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Plasma Thioredoxin, a Novel Oxidative Stress Marker, in Patients with Obstructive Sleep Apnea Before and After Nasal Continuous Positive Airway Pressure

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with increased cardiovascular mortality, and oxidative stress was suggested to play an important role. We hypothesized that the plasma TRX level, a novel oxidative stress marker, is elevated in OSA patients. Plasma TRX and adiponectin levels, which are significantly associated with cardiovascular mortality, were measured in 41 patients with severe OSA before ($n = 41$) and after ($n = 27$) nasal continuous positive airway pressure therapy (nCPAP) for 1 month and in 12 subjects without OSA (non-OSA group). The TRX level was significantly higher ($p = 0.02$) and the adiponectin level was significantly lower ($p = 0.02$) in the OSA group than in the non-OSA group. After 1 month of nCPAP ($n = 27$), the TRX level significantly decreased ($p = 0.03$), and the adiponectin level significantly increased ($p = 0.03$). Among the 14 patients with untreated OSA, the TRX and adiponectin levels did not significantly change over a 1-month interval. Among the 53 (41 OSA + 12 non-OSA) subjects, the TRX level was positively correlated with the respiratory disturbance index ($p = 0.001$) and percentage of time with $SaO_2 < 90\%$ ($p = 0.0002$). The adiponectin level, but not the TRX level, was correlated with the BMI ($n = 53$; $p = 0.02$). Plasma TRX may be a unique marker for evaluating oxidative stress and monitoring the effectiveness of nCPAP in OSA patients. *Antioxid. Redox Signal.* 10, 715–726.

INTRODUCTION

Thioredoxin (TRX) is a small protein that contains a redox-active site and has a variety of biologic functions including cytoprotection against oxidative stress (23). Recent experimental studies showed that TRX is released from cells in response to oxidative stress (31) and plays a protective role against oxidant injury (13). In our previous studies, we found that the plasma/serum level of TRX is elevated in patients with oxidative stress–associated acute and chronic disorders such as viral infection (36), ischemia–reperfusion (21), myocardial infarction (22), chronic heart failure (12), and nonalcoholic steatohepatitis (35). Obstructive sleep apnea (OSA) has been reported to have significant effects on myocardial infarction (17), chronic heart failure (30), and nonalcoholic steatohepatitis (38). However, the blood levels of TRX in patients with OSA have not been investigated.

The mortality rate is increased in untreated patients with OSA, who are at increased risk for cerebrocardiovascular diseases (17). In addition, the prevalence of significant OSA is high (43). Recently, OSA has been associated with inflammation, endothelial dysfunction, and increased oxidative stress

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(34), which are generated by repetitive nocturnal hypoxemia and reoxygenation (Fig. 1). Oxidative damage is involved in the pathogenesis of atherosclerosis and cardiovascular diseases (6), as well as of inflammation (14).

To elucidate the involvement of oxidative stress in OSA, two types of oxidative stress markers have been studied: (a) products of oxidation such as reactive oxygen species, oxidized proteins, lipid oxidation, and DNA degeneration as the end products of oxidative stress; and (b) antioxidant proteins whose gene expression is induced by oxidative stress. An antioxidant protein such as TRX (13, 31) not only has a role as an oxidative stress marker, but also may potentially be protective against oxidative stress. Recently, oxidative stress has been investigated in patients with OSA by measuring the levels of various products of oxidation (3, 5, 15, 32, 41). However, no antioxidant protein has been measured in those reports.

Therefore, it is important and promising to investigate oxidative stress in patients with OSA with a sensitive antioxidant marker, such as plasma TRX, because the plasma TRX level is easy to measure and reflects the cellular response to oxidative stress (12, 22). We hypothesized that the plasma TRX level in OSA patients is elevated and that it is reduced by treatment. We also hypothesized that the plasma TRX level in patients with OSA is associated with inflammation and the pathogenesis of cardiovascular diseases.

Adiponectin is a cytokine produced exclusively by white adipose tissue and appears to play a central role in metabolic syndrome (19) in addition to having antiatherogenic and antiinflammatory effects (39). Adiponectin may play an important role in cardiovascular disorders (28). Therefore, we also measured the plasma adiponectin level in addition to plasma interleukin-6 (IL-6) and serum C-reactive protein (CRP) levels, which are known to be inflammatory markers predictive of cardiovascular diseases (16) and have been reported to be elevated in OSA patients (33, 42). We compared these parameters between the OSA patients and subjects without OSA and investigated the effect of nasal continuous positive airway pressure (nasal CPAP) therapy on these parameters in OSA patients.

METHODS

Subjects

OSA patient group. We enrolled 50 consecutive patients with OSA who were determined to be candidates for nasal CPAP treatment by polysomnography and clinical symptoms. The diagnosis of OSA was established on the basis of clinical symptoms such as excessive daytime sleepiness, unexplained daytime fatigue, choking or gasping during sleep, and an apnea hypopnea index (AHI) of >5 events/h on polysomnography. Five patients were excluded because they had a history of myocardial infarction, brain infarction, chronic cardiac failure, or colon cancer or had a common cold at the time of the study. Polysomnography was performed in the hospital before CPAP treatment. Patients with an AHI of >20 events/h were candidates for nasal CPAP.

