Microalbuminuria in Patients with Obstructive Sleep Apnea–Chronic Obstructive Pulmonary Disease Overlap Syndrome

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Abstract

Rationale: Microalbuminuria is said to reflect systemic vascular damage and endothelial dysfunction and is an established indicator of cardiovascular morbidity and mortality. Patients with obstructive sleep apnea (OSA)–chronic obstructive pulmonary disease (COPD) overlap syndrome have worse survival than those with OSA or COPD alone.

Objectives: This study evaluated the association between overlap syndrome and microalbuminuria.

Methods: Data on patients in whom OSA was suspected and who underwent polysomnography between January 2010 and December 2012 were reviewed. Microalbuminuria was defined as an albumin–creatinine ratio between 20 and 299 mg/g in men and between 30 and 299 mg/g in women.

Measurements and Main Results: Of 740 consecutive patients, 344 were analyzed. Sixty-four were control participants, 248 had OSA only, 4 had COPD only, and 28 had OSA–COPD overlap syndrome. Prevalence of microalbuminuria significantly increased in the order of control, OSA, and overlap syndrome groups (3.1, 12.9, and 32.1%, respectively; $P = 0.0006$). After adjusting for age and sex, multivariate logistic regression analysis demonstrated a significant association of overlap syndrome with microalbuminuria compared with OSA (odds ratio, 2.61; 95% confidence interval, 1.02–6.38; $P = 0.047$), but after adjusting for other confounding factors, the difference in the association did not reach significance (odds ratio, 2.54; 95% confidence interval, 0.93–6.72; $P = 0.070$). Of 63 patients reevaluated after 3 months of continuous positive airway pressure therapy, the logarithm of the albumin–creatinine ratio in 36 patients with good compliance significantly decreased, but there was no difference in patients with poor compliance.

Conclusions: OSA–COPD overlap syndrome was more prevalent than OSA alone in patients with microalbuminuria, but the difference might be mediated by conventional risk factors rather than the addition of COPD itself.

Keywords: albumin–creatinine ratio; obstructive sleep apnea; chronic obstructive pulmonary disease

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Microalbuminuria reflects systemic vascular damage (1, 2) and is an established indicator of cardiovascular morbidity and mortality (3, 4). Also, urinary albumin has a dose-dependent relationship with all-cause mortality in the general population (5). Calculation of the albumin–creatinine ratio could estimate urine albumin excretion in a broad range of subjects (6).

Obstructive sleep apnea (OSA) is a common condition involving sleep-disordered breathing characterized by intermittent hypoxia (7). OSA is closely related to cardiovascular disease (8), and severe untreated OSA is associated with high cardiovascular disease mortality (9). There have been several reports about the

use of the albumin–creatinine ratio in patients with OSA to elucidate the association between OSA and cardiovascular disease. Faulx and colleagues showed that the albumin–creatinine ratio was correlated with the apnea–hypopnea index (AHI) (10). Also, the albumin–creatinine ratio was reported to decrease on the day after continuous positive airway pressure (CPAP) treatment, and that effect remained the same after 3 months of treatment (11, 12).

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible (13), and cardiovascular disease is a major cause of mortality in COPD (14). The association between COPD and microalbuminuria was also investigated, and Casanova and colleagues demonstrated a higher prevalence of microalbuminuria and a higher albumin–creatinine ratio in patients with COPD compared with subjects without COPD (15). The albumin–creatinine ratio was also reported to be positively correlated with the BODE (*b*ody mass index, airflow *o*bstruction, *d*yspnea, and *e*xercise capacity) index and negatively correlated with Pa_{O_2} in COPD (15, 16).

The coexistence of OSA and COPD is called "OSA–COPD overlap syndrome." Overlap syndrome occurs in 0.5% of the general adult population (17), and survival of patients with overlap syndrome was reported to be worse than that of patients with COPD or OSA alone; however, CPAP treatment improved survival to the same level as in a COPD-only group (18). Although the increased incidence of COPD exacerbations might be associated with greater mortality (18), there is no clear mechanistic explanation for this worse survival. Both OSA and COPD are associated with endothelial dysfunction (19, 20), which results in microalbuminuria (1, 2, 21). Because a relationship between OSA or COPD and microalbuminuria was shown (10, 15) and the unfavorable aspects of these conditions are closely related to cardiovascular disease mortality (9, 14), overlap syndrome, which has a poor prognosis, might also be associated with a high prevalence of microalbuminuria.

