

General Medicine 推薦論文

Interleukin-18 and chronic kidney disease in patients with obstructive sleep apnea syndrome

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ABSTRACT

Background: Obstructive sleep apnea syndrome (OSAS) and chronic kidney disease (CKD) are common diseases encountered in primary care. These diseases share the same pathophysiology of chronic inflammation. In recent years, it was reported that the inflammasome participates in chronic inflammation, and interleukin (IL)-18 has received significant attention as an inflammasome marker. IL-18 is also closely associated with renal function, and is a stronger predictive marker of renal function disorder than high-sensitivity C-reactive protein (hsCRP) or IL-6. OSAS is also reported to be an independent risk factor of CKD. However, other basal diseases associated with OSAS and severe renal function disorders may also be CKD risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia. So it should be carefully interpreted. Therefore, we investigated renal function in OSAS patients with no potentially confounding disorders using IL-18.

Methods: We assessed OSAS severity (apnea–hypopnea index [AHI]); renal function (estimated glomerular filtration rate); and hsCRP, IL-6, and IL-18 levels in 23 patients newly diagnosed with OSAS and free from other diseases

Results: Serum levels of IL-18 demonstrated a significant negative correlated with eGFR ($P < 0.05$).

Conclusions: Even when renal dysfunction is mild, chronic inflammation is present in OSAS patients. We hypothesize that IL-18 is a useful marker to detect chronic inflammation in OSAS patients and that this chronic inflammation contributes to CKD.

These results suggest that IL-18 is an associative marker for OSAS and renal function disorder, and can help achieve early treatment intervention in primary care.

Key Words: Chronic inflammation, chronic kidney disease, obstructive sleep apnea syndrome, interleukin-18, interleukin-6, high-sensitivity C-reactive protein

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) and chronic kidney disease (CKD) are common diseases encountered in primary care. Chronic inflammation, caused by oxidative stress and endothelial cell dysfunction, represents a common pathophysiology
5 between OSAS and CKD. Chronic inflammation has already been recognized as an important factor in cardio-renal association, whereby even a slight disorder in renal function can be a risk factor for cardiovascular disease (CVD). Chronic inflammation is closely involved in arteriosclerosis and can be identified by high-sensitivity C-reactive protein (hsCRP), which is produced by interleukin-6 (IL-6) acting on the liver. Elevated
10 hsCRP and IL-6 are predictive markers of cardiovascular events¹⁻³. In recent years, interleukin-18 (IL-18) has also been proposed as such a marker. IL-18 has a closer association with renal function, and is also a better predictive marker of renal function disorder than hsCRP or IL-6 without influence of the creatinine clearance^{4,5}.

In addition, IL-18 is closely associated with chronic inflammation. In recent studies, it
15 was reported that the inflammasome participates in chronic inflammation. Inflammasomes are large intracellular multiprotein complexes that play a central role in chronic inflammation and form in response to bacteria and stress signals. Activated inflammasomes promote the secretion of interleukin-1 β (IL-1 β) and IL-18, and these

cytokines are involved in host defense against pathogen infections⁶⁻⁸. In recent years, these cytokines have been established to play an important role in lifestyle-related diseases, such as CKD and arteriosclerotic diseases. There are many reports indicating the association between such diseases and cytokines that are derived from
5 inflammasomes^{9, 10}. IL-18 is derived directly from inflammasomes, while hsCRP and IL-6 are downstream targets of IL-1 β . Thus, IL-18 is more useful for the evaluation of chronic inflammation and renal function disorder.

On the other hand, recent studies reported increased CKD in OSAS patients^{11, 12}. The findings of these studies should be carefully interpreted, since basal diseases that are
10 easily complicated with OSAS and severe renal function disorders can be independent risk factors of CKD, including hypertension, diabetes mellitus, and hyperlipidemia.

OSAS is not only a disease to cause simple sleepiness, but also causes arteriosclerotic disease and coronary artery diseases¹³. In primary care, it has big significance to clear the association OSAS and CKD, and the cytokine senses them. This study was
15 conducted to assess the association OSAS and renal function disorders in OSAS patient using IL-18, hsCRP and IL-6.