Hypertension was defined as a diastolic pressure >90 mm Hg, a systolic pressure >140 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level of >126 mg/dl, increased blood glucose level of >200 mg/dl 2 h after a 75-g oral glucose load, or the use of antidiabetic medication. Hyperlipidemia was defined as a total blood cholesterol level of >220 mg/dl, triglyceride level of >150 mg/dl, or the use of lipid-lowering medication. The OSA patients in this study received the same medical regimen beginning 1 month before the start of this study and throughout the study.

OSA untreated group. When a patient is diagnosed with severe OSA at our hospital, nasal CPAP therapy is started about 1 month later. To investigate whether significant changes in the plasma TRX level occur in OSA patients who have not received CPAP treatment, 15 OSA patients were randomly selected from the 45 patients, and we planned to obtain blood samples from them in the morning twice at about a 1-month interval before nasal CPAP treatment was started. One patient did not return to our clinic for follow-up. Therefore, 14 patients [13

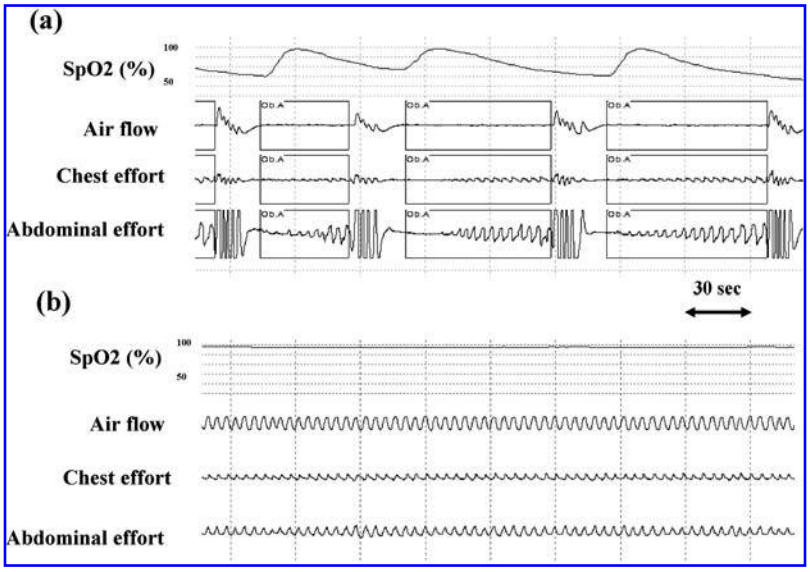

FIG. 1. Polysomnographic data of one of the OSA patients in this study who underwent nasal CPAP therapy (man, 53 years old; body mass index, 29.3 kg/m^2). (**a**) Polysomnographic data of the OSA patient before nasal CPAP treatment. After cessations of nasal and oral air flow with paradoxic chest and abdominal motions, periodical desaturations were observed. (**b**) Polysomnographic data of the same OSA patient after nasal CPAP treatment for 3 days. The periodic cessations of air flow and desaturations disappeared. SpO_2, Oxygen saturation measured with pulse oximetry; Ob A., obstructive sleep **a**pnea.

TABLE 1. BASELINE CHARACTERISTICS OF THE OSA SUBJECTS AND NON-OSA SUBJECTS

Variable	*OSA*	*Non-OSA*	p	p*
Number	41	12		
Male/Female (no.)	38/3	11/1	0.96	
Age (yr)	49.8 ± 10.0	46.7 ± 11.2	0.22	
Body mass index (kg/m^2)	29.4 ± 4.2	25.7 ± 4.1	**0.004**	
Respiratory disturbance index (events/h)	48.5 ± 18.2	2.80 ± 1.7	**<0.0001**	
Lowest SaO_2 (%)	65.4 ± 15.3	86.3 ± 6.1	**<0.0001**	
% of time SaO_2 <90% (%)	25.9 ± 2.4	0.50 ± 0.73	**<0.0001**	
Current smoking (no.)	11	3	0.92	
Hypertension (no.)	27	6	0.41	
Diabetes mellitus (no.)	10	3	0.97	
Hyperlipidemia (no.)	16	4	0.77	
Thioredoxin (ng/ml)	41.0 ± 24.4	23.9 ± 14.7	**0.02**	**0.04**
Adiponectin (μg/ml)	3.84 ± 1.66	5.82 ± 3.09	**0.02**	**0.03**
IL-6 (pg/ml)	1.56 ± 2.49	0.99 ± 0.94	0.77	0.92
CRP (mg/dl)	0.172 ± 0.147	0.087 ± 0.096	**0.02**	0.07

Data are expressed as mean ± SD.
*p**, *p* value after adjustment for BMI; OSA, obstructive sleep apnea.

men, one woman; age, 52.7 ± 8.3 years; AHI, 49.1 ± 24.1 events/h; body mass index (BMI), 28.2 ± 3.2 kg/m^2] were included in the OSA-untreated group.