For this reason, the investigation of microalbuminuria in overlap syndrome might lead to elucidating the mechanism of the higher mortality in overlap syndrome. We hypothesized that the prevalence of microalbuminuria in overlap syndrome was greater than in OSA or COPD alone, that there is a higher albumin–creatinine ratio in those with OSA–COPD overlap syndrome compared with those with OSA or COPD alone, and that the albumin–creatinine ratio decreases after CPAP treatment in overlap syndrome as well as in OSA. The aim of this study was to evaluate the prevalence of microalbuminuria and the albumin–creatinine ratio values in OSA, COPD, and overlap syndrome and to evaluate changes in the albumin–creatinine ratio before and after CPAP treatment.

Methods

The online supplement provides additional details on methods.

Patients

We examined data on consecutive patients who underwent diagnostic full overnight polysomnography (PSG) at the Sleep Unit of Kyoto University Hospital between January 2010 and December 2012. All had been referred to our sleep unit under suspicion of OSA, with symptoms such as daytime sleepiness or habitual snoring. Inclusion criteria were described as follows: age at least 40 years, and no prior diagnosis with or treatment for OSA.

Exclusion criteria were described as follows: sleep-disordered breathing from other than OSA, unknown smoking history, no spirometry data, no laboratory data, pregnancy or active menstruation, cardiovascular disease, kidney disease, systemic inflammatory disease (i.e., connective tissue diseases, sarcoidosis), macroalbuminuria (albumin–creatinine ratio, $\geq$300 mg/g), taking medications that may influence the albumin–creatinine ratio (i.e., steroids, nonsteroidal antiinflammatory drugs, lithium), and uncontrolled comorbidity (i.e., malignancy, active infection).

To avoid distorting this study's aim, patients with cardiovascular disease, which may affect results for microalbuminuria, were excluded. However, because many patients with OSA tended to have hypertension and the prevalence of hypertension increased according to the severity of OSA (22, 23), we included patients taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), which might influence urinary albumin excretion, according to previous reports (10, 15). For the same reason, we included patients taking statins.

The Kyoto University Graduate School and Faculty of Medicine Ethics Committee approved this study (R0113).

Polysomnography, Continuous Positive Airway Pressure Implementation, and Follow-Up

The diagnosis of OSA was confirmed by overnight PSG as previously described (24). We defined patients with an AHI equal to or greater than 5 as having OSA and classified patients with OSA as having mild OSA (AHI, $<$15), moderate OSA (AHI, 15–30), and severe OSA (AHI, $\geq$30). Patients with an AHI equal to or greater than 20 were candidates for nasal CPAP because under the health insurance system in Japan, CPAP is only permitted for patients with OSA with an AHI equal to or greater than 20. They were monitored after CPAP therapy for 3 months. We defined "good compliance" as the use of CPAP for more than 4 hours per night on more than 70% of nights and classified CPAP users into two groups: those with "good compliance" and "poor compliance" according to a previous report (25).

Spirometry and Definitions of Chronic Obstructive Pulmonary Disease and Overlap Syndrome

Spirometry was performed under standardized conditions. Airflow limitation was defined as an FEV_1/FVC ratio less than 70%. However, a bronchodilator could not be administered before the measurement because spirometry was planned for many patients in the hospital. Although we could not perform reversibility testing, participants with airflow limitation and a smoking history of at least 10 pack-years were clinically considered to have a diagnosis of COPD. Three patients with airflow limitation and a smoking history of 10 pack-years had a history of asthma and were therefore excluded from the COPD group.

The severity of airflow limitation was stratified by FEV_1 (percent predicted) in accordance with criteria specified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) ($\geq$80, stage I; 50–80, stage II; 30–50, stage III; $<$30, stage IV) (26). When patients had COPD and OSA, we defined them as having overlap syndrome. Those who did not meet the

criteria for COPD or OSA were defined as control participants.

Measurement of the Albumin–Creatinine Ratio and Definition of Microalbuminuria

We performed blood and urine tests the morning after PSG. The albumin–creatinine ratio was defined as (urine albumin [mg])/(urine creatinine [g]). Microalbuminuria was considered present when the albumin–creatinine ratio was between 20 and 299 mg/g in men and between 30 and 299 mg/g in women according to previous reports (15, 27).

