26, p=0.003), BMI (r=0.32, p=0.0002), neck circumference (r=0.33, p=0.0001), and A-aDO_2 (r=0.37, p< 0.0001) and a negative correlation with PaO_2 (r=−0.31, p= 0.0003) (Table E1). Examination of cephalometric parameters showed that the AHI had a significant positive correlation with the tongue area (r=0.18, p=0.04), PNS–P (r=0.30, p=0.0004), TGL (r=0.23, p=0.008), and MP–H (r=0.28, p=0.001) (Table E2). Regarding pulmonary function, there was a significant negative correlation between the AHI and only with the expiratory reserve volume (ERV) (r=−0.28, p=0.001) and %ERV (r=−0.24, p=0.007) (Table E3). The results of IOS measurements revealed that the AHI had a significant positive correlation with R5 (r=0.22, p=0.01) in the sitting position and Z5 (r= 0.19, p=0.03), R5 (r=0.24, p=0.006), and R20 (r=0.25, p= 0.004) in the supine position (Table E3).

Stepwise multiple regression analysis was performed to examine the relationships with AHI using the preselected variables that were significantly related to AHI in the above analyses (Table 3). Age, BMI, MP–H by cephalometry, and R20 in the supine position on IOS significantly explained 28% of the variance in AHI [r^2 (coefficient of determination)=0.08, 0.09, 0.05, and 0.06, respectively].

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to the AHI based on the severity of OSA

We then compared the predominant determinants of AHI between 83 moderate-to-severe (AHI≥15) and 51 non-to-mild (AHI<15) OSA subjects. The clinical characteristics and polysomnographic data for these patients are shown in Table 4. The BMI and neck circumference were significantly higher, and the PaO_2 was significantly lower in moderate-to-severe OSA than in non-to-mild OSA (p= 0.007, 0.002, and 0.004, respectively). As we did for the overall group of 134 patients, we performed stepwise multiple regression analyses to account for AHI in the moderate-to-severe and the non-to-mild groups, using the preselected variables that were significantly related to AHI. They included BMI, neck circumference, PaO_2, A-aDO_2, R5 and R20 in the sitting position, and Z5, R5, and R20 in the supine position in moderate-to-severe OSA and included age, $PaCO_2$, VC, ERV, FEV_1, RV/TLC, and $\%DL_{CO}$ in non-to-mild OSA. In moderate-to-severe OSA, neck circumference and R20 in the supine position on IOS (r^2=0.11 and 0.10, respectively) significantly explained 21% of the variance in AHI. By contrast, in non-to-mild OSA, age and ERV (r^2=0.19 and 0.10, respectively) significantly explained 29% of the variance in AHI.

Table 4 Comparison of clinical characteristics and polysomnographic data between groups based on the severity of OSA

	AHI≥15 (n=83)	AHI<15 (n=51)	p value
Age (years)	57.6±12.3	54.7±17.4	0.26
BMI (kg/m^2)	27.2±4.6	25.2±3.2	0.007
Neck circumference (cm)	40.9±3.5	39.1±2.3	0.002
Smoking history (current/ex/never)	18/46/19	9/24/18	0.18
Brinkman index	578±595	446±613	0.22
AHI (events/h)	38.1±20.6	6.5±4.4	<0.0001
Logarithmic AHI	3.5±0.5	1.5±1.2	<0.0001
Minimum SpO_2 (%)	74.5±10.4	86.3±5.0	<0.0001
SpO_2 <90% time/TST (%)	22.9±23.7	1.6±2.4	<0.0001
$PaCO_2$ (kPa)	5.6±0.5	5.7±0.4	0.32
PaO_2 (kPa)	11.1±1.4	11.9±1.5	0.004
A-aDO_2 (kPa)	1.9±1.4	1.0±1.5	0.0008

Data presented as mean ± SD. Unpaired t tests were performed except for the chi-square test for smoking history

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

Relative contributions of obesity, craniofacial structure, pulmonary function, and IOS measurements to AHI based on the magnitude of obesity

We then compared the predominant determinants of AHI between 79 obese (BMI≥25) and 55 nonobese (BMI<25) subjects. The clinical characteristics and the polysomnographic data on these patients are shown in Table 5. There was a trend for more current smokers or ex-smokers to be present among the obese subjects. Neck circumference and the mean AHI were significantly higher, and the PaO_2 was significantly lower in obese subjects than in nonobese subjects (p<0.0001, p=0.002, and p<0.0001, respectively). We also performed stepwise multiple regression analyses to account for AHI in obese and nonobese subjects using the preselected variables that were significantly related to AHI. They included BMI, neck circumference, PaO_2, A-aDO_2, PNS–P, TGL, MP-H, ERV, and R5 and R20 in the sitting and supine positions in obese subjects and age and A-aDO_2 in nonobese subjects. In obese subjects, A-aDO_2, MP-H by cephalometry, and R20 in the sitting position on IOS (r^2=0.08, 0.10, and 0.07, respectively) significantly accounted for 25% of the variance in AHI. In contrast, in nonobese subjects, age alone was significantly related to AHI (r^2=0.25).