OSA treatment group. To investigate the effect of nasal CPAP treatment, the remaining 30 patients with OSA underwent CPAP titration manually, received CPAP treatment [pressure (mean ± SD), 9.6 ± 3.1 cm H_2O], and underwent polysomnography on the third night of CPAP therapy. Thereafter, they received nasal CPAP therapy for 1 month at home before revisiting the outpatient clinic. Three patients refused to use nasal CPAP continuously. We checked the use time by reading the time counter in each CPAP machine, and the remaining 27 patients used nasal CPAP for >4 h/night. These 27 patients (25 men, two women; age, 48.3 ± 10.7 years; AHI, 48.2 ± 14.8 events/h; BMI, 30.1 ± 4.6 kg /m^2) were included in the OSA treatment group. Blood samples were collected in the morning before and 1 month after beginning CPAP use. The BMI after 1 month of nasal CPAP did not significantly differ from that before CPAP therapy was started ($p = 0.26$). Forty-one (14 untreated and 27 treatment) OSA patients were studied (Tables 1 and 2).

Non-OSA volunteer group. Twelve volunteers (11 men, one woman; age, 46.7 ± 11.2 years; BMI, 25.7 ± 4.1 kg/m^2) who did not have OSA were enrolled in the non-OSA group. They were not heavy snorers. In all of the volunteers, the arterial oxygen saturation was continuously monitored during sleep with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) over two consecutive nights. The severity of sleep ap-

TABLE 2. BASELINE CHARACTERISTICS OF THE OSA TREATMENT GROUP AND OSA UNTREATED GROUP

Variable	*OSA treatment*	*OSA untreated*	p
Number	27	14	
Male/Female (no.)	25/2	13/1	0.99
Age (yr)	48.3 ± 10.7	52.7 ± 8.29	0.21
Body mass index (kg/m^2)	30.1 ± 4.6	28.2 ± 3.16	0.25
Apnea–hypopnea index (events/h)	48.2 ± 14.8	49.1 ± 24.1	0.83
Lowest arterial O_2 saturation (%)	65.2 ± 16.5	65.8 ± 13.4	0.67
Arterial O_2 <90% (% of time)	29.3 ± 22.9	19.3 ± 20.6	0.21
Thioredoxin (ng/ml)	43.6 ± 23.0	35.9 ± 27.1	0.15
Adiponectin (μg/ml)	3.55 ± 1.37	4.40 ± 2.04	0.20
IL-6 (pg/ml)	1.68 ± 2.87	1.33 ± 1.59	0.70
CRP (mg/dl)	0.178 ± 0.156	0.161 ± 0.130	0.46
Hypertension (no.)	18	9	0.90
Diabetes mellitus (no.)	6	4	0.74
Hyperlipidemia (no.)	10	6	0.76
Current smoking (no.)	8	3	0.67

Data are expressed as mean ± SD.
OSA, obstructive sleep apnea.

nea in the volunteers was quantified by the 3% oxygen desaturation index (3%ODI), which was the number of oxygen desaturations of 3% or more below the baseline level per hour during sleep. This index correlates well with the conventional AHI (26). Subjects who had a 3%ODI of <5 were diagnosed as not having OSA. The 3%ODI of the 12 volunteers was 2.8 ± 1.7 (range, 1.74–3.86).

The rates of hypertension, diabetes mellitus, hyperlipidemia, and current smoking habit among the non-OSA group were not significantly different from those among the 41 OSA patients (see Table 1). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, the BMI was adjusted in the data analysis afterward. Blood samples were obtained from the non-OSA subjects at 8:00 in the morning after fasting beginning at 20:00 on the previous night.

This study was approved by the medical ethics committee of our university and was in accordance with the recommendations found in the Helsinki Declaration of 1975. All patients and subjects in the study groups provided written informed consent for participation in this study.

Polysomnography

Polysomnography was started at 21:00 and ended at 7:30 the following morning (see Fig. 1). Polysomnography was performed as previously described (4). Surface electrodes were attached by 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 (29). Ventilation was monitored by inductive plethysmography (Respitrace: Ambulatory Monitoring; Ardsley, NY). Airflow was monitored by thermistors (Nihon Kohden, Tokyo, Japan) that were placed at the nose and the mouth. Arterial oxygen saturation (SaO_2) was monitored continuously with a pulse oximeter (Pulsox-24; Minolta, Osaka, Japan) (see Fig. 1).

Apnea was defined as a complete cessation of airflow at the nose and mouth that lasts for ≥10 sec. Hypopnea was defined as a decrease in thoracoabdominal motion of ≥50% that lasts for ≥10 sec and associated with a decrease in the baseline SaO_2 of ≥3% (1). All AHI values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. Lowest SaO_2 during sleep and percentage of time of SaO_2 <90% during sleep also were calculated in each patient.