Statistical Analysis

To evaluate the clinical features of OSA, COPD, and OSA–COPD overlap syndrome, we classified the participants into four groups: control, OSA, COPD, and overlap syndrome. All values are expressed as means ± standard deviation or as numbers (percent) unless stated otherwise. The overall significance of intergroup differences was determined by analysis of variance or the Kruskal–Wallis test, as appropriate, but the COPD group was excluded from this intergroup analysis because of the small number of patients (n = 4). Because distribution of the albumin–creatinine ratio levels was right-skewed, the outcome was transformed using the natural logarithm to achieve approximate normality.

Continuous variables were compared using an unpaired Student *t* test or Mann–Whitney *U* test, as appropriate. Categorical variables were compared using a χ^2 test or Fisher exact test, as appropriate. To sort out the more critical OSA groups, we classified patients with OSA as having mild OSA, moderate OSA, or severe OSA, and performed the analysis in the same manner as for the four study groups.

To test our hypothesis that overlap syndrome was highly associated with microalbuminuria, we performed multivariate logistic regression analysis. We set three models: unadjusted (model 1), adjusted for age and sex (model 2), and adjusted for other confounders including comorbidities, medications, and laboratory findings (model 2 + body mass index [BMI], smoking status, hypertension, diabetes, ACE inhibitor or ARB use, statin use, Pa_{O_2}, and glomerular filtration rate [GFR]) (model 3).

To compare clinical variables before and after CPAP therapy, a paired *t* test, Wilcoxon signed rank test, or a χ^2 test was used, as appropriate. A two-tailed *P* value less than 0.05 was deemed statistically significant. All statistical analyses were performed with JMP 11.2.0 software (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics of Study Patients

During the study period, 740 patients underwent PSG, and finally, data on 344 patients were analyzed (Figure 1). Sixty-four patients were control participants, 248 had OSA only (mild, 78; moderate, 92; severe, 78), 4 had COPD only, and 28 had overlap syndrome. Table 1 shows the baseline characteristics of the 344 patients. BMI was significantly higher in the OSA group, whereas FEV_1 (percent predicted) was significantly lower in the overlap syndrome group. The severity of COPD and overlap syndrome was 3/0/1/0 and 20/7/1/0 (GOLD stage I/II/III/IV, respectively; $P = 0.17$). There was no significant difference in GFR among the groups.

Microalbuminuria in Overlap Syndrome

The logarithm of the albumin–creatinine ratio and the prevalence of microalbuminuria in control, OSA, and OSA–COPD overlap syndrome participants are shown in Table 1 and Figure 2A. The prevalence of microalbuminuria significantly increased in the order of the control, OSA, and overlap syndrome groups (3.1, 12.9, and 32.1%, respectively;

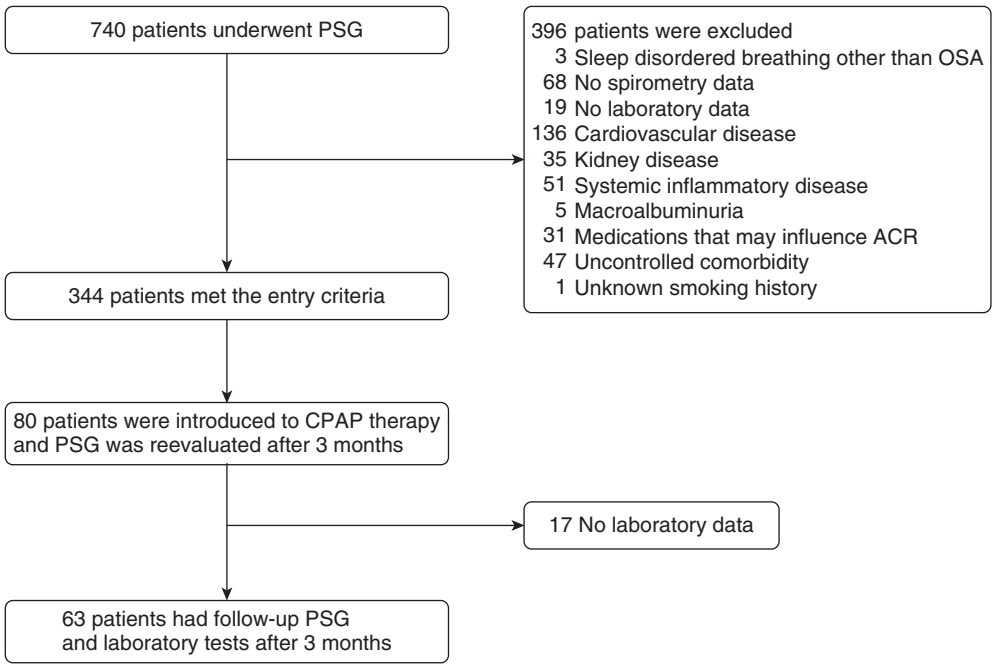

Figure 1. Flowchart of patient participation. ACR = albumin–creatinine ratio; CPAP = continuous positive airway pressure; PSG = polysomnography; OSA = obstructive sleep apnea.