METHODS

Patients

Fifty-three men and thirteen women with newly diagnosed OSAS (age 20-75 years) in 2001 to 2009 were enrolled in this study (Table 1). Their baseline characteristics were recorded, and they underwent polysomnography. Forty-three participants had other
5 diseases including hypertension, diabetes mellitus, and hyperlipidemia. Sixteen men and seven women with newly diagnosed OSAS (age 24-72 years) in 2001 to 2009 were extracted from all patients (Table 2). Their baseline characteristics were recorded, and they underwent polysomnography. All participants were free from other diseases including hypertension, diabetes mellitus, and hyperlipidemia and were taking no
10 medications. This study was approved by the Ethics Committee of Nagasaki University Hospital, and all participants provided informed consent.

Polysomnography

Full polysomnographic monitoring was performed with the EMBLA S7000 system
15 (Chest Co., Ltd., Fukuoka, Japan). An AHI score greater than 5/hour in conjunction with sleep-related symptoms was considered diagnostic of OSAS. $AHI \geq 5$ and < 20 indicated mild OSAS, $AHI \geq 20$ and < 30 indicated moderate OSAS, and $AHI \geq 30$ indicated severe OSAS.

Data Collection

We obtained blood samples early in the morning after an overnight fast subsequent to a day of full polysomnographic monitoring. Samples of peripheral venous blood were collected and stored at -40°C until the time of assay. Serum creatinine was measured by enzymatic method, and serum IL-6 was measured by chemiluminescent enzyme immuno assay (CLEIA) and IL-18 was measured by enzyme-linked immunosorbent assay (ELISA). Nephelometric immunoassay was used to measure serum hsCRP.

Estimated glomerular filtration rate (eGFR) was calculated by the following formula¹⁴:

$$\text{eGFR} = 194 \times \text{standardized Scr}^{-1.094} \times \text{Age}^{-0.287} (\times 0.739[\text{if female}]). \text{eGFR} \geq 90$$

indicated CKD stage G1, $\text{eGFR} \geq 60$ and < 89 indicated CKD stage G2, $\text{eGFR} \geq 30$ and < 59 indicated CKD stage G3, $\text{eGFR} \geq 15$ and < 29 indicated CKD stage G4, and $\text{eGFR} < 14$ indicated CKD stage G5. Serum creatinine was measured by standard procedures.

In this study, all patients corresponded to CKD stage G1 and G2.

15 Statistical analysis

Data are expressed as mean \pm SD, and P values < 0.05 were considered significant. The significance of differences between groups was analyzed by t test and one-way ANOVA. Associations between cytokines and eGFR or AHI were analyzed by Spearman's rank

correlation coefficient. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0)¹⁵.

5 RESULTS

Patients with complications

All patients' background characteristics are summarized in Table 1. All patients were CKD stage G1–G3. At CKD stage G1, there were eleven men and one woman. Hypertension accounted for 18.2% of their complications, diabetes mellitus for 45.5%, and hyperlipidemia for 18.2%. At CKD stage G2, there were 36 men and 11 women. Hypertension accounted accounts for 48.9% of their complications, diabetes mellitus for 19.1%, and hyperlipidemia for 14.9%. At CKD stage G3, there were seven men and one woman. Hypertension accounted for 87.5% of their complications, and diabetes mellitus for 37.5%. All patients had mild to severe OSAS. Fourteen men and six women had mild OSAS. Hypertension accounted for 35% of their complications, diabetes mellitus for 10%, and hyperlipidemia for 10%. Fifteen men and three women had moderate OSAS. Hypertension accounted for 55.6% of their complications, diabetes mellitus for 1%, and hyperlipidemia for 22.2%. Twenty-four men and four women had severe OSAS.

Hypertension accounted for 53.6% of their complications, diabetes mellitus for 21.4%, and hyperlipidemia for 39.3%.

When we examined each cytokine according to stage of CKD or severity of OSAS, we did not observe any significant differences across groups.