Respiratory disturbance index

The respiratory disturbance index (RDI) (27) was defined as (a) AHI in OSA patients and (b) 3% ODI in the volunteers.

Measurement of plasma/serum factors

Blood samples were drawn at 8:00 in the morning after the subjects had fasted beginning at 20:00 the previous night. Blood samples were centrifuged immediately at 3,000 rpm at 4°C for 10 min. The separated samples were stored at −80°C until assay. The plasma levels of TRX (Redox Bioscience, Kyoto, Japan; intra- and interassay coefficients of variation were 3.7% and 4.8%, respectively) and adiponectin (Otsuka Pharmaceuticals, Tokyo, Japan; intra- and interassay coefficients of variation were 4.1% and 4.7%, respectively) were measured with enzyme-linked immunosorbent assay. The plasma level of IL-6 (R&D Systems, Minneapolis, MN; intra- and interassay coefficients of variation were 7.8% and 4.6%, respectively) was measured with the chemiluminescent enzyme immunoassay. The serum levels of high-sensitivity CRP (Dade Behring, Liederbach, Germany; intra- and interassay coefficients of variation were 1.7% and 4.9%, respectively) were measured by nephelometry.

Data analysis

Data were expressed as mean ± SD. The data for each parameter did not show a normal distribution. The Mann–Whitney *U* test was used to compare two groups. Differences between two intervals were compared with the Wilcoxon signed-rank test. Correlation analyses were performed with Spearman's correlation coefficients (*Rs*). The BMI was significantly lower in the non-OSA group than in the OSA group. Therefore, multiple linear regression analysis was performed, with plasma TRX level as the dependent variable. Logarithmic transformation was performed on the plasma TRX levels to correct for the abnormal distribution of the values. This transformed variable was used in the model. The independent variables that were entered were BMI and OSA (presence or absence of OSA). Similarly, we performed multiple linear regression analysis with adiponectin, IL-6, and CRP levels as the dependent variables. Statistical analyses were performed by using StatView software for Windows (Version 5.0; Abacus Concepts, Berkeley, CA). A p value of <0.05 was considered to be significant.

RESULTS

Effect of OSA on biomarkers

The plasma TRX level was significantly higher in the 41 OSA subjects before nasal CPAP therapy than in the 12 non-OSA subjects (41.0 ± 24.4 *vs.* 23.9 ± 14.7 ng/ml; $p = 0.02$). Conversely, the plasma adiponectin level was significantly lower in the OSA subjects than in the non-OSA subjects (3.84 ± 1.66 *vs.* 5.82 ± 3.09 μg/ml; $p = 0.02$) (see Table 1 and Fig. 2). The serum CRP level was significantly higher in the OSA subjects than in the non-OSA subjects (0.172 ± 0.147 *vs.* 0.087 ± 0.096 mg/dl; $p = 0.02$), whereas the plasma IL-6 level did not significantly differ between the two groups (1.56 ± 2.49 *vs.* 0.99 ± 0.94 pg/ml; $p = 0.77$) (see Table 1 and Fig. 2).

We divided the 53 subjects into the RDI<40 not-severe OSA group (NS-OSA: $n = 26$) and the 40≤RDI very severe OSA group (VS-OSA: $n = 27$). The plasma TRX level was significantly higher in the VS-OSA subjects before nasal CPAP therapy than in the NS-OSA subjects ($p = 0.002$). The serum CRP and plasma IL-6 levels were also significantly higher in the VS-OSA subjects than in the NS-OSA subjects ($p = 0.05$ and $p = 0.006$). Conversely, the plasma adiponectin level was significantly lower in the VS-OSA subjects than in the NS-OSA subjects ($p = 0.03$).

We also divided the subjects into the RDI<20 non-OSA (N-OSA: $n = 12$), 20≤RDI<40 moderate OSA (M-OSA: $n = 14$),