$P = 0.0006$), and there was a significant intergroup difference between each group.

When the severity of OSA was divided according to the AHI and the prevalence of microalbuminuria was evaluated among control, mild OSA, moderate OSA, severe OSA, and overlap syndrome groups, the prevalence of microalbuminuria also significantly increased in order of the control, mild OSA, moderate OSA, severe OSA, and overlap syndrome groups (3.1, 5.1, 12.0, 21.8, and 32.1%, respectively; $P < 0.0001$) (Figure 2B). However, a significant intergroup difference was seen between the overlap syndrome group and only the control and mild OSA groups. On *post hoc* analysis, AHI was significantly higher in the severe OSA group than in the overlap syndrome group (49.3 ± 15.5 vs. 27.2 ± 17.1, respectively; $P < 0.0001$). The logarithm of the albumin–creatinine ratio was significantly positively correlated with AHI ($\rho = 0.16$; $P = 0.0030$).

Multivariate logistic regression analysis of microalbuminuria is shown in Table 2. After adjusting for age and sex, patients with overlap syndrome were independently at risk of microalbuminuria compared with patients with OSA (odds ratio, 2.61; 95% confidence interval, 1.02–6.38; $P = 0.047$) (model 2). Even after adjusting for other confounding factors, overlap syndrome presented an independent risk of microalbuminuria compared with control subjects (odds ratio, 6.34; 95% confidence interval, 1.23–49.39; $P = 0.027$); however, compared with OSA, there was a tendency toward an independent risk of microalbuminuria in the overlap syndrome group, but a significant difference was not found (odds ratio, 2.54; 95% confidence interval, 0.93–6.72; $P = 0.070$) (model 3).

In this model, increased BMI and the presence of diabetes were also independent risk factors (odds ratio, 1.53; 95% confidence interval, 1.03–2.27; $P = 0.037$, per 5-unit increase, and odds ratio, 2.33; 95% confidence interval, 1.07–4.99; $P = 0.034$, respectively). The use of ACE inhibitors, ARBs, or statins was not associated with the presence of microalbuminuria.

Microalbuminuria in Patients with Continuous Positive Airway Pressure Treatment at the 3-Month Follow-Up

Of the study patients, 63 underwent PSG and laboratory tests after 3 months of CPAP therapy (Figure 1). Of these patients, 59 had OSA and 4 had overlap syndrome, and 36 were in the good compliance group and 27 were in the poor compliance group. Table 3 shows changes in the logarithm of the albumin–creatinine ratio and the

Table 1. Baseline characteristics of study patients (n = 344)