Discussion

We simultaneously analyzed the interrelationships between OSA and obesity, anatomical abnormalities measured by cephalometry, and functional abnormalities measured by pulmonary function testing and IOS. By multiple regression analysis, we found that age, BMI, MP-H by cephalometry, and R20 on IOS significantly contributed to AHI. In addition, separate analyses revealed that significant determinants of OSA differed between moderate-to-severe OSA and non-to-mild OSA and between obese subjects and nonobese subjects.

In addition to age and obesity (BMI), an anatomical abnormality (inferior displacement of the hyoid bone) and a functional abnormality (increased proximal airway resis-

Table 5 Comparison of clinical characteristics and polysomnographic data between groups based on the magnitude of obesity

	BMI≥25 (n=79)	BMI<25 (n=55)	p value
Age (years)	55.9±13.2	57.3±16.3	0.58
BMI (kg/m^2)	28.9±3.7	22.9±1.4	<0.0001
Neck circumference (cm)	41.7±3.0	38.1±2.2	<0.0001
Smoking history (current/ex/never)	19/44/16	8/26/21	0.02
Brinkman index	611±618	408±566	0.054
AHI (events/h)	31.0±25.6	18.9±14.6	0.002
Logarithmic AHI	3.0±1.2	2.5±1.3	0.03
Minimum SpO_2 (%)	77.1±11.5	81.8±8.2	0.009
SaO_2 <90% time/TST (%)	20.7±25.5	6.3±8.2	<0.0001
$PaCO_2$ (kPa)	5.6±0.5	5.6±0.4	0.47
PaO_2 (kPa)	10.9±1.5	12.0±1.4	<0.0001
A-aDO_2 (kPa)	2.1±1.4	0.9±1.4	<0.0001

Data presented as mean ± SD. Unpaired t tests were performed except for the chi-square test for smoking history

BMI body mass index, *AHI* apnea/hypopnea index, *TST* total sleep time, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PaO_2* arterial partial pressure of oxygen, *A-aDO_2* alveolar–arterial oxygen tension difference

tance) were significantly related to OSA. Obesity and age have been considered to be the characteristic risk factors for OSA [29]. On the other hand, certain forms of craniofacial abnormalities measured by cephalometry [3–5], reduced lung volume [8–11], and increased upper airway resistance [12, 13] also have been suggested as predisposing factors for upper airway obstruction during sleep. Although these factors may be significantly affected by age and obesity [15–17, 30, 31], the relative contributions of anatomical and functional abnormalities, age, and obesity to OSA have remained to be elucidated. Our findings indicate that OSA is the result of independent interrelationships among anatomical abnormalities, functional abnormalities, age, and obesity, which reflects a multi-factorial pathophysiological feature of OSA.

We found that, compared with pulmonary function, airway resistance on IOS was related more closely to AHI. Structurally, the pharyngeal airway is surrounded by soft tissue, which is enclosed by bony structures and is caudally pulled by the thorax. As has been suggested, an imbalance between the amount of soft tissue and the size of the surrounding bony structures [32] and decreased thoracic traction [33] due to a reduced lung volume may result in increased tissue pressure surrounding the pharyngeal airway and decreased longitudinal tension of the pharyngeal airway wall, leading to increased upper airway resistance. Moreover, airway resistance was shown to increase when the body position changed from a sitting to a supine position [34]. In nonobese subjects, the falls in lung volume in a supine position are likely to lead to increased airway resistance, while in obese subjects in a supine position, such falls are smaller than in nonobese subjects and can only partly explain an increase in airway resistance [34]. Hence, there must be additional causes and sites of increased airway resistance in obese subjects. Our results showed the importance and usefulness of demonstrations of increased airway resistance on IOS in explaining the severity of OSA.

In one subgroup analysis, predominant determinants of AHI differed depending on the severity of OSA. In moderate-to-severe OSA, neck circumference and airway resistance were predominantly related to AHI, whereas in non-to-mild OSA, age and ERV were predominantly related to AHI. There was no overlap in those factors that were significantly associated with AHI, indicating a different pathogenesis of the disease between moderate-to-severe versus non-to-mild OSA. Asians were reported to have more severe OSA than Caucasians even when the BMI was similar between the two groups [7]. Our results indicate the importance of increased fat deposition adjacent to the upper airway rather than total body fat volume in Japanese individuals with moderate-to-severe OSA, which may partially explain this difference. Although it has been suggested that the consequences of craniofacial abnormalities are more severe in Japanese than in Caucasian OSA patients [3], craniofacial abnormalities were not significantly related to AHI in both moderate-to-severe and non-to-mild OSA groups in the present study after adjustment for other risk factors, although further study is needed. Moreover, that age independently correlated with non-to-mild OSA but not moderate-to-severe OSA may partly support the evidence that with increasing age, OSA prevalence increases but that its severity does not [19, 29].