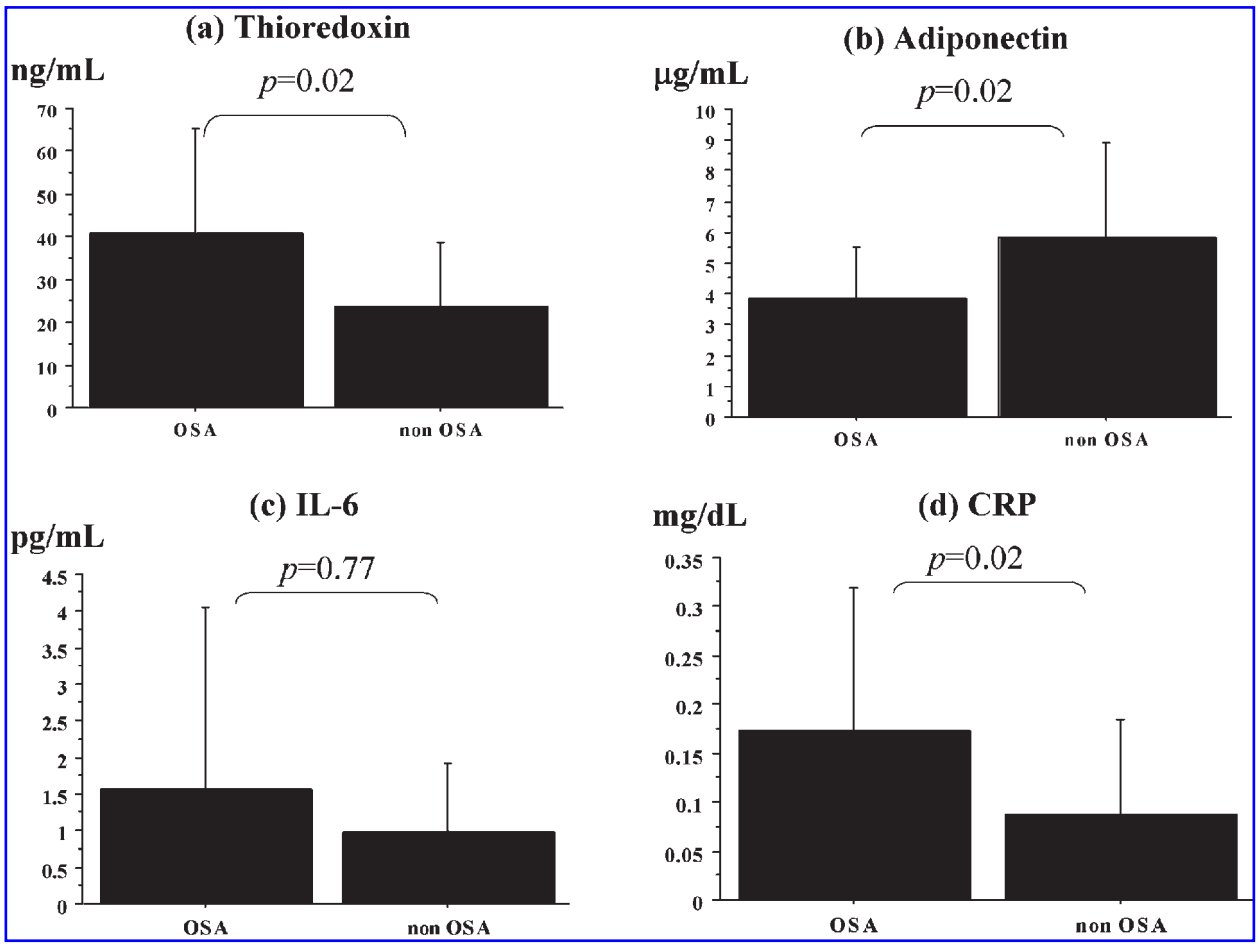

FIG. 2. Comparison of the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels between the OSA group before nasal CPAP therapy and the non-OSA group. The plasma TRX level was significantly greater in the OSA group ($n = 41$) than in the non-OSA group ($p = 0.02$). Conversely, the plasma adiponectin level was significantly lower in the OSA group than in the non-OSA group ($p = 0.02$). The serum CRP level was significantly greater in the OSA group than in the non-OSA group ($p = 0.02$). The plasma IL-6 level did not differ significantly between the OSA and the non-OSA group ($p = 0.77$). OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein.

and 40≤RDI severe OSA (S-OSA: $n = 27$) groups. The plasma TRX level was significantly higher in the S-OSA subjects before nasal CPAP therapy than in the N-OSA subjects ($p = 0.004$) and in the M-OSA subjects ($p = 0.02$). The plasma TRX level was not significantly different between the M-OSA subjects before nasal CPAP therapy and the N-OSA subjects ($p = 0.5$).

Relations between various parameters before nasal CPAP treatment and plasma TRX

The following correlation analyses were performed by using the baseline laboratory data of the 41 OSA subjects and the laboratory data of the 12 non-OSA subjects. The plasma TRX level was positively correlated with RDI ($p = 0.001$; $Rs = 0.45$) and the percentage of time with $SaO_2 < 90\%$ ($p = 0.0002$; $Rs = 0.52$) (Fig. 3). In addition, the plasma TRX level was positively correlated with the plasma IL-6 ($p = 0.009$; $Rs = 0.36$) and serum CRP levels ($p = 0.0002$; $Rs = 0.51$), and negatively correlated with the plasma adiponectin level ($p = 0.02$; $Rs = -0.32$) (Fig. 4). The adiponectin level was negatively correlated with RDI ($p = 0.01$; $Rs = -0.35$) and with the percentage of time with $SaO_2 < 90\%$ ($p = 0.04$; $Rs = -0.29$) (see Fig. 3). The plasma TRX level was not correlated with BMI ($p = 0.09$; $Rs = 0.23$), whereas the plasma adiponectin level ($p = 0.02$; $Rs = -0.32$) and the serum CRP level ($p = 0.0009$; $Rs = 0.46$) were significantly correlated with BMI (Fig. 5).