	Control (*n = 64*)	OSA (*n = 248*)	COPD (*n = 4*)	Overlap (*n = 28*)	*P* Value*
Clinical background					
Age,† yr	58.9 ± 11.1	60.8 ± 11.0	71.5 ± 4.7	65.1 ± 11.5	0.051
Sex (men)	21 (33%)	171 (69%)	4 (100%)	28 (100%)	<0.0001
BMI,† kg/m^2	23.7 ± 4.2	26.1 ± 5.0‡	25.3 ± 1.5	25.7 ± 4.1	0.0025
Current smoker	6 (9%)	27 (11%)	0 (0%)	5 (18%)	0.48
Hypertension	26 (41%)	147 (59%)	2 (50%)	24 (86%)	0.0002
Diabetes	10 (16%)	52 (21%)	0 (0%)	9 (32%)	0.20
ACE inhibitor or ARB use§	9 (14%)	77 (31%)	1 (25%)	12 (43%)	0.0062
Statin use‖	9 (14%)	48 (19%)	0 (0%)	8 (29%)	0.26
Sleep parameters					
AHI, events/h	2.3 ± 1.4	26.6 ± 18.6‡	3.3 ± 1.9	27.2 ± 17.1‡	<0.0001
CT_{90}, %	0.4 ± 1.7	14.5 ± 21.4‡	0.3 ± 0.3	16.0 ± 21.5‡	<0.0001
Minimum Sp_{O_2}, %	88.9 ± 4.2	78.5 ± 8.6‡	88.8 ± 4.3	77.6 ± 10.6‡	<0.0001
4% ODI, events/h	1.8 ± 1.4	25.2 ± 19.0‡	2.6 ± 2.1	26.0 ± 20.7‡	<0.0001
Spirometry					
FVC,† % predicted	110.4 ± 14.3	108.6 ± 17.6	104.8 ± 21.8	111.0 ± 20.7	0.64
FEV_1,† % predicted	106.9 ± 16.1	104.4 ± 18.5	90.0 ± 32.7	86.0 ± 19.9‡¶	<0.0001
FEV_1/FVC,† %	78.8 ± 6.8	77.9 ± 6.4	61.3 ± 11.2	62.7 ± 8.5‡¶	<0.0001
D_{LCO},† % predicted	81.6 ± 14.6	84.0 ± 15.7	69.3 ± 13.2	82.0 ± 24.0	0.52
Arterial blood gas**					
Pa_{O_2},† mm Hg	85.7 ± 11.2	81.4 ± 10.1‡	80.3 ± 9.2	78.9 ± 9.5‡	0.0030
Pa_{CO_2},† mm Hg	40.0 ± 3.7	40.9 ± 3.5	39.5 ± 4.5	40.2 ± 3.3	0.14
Blood tests					
GFR,† ml/min	75.4 ± 16.9	74.7 ± 15.6	66.1 ± 3.9	75.8 ± 16.2	0.91
Logarithm ACR,† mg/g	1.72 ± 0.68	1.91 ± 0.95	1.57 ± 0.76	2.25 ± 1.17‡	0.046

Definition of abbreviations: ACE = angiotensin-converting enzyme; ACR = albumin–creatinine ratio; AHI = apnea–hypopnea index; ARB = angiotensin II receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CT_{90} = cumulative percentage of sleep time with $Sp_{O_2} < 90\%$; D_{LCO} = diffusing capacity of the lung for carbon monoxide; GFR = glomerular filtration rate; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

Data are expressed as means ± SD or as numbers (%).

*COPD group was excluded from this intergroup analysis because of the small number of patients. When a significant difference was found among three groups, *post hoc* analysis was performed to identify where the difference was significant.

†Analysis of variance was used, and the other continuous variables were calculated by Kruskal–Wallis test.

‡$P < 0.05$ versus control.

§Data on ACE inhibitor or ARB use were collected for 342 patients (control/OSA/COPD/overlap syndrome, 64/246/4/28).

‖Data on statin use were collected for 343 patients (control/OSA/COPD/overlap syndrome, 64/247/4/28).

¶$P < 0.05$ versus OSA.