Another subgroup analysis showed that in obese subjects, A-aDO_2, the distance between the hyoid bone and mandible, and airway resistance were predominantly related to AHI. Recent studies suggested that subclinical lung injury may be present in OSA possibly through local oxidative stress in the alveolus [35, 36]. Although the magnitude of the injury might not be great, given the effect of ventilation–perfusion inequality due to obesity [16], A-aDO_2 can be significantly related to AHI in obese OSA subjects. The position of the hyoid bone is correlated with accumulations of adipose tissue in pharyngeal regions, and its inferior displacement may give rise to the posterior relocation of the tongue and reduce upper airway patency [3, 37, 38]. Abdominal fat is likely to have direct effects on the downward movement of the diaphragm and is associated with increased airway resistance through the reduction in lung volume [16, 39]. Our results may also imply the importance of abundant parapharyngeal and intraabdominal distribution of adipose tissue in obese subjects. Additionally, in nonobese subjects, age alone had a significant relationship with the AHI. The unexplained variance by age may be related to structural or functional abnormalities that were not measured, indicating the complicated pathogenesis of OSA in lean individuals.

Unfortunately, the four crucial features in our study account for only 28% of the variance in AHI. There are several possible explanations. Firstly, various determinants of OSA, not limited to obesity, might be characteristic in Japanese subjects. Secondly, all of our anatomical and functional measurements were obtained during wakefulness, which may have limited relevance to the sleeping state. Furthermore, some cephalometric measurements, including that of the position of the hyoid bone, may be affected by muscle contraction required for central occlusion of the jaw. Thirdly, we did not evaluate the degree of ventilatory control stability. It is termed "loop gain", whose increase is suggested to play an important role in the pathogenesis of OSA [40, 41]. Additional assessments might have explained a certain proportion of the residual variance in AHI.

As a limitation, the present study had a small sample size (especially non-OSA subjects) with only male subjects from one university hospital, which might have limited the

generalization of the results. Moreover, we only studied Japanese subjects and did not directly assess inter-ethnic differences in OSA risk factors. Considering that OSA is highly prevalent worldwide, inter-ethnic differences in OSA risk factors is an important issue. Although we discussed inter-ethnic differences by comparing the results with previous studies, such as those of a recent study by Lee et al. [7], further studies directly comparing OSA risk factors in different ethnic groups would more clearly elucidate those risk factors. Another limitation is that we assessed craniofacial structures only by cephalometry. Our limited measures of craniofacial morphology may underestimate the actual contributions of craniofacial morphology, especially of upper airway anatomical imbalance. Additional three-dimensional, volumetric evaluations using computed tomography [42] or magnetic resonance imaging [43] might show more sensitively the impact of anatomical imbalance on the pathogenesis of OSA.

OSA is a multi-factorial disease in which age and obesity play important roles. However, aside from age and obesity, our results indicated that both anatomical and functional abnormalities play significant roles in the pathogenesis of OSA. The severity of OSA or obesity appears to determine the relative contribution of these abnormalities to sleep-related collapse of the upper airway.

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Letters to the Editor

Beneficial effects of continuous positive airway pressure therapy in a pediatric intestinal transplant recipient with obstructive sleep apnea

To the editor,

The association of pediatric obstructive sleep apnea (OSA) with mortality and respiratory diseases was demonstrated in a recent study [1]. We encountered a pediatric intestinal posttransplant recipient with OSA in whom continuous positive airway pressure (CPAP) therapy may have a preventive effect on respiratory tract infection.

A 3-year-old Japanese boy received an intestinal transplant from a living donor (his mother) because of short-bowel syndrome. During the 5 years following transplantation, he required hospitalization 19 times, including four episodes of acute rejection and three of respiratory tract infection. At the age of four, he developed severe pneumonia and congestive heart failure and needed noninvasive positive pressure ventilation. He was subsequently hospitalized twice for pneumonia. At the age of eight, severe pediatric OSA was diagnosed based on daytime sleepiness, snoring, and 3% oxygen desaturation index (3% ODI) of 10.1 [2]. Nasal auto-set CPAP therapy with the pressure between 4 and 12 cm H_2O was started, and the 3% ODI decreased from 10.1 to 1.8. After the beginning of CPAP therapy, the number of hospitalizations markedly decreased to six times during the next seven years. The causes of six hospitalizations were abdominal problems (including suspected rejection) for five of the times and influenza without pneumonia for another time. He experienced no further episodes of severe respiratory tract infection.

This course suggests a significant association between OSA and respiratory tract infection. Pulmonary aspiration of gastric contents is common in children with apnea episodes or recurrent pneumonia [3]. CPAP therapy can reduce gastroesophageal reflux [4], which may prevent pneumonitis from gastric acid aspiration. CPAP therapy was also reported to decrease the risk of postoperative pulmonary complications, atelectasis, and pneumonia in patients undergoing abdominal surgery [5]. In patients with OSA, CPAP therapy can also decrease microatelectasis that otherwise would facilitate lower respiratory tract infection. The detection of OSA and application of CPAP therapy can provide an additional benefit in managing immunosuppressed children, especially when experiencing recurrent airway infections.

Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.10.019.

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Recurrent hypersomnia due to occult hepatic encephalopathy

To the Editor

Hepatic encephalopathy can give rise to stupor. However, the pathology is typically structural damage and is usually chronic rather than intermittent. We report a case of hepatic vascular dysfunction giving rise to recurrent hypersomnia.