Multiple linear regression analysis was performed on the 53 subjects, with plasma TRX level as the dependent variable and BMI and OSA as the independent variables. BMI was not significantly associated with the plasma TRX level ($p = 0.45$). Conversely, OSA was significantly associated with the plasma TRX level ($p = 0.04$). The adjusted correlation coefficient (R) for the model was 0.36. After adjustment for BMI, age, and current smoking habit, the difference in plasma TRX levels between the OSA patients and non-OSA subjects was significant ($p = 0.04$; $R = 0.38$). The RDI was more significantly associated with the TRX level ($p = 0.02$) than with the adiponectin level ($p = 0.13$) independent of BMI ($R = 0.43$). Moreover, after adjustment for BMI, age, current smoking habit, and co-

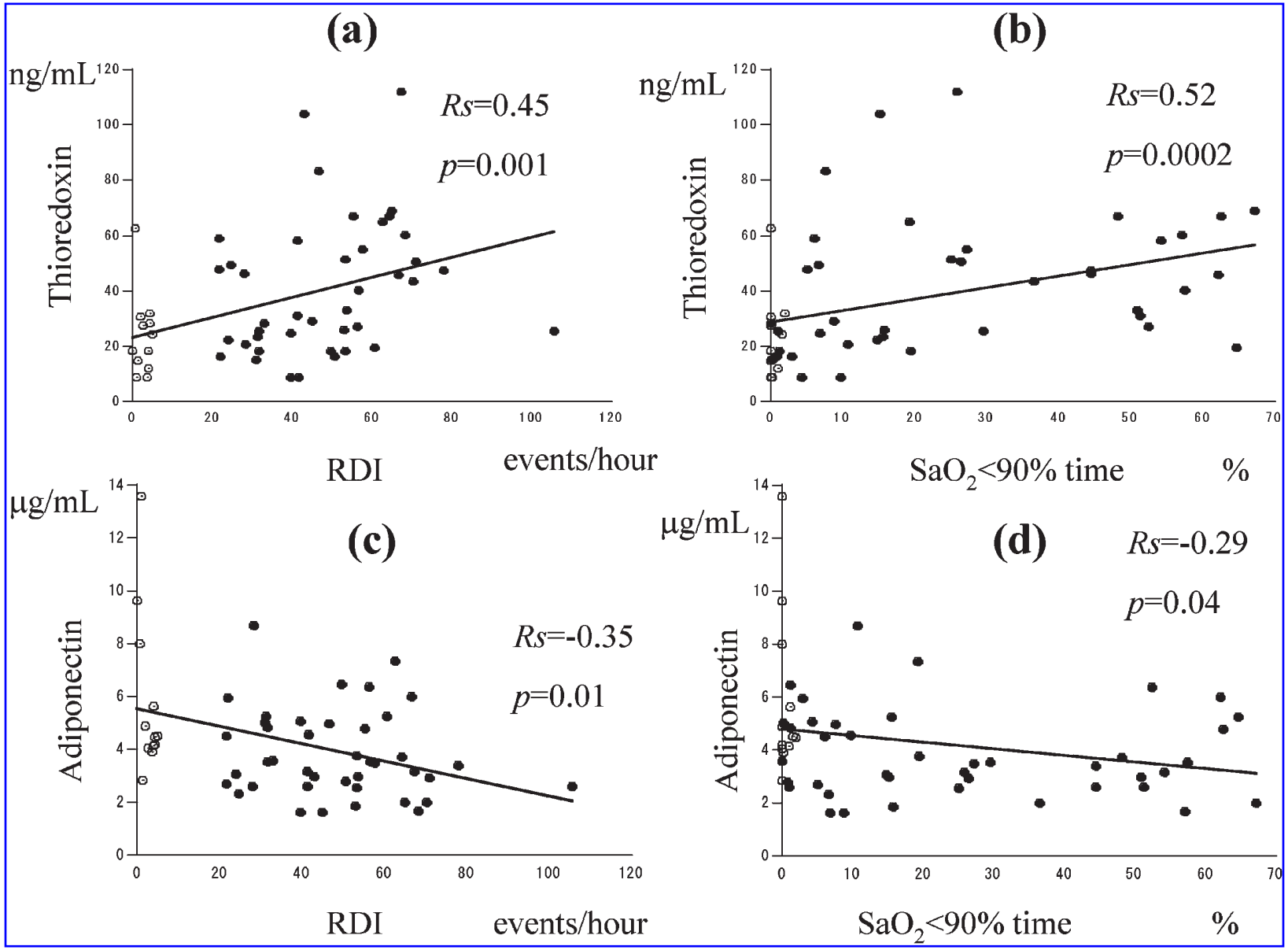

FIG. 3. Correlation analyses between the plasma thioredoxin or adiponectin level and RDI or $SaO_2 < 90\%$ of the time. The correlation analyses included the baseline laboratory data of the OSA subjects ($n = 41$) and the laboratory data of the non-OSA subjects ($n = 12$). The plasma thioredoxin level was positively correlated with RDI and with $SaO_2 < 90\%$ of the time. The plasma adiponectin level was negatively correlated with RDI and with $SaO_2 < 90\%$ of the time. *Solid circles*, OSA subjects, $n = 41$; *open circles*, subjects in the non-OSA group, $n = 12$. RDI, respiratory disturbance index; SaO_2, arterial O_2 saturation.