**Pa_{O_2} and Pa_{CO_2} were measured in 340 patients (control/OSA/COPD/overlap syndrome, 64/244/4/28).

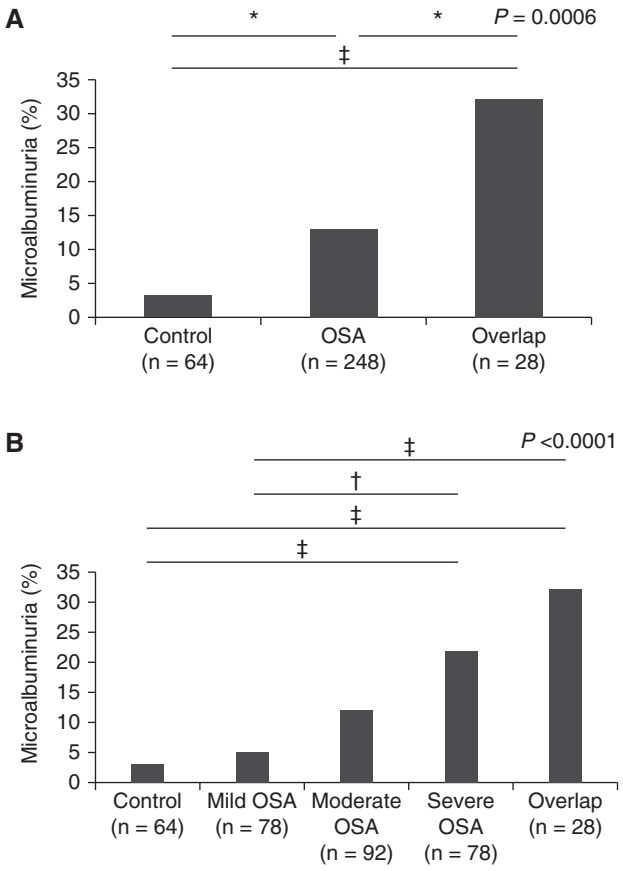

Figure 2. (*A*) Comparison of the prevalence of microalbuminuria among participants in the control, OSA, and overlap syndrome groups. (*B*) Comparison of the prevalence of microalbuminuria among participants in the control, mild OSA, moderate OSA, severe OSA, and overlap syndrome groups. Data represent unadjusted percentages. The Bonferroni method was used to identify where the difference was significant. In *A*, $P < 0.016$ was deemed statistically significant. In *B*, $P < 0.005$ was deemed statistically significant. OSA = obstructive sleep apnea. $^{*}P < 0.01$; $^{\dagger}P < 0.005$; $^{\ddagger}P < 0.001$.

prevalence of microalbuminuria from baseline to the 3-month follow-up according to compliance with CPAP. In the good compliance group the logarithm of the albumin–creatinine ratio was significantly decreased after CPAP therapy but did not differ after CPAP therapy in the poor compliance group. The four patients with overlap syndrome all belonged to the poor compliance group, and the logarithm of the albumin–creatinine ratio decreased after CPAP treatment but not significantly (from 2.13 ± 0.85 to 1.74 ± 1.01; $P = 0.15$).

Discussion

To the best of our knowledge, this is the first study showing that OSA–COPD overlap syndrome was more prevalent than OSA alone in those with microalbuminuria. After adjusting for age and sex, overlap syndrome was an independent risk factor for microalbuminuria compared with OSA ($P = 0.047$), but after adjusting for other confounding factors the significance disappeared although the tendency remained ($P = 0.070$), and a higher BMI and the presence of diabetes were significantly related to microalbuminuria. In the good compliance group, the logarithm of the albumin–creatinine ratio was significantly decreased after CPAP therapy but did not differ in the poor compliance group.

OSA and COPD, respectively, were shown to be related to an increase in microalbuminuria (10, 15), but microalbuminuria in the OSA–COPD overlap syndrome has not been investigated to date. Previously microalbuminuria was investigated from the viewpoint of glomerular and tubular albumin kinetics in the diabetic rat model (28). Also, coincident intermittent hypoxia and emphysema were reported to be related to systematic and endothelial inflammation in a rat model (29). This might strengthen our findings about the association between overlap syndrome and microalbuminuria.

In this study, the severity of OSA was significantly associated with the albumin–creatinine ratio, which was compatible with a previous report (10). Urinary albumin secretion in OSA may result from the influence of sleep-related pathophysiologic changes (intermittent hypoxemia, increased sympathetic nerve traffic, and metabolic dysregulation) in glomerular endothelial function (10, 12, 30). Also, the impact of renal hemodynamics and intrarenal hypoxia was considered important in the pathogenesis of proteinuria.

Zalucky and colleagues reported that the severity of nocturnal hypoxemia was associated with renal renin–angiotensin system activation (31), and Nicholl and colleagues reported that CPAP therapy was associated with improved renal hemodynamics and down-regulation of renal renin–angiotensin system activity (32). Although there have been several reports on the adjusted albumin–creatinine ratio in OSA (10–12), data on the prevalence of microalbuminuria and results after adjusting for other confounders have been lacking.

In this study, the prevalence of microalbuminuria in OSA–COPD overlap syndrome was higher than in OSA. In addition, the prevalence of microalbuminuria was higher, although not significantly so, in those with overlap syndrome compared with those with severe OSA. Among participants without a history of cardiovascular disease, this result itself might suggest that overlap syndrome with a higher prevalence of microalbuminuria was more related to the cardiovascular disease mortality. Also, the relation to microalbuminuria in OSA alone was not independent after adjusting for other confounders, whereas the presence of overlap syndrome was an independent determinant factor for microalbuminuria, which indicates a high impact of overlap syndrome in relation to microalbuminuria.