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Patients free from other diseases

The background characteristics of patients free from other diseases are summarized in Table 2. These patients had only CKD stage G1–G2. Four men and one woman had CKD stage G1, and 12 men and six women had CKD stage G2. The patients' OSAS symptoms ranged from mild to severe. Seven men and five women had mild OSAS, five men and one woman had moderate OSAS, and four men and one woman had severe OSAS. They had no other complications.

We examined each cytokine according to stage of CKD and severity of OSAS. Serum IL-18 levels in patients with CKD stage G1 were significantly lower than those in patients with CKD stage G2 ($P < 0.05$). There was no significant difference in hsCRP or IL-6. We examined the correlation between each cytokine and eGFR or AHI (Table 3, Fig. 1). The only significant relationship observed was a negative correlation between IL-18 and eGFR.

Patients per complications

We compared patients according to whether or not they had complications (Table 4).

Levels of AHI in patients free from other diseases were significantly lower than those in
5 patients with complications. No significant difference was observed in eGFR or
cytokines.

DISCUSSION

While complications such as basal diseases and renal function disorders were not
10 controlled in patients of this study, there was no significant association between
cytokines, including IL-18, and eGFR or AHI. These patients had basal diseases
including diabetes mellitus. Especially among patients with CKD stage G1, 45.2%
patients had diabetes mellitus, and some patients' eGFR levels indicated hyperfiltration.
Thus, it was not suitable to evaluate the association between eGFR and IL-18.
15 Furthermore, these basal diseases that are often found in combination with OSAS can
also be independent risk factors of CKD. In addition, there were CKD stage G3 patients
in this group. Severe renal function disorders can also be independent risk factors of
OSAS¹⁶. Therefore, these patients could not be included while ascertaining the

association of OSAS with renal function disorders. Thus, we considered that these patients were not suitable for evaluating the association between OSAS and renal function.

Therefore, we considered that the association between OSAS and renal function might be apparent in patients when complications and severe renal function disorders are controlled for. IL-18 might be more suitable to examine the association between OSAS and renal function disorders in OSAS patients than previously used cytokines, such as hsCRP and IL-6. Serum levels of IL-18 are elevated nonspecifically in many pathophysiological conditions and should be interpreted with caution in the presence of complications such as lifestyle-related diseases and cardiovascular diseases. We considered this to be another reason why controlling basal diseases was important.

Therefore, we examined patients free from other diseases, among whom we observed a significant correlation between eGFR and IL-18. We observed chronic inflammation in OSAS patients who were free from other diseases and with mild renal function disorders. It should be noted that IL-18 demonstrated a closer association with eGFR than hsCRP or IL-6. Our results suggest that chronic inflammation is already elicited even in mild renal dysfunction that cannot be detected by hsCRP and IL-6, and that IL-18 is useful to sense chronic inflammation. We hypothesize that chronic

inflammation from OSAS leads to CKD in the future. These results further indicate that IL-18 is an associative marker for OSAS and renal function disorder, and may be useful in achieving early treatment intervention in primary care. However, further research is necessary to elucidate the mechanism underlying the connection between OSAS and

5 CKD onset.

In this study, we did not demonstrate an association between IL-18 and AHI. IL-18 is expected to associate with AHI or eGFR, since OSAS and CKD share the same pathophysiology of chronic inflammation. Ideally, the severity of OSAS should be determined based not only on AHI score but also on levels of desaturation and clinical

10 manifestations. Carpagnano et al. showed that levels of desaturation cause oxidative stress and inflammation¹⁷. Thus, more research including parameters of desaturation is needed.

In addition, we found no significant differences among cytokines, renal functions, and AHI according to the presence or absence of underlying disease. The 43 patients

15 with complications would be expected to demonstrate higher serum levels of cytokines and lower levels of eGFR. As mentioned previously, some patients' eGFR levels indicated hyperfiltration, making them unsuitable for evaluation.

CONCLUSIONS

Even when renal dysfunction was mild, chronic inflammation was present in OSAS patients. We hypothesize that IL-18 is a useful marker to detect chronic inflammation in OSAS patients and that this chronic inflammation is a factor leading to CKD. These
5 results suggest that IL-18 is an associative marker for OSAS and renal function disorder, and may help to achieve early treatment intervention in primary care.