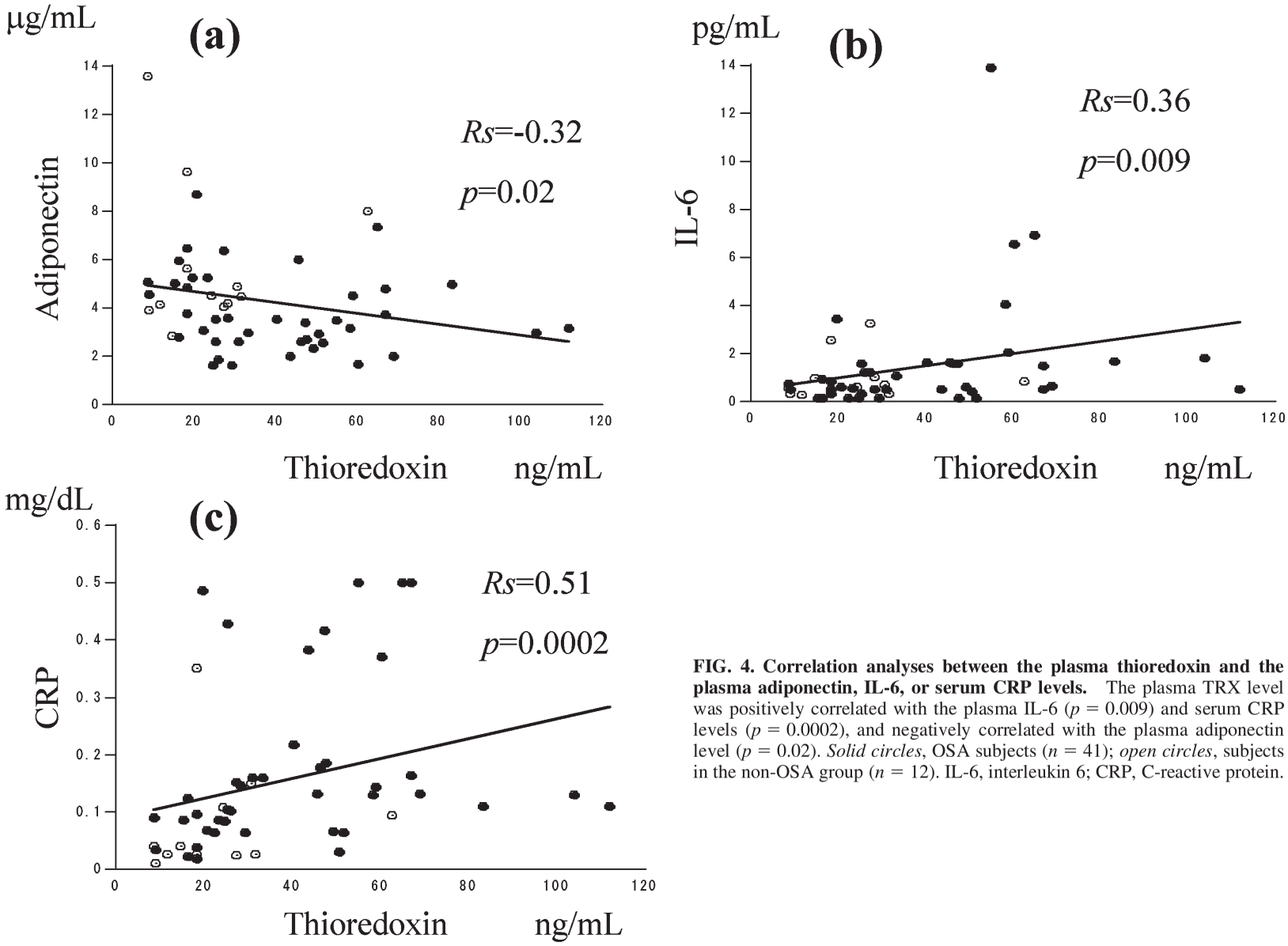

FIG. 4. Correlation analyses between the plasma thioredoxin and the plasma adiponectin, IL-6, or serum CRP levels. The plasma TRX level was positively correlated with the plasma IL-6 ($p = 0.009$) and serum CRP levels ($p = 0.0002$), and negatively correlated with the plasma adiponectin level ($p = 0.02$). *Solid circles*, OSA subjects ($n = 41$); *open circles*, subjects in the non-OSA group ($n = 12$). IL-6, interleukin 6; CRP, C-reactive protein.