At present, low-grade microalbuminuria (even within normal limits) is considered a marker for subclinical vascular damage and is likely to emerge later in the atherosclerotic process (4, 33). Poor endothelial function might cause higher prevalence of

Table 2. Multivariate logistic regression analysis of microalbuminuria in the study patients (n = 340)

	Model 1: Unadjusted		Model 2: Adjusted for Age and Sex		Model 3: Adjusted for Age, Sex, and Other Confounders (BMI, Smoking Status, Hypertension, Diabetes, ACE Inhibitor or ARB Use, Statin Use, Pa_{O_2}, and GFR)*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Group 1†						
Control	1.0		1.0		1.0	
OSA	4.59 (1.34–28.82)	0.012	3.68 (1.03–23.54)	0.044	2.49 (0.65–16.41)	0.20
Overlap syndrome	14.68 (3.43–101.98)	0.0001	9.61 (2.04–70.84)	0.0033	6.34 (1.23–49.39)	0.027
Group 2‡						
OSA	1.0		1.0		1.0	
Overlap syndrome	3.20 (1.28–7.53)	0.014	2.61 (1.02–6.38)	0.047	2.54 (0.93–6.72)	0.070
Age (yr), per 10-unit increase			1.62 (0.41–6.57)	0.49	1.12 (0.77–1.63)	0.55
Sex (men)			1.81 (0.80–4.50)	0.16	2.06 (0.80–5.92)	0.14
BMI (kg/m^2), per 5-unit increase					1.53 (1.03–2.27)	0.037
Current smoker					0.77 (0.21–2.30)	0.66
Hypertension					1.60 (0.63–4.18)	0.32
Diabetes					2.33 (1.07–4.99)	0.034
ACE inhibitor or ARB use					1.16 (0.50–2.74)	0.73
Statin use					0.38 (0.12–1.03)	0.059
Pa_{O_2} (mm Hg), per 10-unit increase					0.79 (0.53–1.14)	0.21
GFR (ml/min), per 10-unit increase					0.97 (0.77–1.22)	0.79

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; CI = confidence interval; GFR = glomerular filtration rate; OR = odds ratio; OSA = obstructive sleep apnea.
*Model 3 analyzed 333 patients (data on 2 patients for ACE inhibitor or ARB use, 1 for statin use, and 4 for Pa_{O_2} were lacking).
†Results for group 1 show the odds ratio for microalbuminuria when the control was defined as the reference.
‡Results for group 2 show the odds ratio for microalbuminuria when OSA was defined as the reference.

microalbuminuria, which is possibly associated with the higher mortality in overlap syndrome. A further study to elucidate the clear association between the high prevalence of microalbuminuria and poor mortality in overlap syndrome should be performed.

We found that adding COPD to OSA resulted in a tendency toward an association with microalbuminuria. However, the association did not reach a significant value in the fully adjusted model, although the prevalence of microalbuminuria itself in overlap syndrome was higher than in OSA.

In this study, COPD in patients with overlap syndrome was not severe. However, previous studies of COPD did not show a relationship between microalbuminuria and the severity of COPD (FEV_1 percent predicted), which might indicate that airflow obstruction only was not an important factor in microalbuminuria and furthermore was not an important factor in the endothelial dysfunction in COPD (15, 16, 34). It is said that the hypoxia in COPD is derived from the ventilation–perfusion mismatch, and microvascular damage caused by hypoxia in COPD was reported to be associated with kidney damage (35). Also, a hypoxemic state during the day might be related to more profound hypoxemia at night (36), and low daytime Pa_{O_2} was reported to be an independent risk factor for the presence of microalbuminuria (15, 16).

Because the inflammatory effects of cigarette smoking are well known (37), hypoxemia during both night and day in addition to cigarette smoking might cause an abnormal inflammatory response and endothelial dysfunction, which might result in worse microalbuminuria (38). However, the participants in this study were not very hypoxemic during the day, which might attenuate the impact of additive COPD. In the fully adjusted model, increased BMI and the presence of diabetes were risk factors for the presence of microalbuminuria independent of the presence of overlap syndrome. Therefore, in terms of microalbuminuria, we must be aware of conventional risk factors such as increased BMI (39) or diabetes (40) and lack of adequate control of these conditions (41–43) even when the patients had overlap syndrome.

In this study, the albumin–creatinine ratio decreased after CPAP treatment in the patients with OSA with good compliance. This result was compatible with previous studies (11, 12). However, there has been no randomized controlled trial of changes in the albumin–creatinine ratio during CPAP therapy, and even more important, changes according to the compliance have not been evaluated to date. The albumin–creatinine ratio decreased after CPAP treatment in the patients with OSA but did not significantly differ in the overlap syndrome group, probably because of the small number of participants with overlap syndrome or poor compliance. CPAP therapy is the gold standard for treatment of OSA and improves the prognosis for severe OSA (9, 44); it is also known to improve the prognosis for overlap syndrome (18, 45).