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CONFLICTS OF INTEREST

The authors have no conflict of interest with regard to this study.

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FIGURE LEGENDS

Figure 1. Correlation between IL-18 and eGFR

Fig.1 :Correlation between IL-18 and eGFR

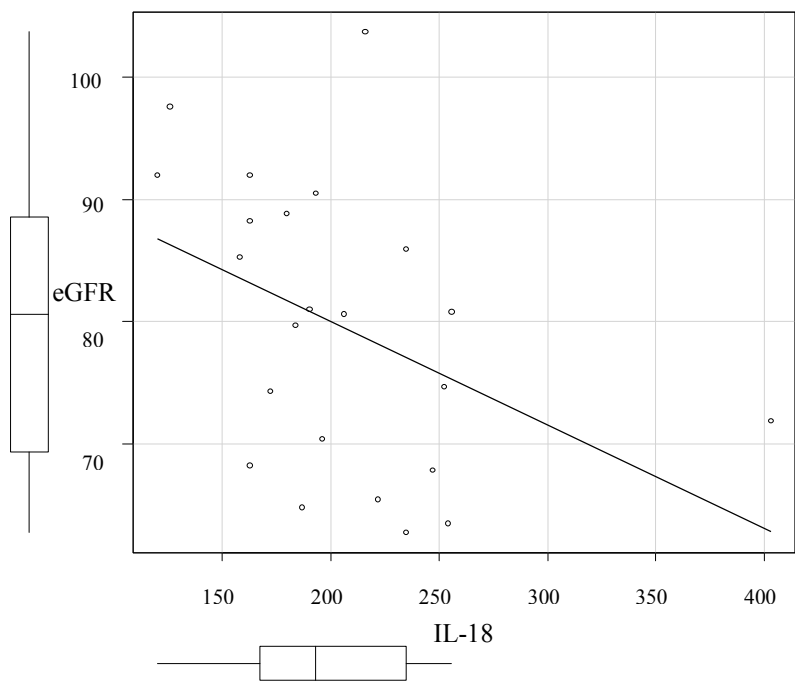


Table 1: Characteristics and biochemical markers of the all patients

	Sex, m/f	Age, y	BMI	AHI, events/h	eGFR, ml/min/1.73 m ²	hsCRP, ng/ml	IL-6, pg/ml	IL-18, pg/ml	Complications, n (%)		
									HT	DM	HL
eGFR \geq 90 (Stage 1 CKD)	10/1	36.1 \pm 9.2 *	30.9 \pm 4.7*	41.4 \pm 31.7	-	2093.5 \pm 2763.1	2.8 \pm 1.6	210.5 \pm 66.1	2 (18.2)	5 (45.5)	2 (18.2)
60 < eGFR < 89 (Stage 2 CKD)	36/11	54.3 \pm 11.7*	27.4 \pm 5.1*	29.3 \pm 19.8	-	1622.0 \pm 2882.8	3.1 \pm 2.2	213.1 \pm 80.0	23 (48.9)	9 (19.1)	7 (14.9)
30 < eGFR < 59 (Stage 3 CKD)	7/1	62.1 \pm 8.9 *	25.2 \pm 3.0*	24.1 \pm 20.0	-	3794.5 \pm 7994.7	3.3 \pm 1.6	220.6 \pm 65.0	7 (87.5)	3 (37.5)	0 (0)
Mild OSAS	14/6	52.2 \pm 13.7	26.1 \pm 3.8*	-	76.0 \pm 13.9	1592.3 \pm 2644.4	2.4 \pm 1.2	209.2 \pm 70.1	7 (35.0)	2 (10.0)	2 (10.0)
Moderate OSAS	15/3	56.7 \pm 12.0	25.8 \pm 3.8*	-	68.7 \pm 18.1	2672.6 \pm 6088.6	3.0 \pm 1.8	187.1 \pm 58.4	10 (55.6)	1 (5.6)	4 (22.2)
Severe OSAS	24/4	49.4 \pm 13.5	30.2 \pm 5.6*	-	82.0 \pm 19.8	1779.0 \pm 2436.3	3.6 \pm 2.5	223.7 \pm 84.5	15 (53.6)	6 (21.4)	11 (39.3)