In this study, in the good compliance group, the logarithm of the albumin–creatinine ratio was significantly decreased after CPAP therapy, whereas in the poor compliance group it did not differ significantly, which might suggest the merits of good compliance with CPAP in terms of microalbuminuria. A decrease in microalbuminuria might be partly related to the mechanism of improvement in prognosis among CPAP users with overlap syndrome (18).

Table 3. Changes in clinical variables from baseline to after continuous positive airway treatment according to compliance

	Good Compliance (*n* = 36)			Poor Compliance (*n* = 27)		
	Before CPAP	After CPAP	*P* Value	Before CPAP	After CPAP	*P* Value
Clinical background						
Age, yr	60.5 ± 10.5	—	—	54.4 ± 10.8	—	—
Sex (men)	32 (89%)	—	—	21 (78%)	—	—
BMI,* kg/m^2	25.7 ± 5.0	26.0 ± 5.0	0.24	28.7 ± 6.7	28.8 ± 6.4	0.86
Sleep parameters						
AHI, events/h	35.2 ± 23.7	1.8 ± 2.2	<0.0001	36.1 ± 23.7	1.7 ± 1.1	<0.0001
CT_{90}, %	19.6 ± 25.8	0.2 ± 0.5	<0.0001	23.0 ± 27.8	0.5 ± 0.7	<0.0001
Minimum Sp_{O_2}, %	76.3 ± 12.1	91.5 ± 2.5	<0.0001	76.9 ± 8.2	90.8 ± 3.4	<0.0001
4% ODI, events/h	33.1 ± 23.5	1.0 ± 1.4	<0.0001	35.9 ± 25.6	1.1 ± 0.9	<0.0001
Laboratory tests						
Logarithm ACR,* mg/g	1.93 ± 0.90	1.68 ± 0.85	0.043	1.72 ± 0.80	1.65 ± 0.84	0.48
Microalbuminuria†	6 (16.7%)	1 (2.8%)	0.053	2 (7.4%)	1 (3.7%)	0.50

Definition of abbreviations: ACR = albumin–creatinine ratio; AHI = apnea–hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; CT_{90} = cumulative percentage of sleep time with $Sp_{O_2} < 90\%$; GFR = glomerular filtration rate; ODI = oxygen desaturation index; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.
Data are expressed as means ± SD or as numbers (%).
*A paired *t* test was used, and the other continuous variables were calculated by Wilcoxon signed rank test.
†Fisher exact test was used.

Limitations

We recognize several limitations in this study. First, spirometry was conducted without the use of a bronchodilator, which might result in the inclusion of patients who had reversible airflow limitations, such as bronchial asthma. In this study, to exclude diseases other than COPD as much as possible, we defined COPD according to a combination of smoking status and airflow limitation without a history of bronchial asthma. Second, the number of patients with COPD without OSA was small because this study was conducted in a sleep laboratory and patients potentially with COPD, such as patients with cardiovascular disease, were largely excluded, which could have caused selection bias. In addition, the differences between COPD and overlap syndrome were difficult to evaluate from this study. We compared the differences among control subjects, participants with OSA, and participants with overlap syndrome and found some differences between the characteristics of overlap syndrome and those of OSA; however, the number of participants with overlap syndrome was also small, which might attenuate the power of this study.

Third, data were only from Asian participants. Although there have been few reports about Asian patients with overlap syndrome (46–48), data from a large patient population in other ethnic groups should be investigated because the investigation of overlap syndrome is currently intense due to the clinical importance of its mechanisms and impact. Fourth, the number of participants monitored after CPAP treatment was small, and we had no control group for CPAP treatment. However, it would be difficult to establish such a control group for ethical reasons under the Japanese health insurance system. Therefore, we evaluated changes according to the degree of compliance, which might suggest the merits of good compliance with CPAP treatment.

Conclusions

In this single-center study, OSA–COPD overlap syndrome was more prevalent in individuals with microalbuminuria than OSA alone, but after adjusting for other confounding factors, overlap syndrome was not an independent risk factor for microalbuminuria compared with OSA. Increased BMI and the presence of diabetes were independent risk factors for microalbuminuria, suggesting that the differences between overlap syndrome and OSA regarding microalbuminuria might be mediated by conventional risk factors rather than the addition of COPD itself. The higher prevalence of microalbuminuria might be one of the factors that cause higher mortality in patients with overlap syndrome.

Further study including a larger number of participants with overlap syndrome is warranted to seek an association between the high prevalence of microalbuminuria and the poor mortality in overlap syndrome and to clarify the mechanism of the high mortality in OSA–COPD overlap syndrome. ■

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