eGFR = estimated glomerular filtration rate; AHI = apnea-hypoxia index; hsCRP = highly sensitive C-reactive protein; IL-6 = interleukin-6; IL-18 = interleukin-18; OSAS = obstructive sleep apnea syndrome; CKD = chronic kidney disease; HT = hypertension; DM = diabetes mellitus; HC = hyperlipidemia

Values are mean \pm SD

*P < 0.05 is considered statistically significant

Table 2: Characteristics and biochemical markers of the patients free from other diseases

	Sex, m/f	Age, y	BMI	AHI, events/h	eGFR, ml/min/1.73 m ²	hsCRP, ng/ml	IL-6, pg/ml	IL-18, pg/ml	Complications		
									HT	DM	HL
eGFR \geq 90 (Stage 1 CKD)	4/1	32.4 \pm 9.8 *	28.8 \pm 4.3 *	19.8 \pm 10.4	-	677.8 \pm 627.7	1.8 \pm 0.7	163.6 \pm 41.6*	-	-	-
60 < eGFR < 89 (Stage 2 CKD)	12/6	52.9 \pm 10.0*	25.0 \pm 3.3 *	22.3 \pm 21.3	-	1727.9 \pm 3066.7	3.0 \pm 2.2	216.8 \pm 57.5 *	-	-	-
Mild OSAS	7/5	50.8 \pm 15.2	25.5 \pm 3.7	-	78.9 \pm 12.5	1815.6 \pm 3402.8	2.6 \pm 1.2	217.7 \pm 70.6	-	-	-
Moderate OSAS	5/1	46.7 \pm 12.3	25.4 \pm 3.2	-	79.1 \pm 13.5	553.2 \pm 516.8	1.8 \pm 0.3	173.8 \pm 35.7	-	-	-
Severe OSAS	4/1	45.0 \pm 8.9	27.5 \pm 5.0	-	81.8 \pm 8.9	1877.2 \pm 2728.5	4.4 \pm 3.8	213.2 \pm 35.4	-	-	-

eGFR = estimated glomerular filtration rate; AHI = apnea-hypoxia index; hsCRP = highly sensitive C-reactive protein; IL-6 = interleukin-6; IL-18 = interleukin-18; OSAS = obstructive sleep apnea syndrome; CKD = chronic kidney disease; HT = hypertension ; DM = diabetes mellitus ; HC = hyperlipidemia

Values are mean \pm SD

*P < 0.05 is considered statistically significant

Table 3: Spearman's rank correlation coefficient

	IL-18	hsCRP	IL-6
eGFR	-0.49*	-0.21	-0.28
AHI	-0.14	0.09	0.27

*P < 0.05 is considered statistically significant

Table 4: Characteristics and biochemical markers of the patients

	Sex, m/f	Age, y	AHI, events/h	eGFR, ml/min/1.73 m ²	hsCRP, ng/ml	IL-6, pg/ml	IL-18, pg/ml	Complications		
								HT	DM	HC
Patients with complications	37/6	54.7 ± 12.9	35.2 ± 22.9*	74.8 ± 21.2	2273.2 ± 4337.9	3.3 ± 2.0	219.1 ± 84.0	12	14	14
Patients free from other diseases	16/7	47.8 ± 13.1	22.8 ± 19.6*	79.7 ± 11.4	1450.0 ± 2695.7	2.7 ± 2.0	203.8 ± 57.3	none	none	none

eGFR = estimated glomerular filtration rate; AHI = apnea-hypoxia index; hsCRP = highly sensitive C-reactive protein; IL-6 = interleukin-6; IL-18 = interleukin-18; OSAS = obstructive sleep apnea syndrome; HT = hypertension ; DM = diabetes mellitus ; HC = hyperlipidemia

Values are mean ± SD

*P < 0.05 is considered statistically significant