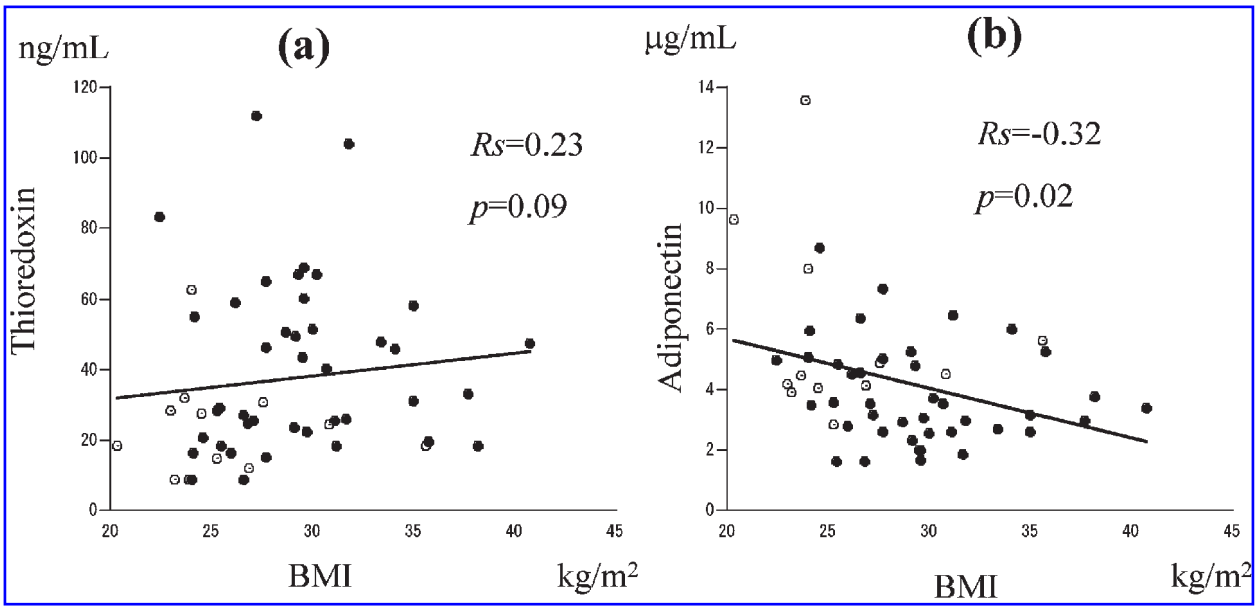

FIG. 5. Correlation analyses between BMI and the plasma thioredoxin or adiponectin level. The plasma adiponectin level, but not the plasma thioredoxin level, was negatively correlated with BMI. *Solid circles*, OSA subjects ($n = 41$); *open circles*, subjects in the non-OSA group ($n = 12$). BMI, body mass index.

morbidities, the difference in plasma TRX level between the OSA patients and non-OSA subjects was still significant ($p = 0.02$; $R = 0.48$). The plasma TRX level was not significantly associated with BMI ($p = 0.15$), whereas it was significantly associated with RDI. ($p = 0.004$; $R = 0.53$).

Effect of nasal CPAP treatment on the biomarkers

In the OSA-treatment group, nasal CPAP for 1 month significantly improved nocturnal hypoxemia/reoxygenation parameters including the RDI (48.2 ± 14.8 to 1.81 ± 1.21 events/h; $p < 0.0001$), lowest nocturnal SaO_2 (65.2 ± 16.5% to 88.1 ± 4.04%; $p < 0.0001$) and the percentage of time with SaO_2 <90% (29.3 ± 22.9% to 0.37 ± 0.45% of time; $p < 0.0001$). Although the BMI did not significantly change, the TRX, IL-6, CRP, and adiponectin levels changed significantly after 1 month of nasal CPAP use. The plasma TRX level (43.6 ± 23.0 to 33.3 ± 20.8 ng/ml; $n = 27$; $p = 0.03$) significantly decreased after 1 month of nasal CPAP treatment. Conversely, the plasma adiponectin level (3.55 ± 1.37 to 3.79 ± 1.14 μg/ml; $p = 0.03$) significantly increased (Table 3, Fig. 6). The plasma IL-6 (1.68 ± 2.87 to 0.634 ± 0.619 pg/ml; $p = 0.0008$) and serum CRP levels (0.178 ± 0.156 to 0.120 ± 0.120 mg/dl; $p = 0.01$) also significantly decreased (see Table 3 and Fig. 6).

We performed correlation analyses between the "basal" serum TRX level before nasal CPAP treatment and the therapeutic response, such as the change in RDI or PaO_2. The TRX level was not correlated with the change in RDI ($p = 0.13$; $Rs = 0.30$), the change in lowest SaO_2 ($p = 0.99$; $Rs = 0.003$), or the change in the percentage of time with SaO_2 <90% ($p = 0.11$; $Rs = 0.31$).

In the OSA-untreated group, the TRX, IL-6, CRP, and adiponectin levels did not significantly differ (all the p values

Table 3. Changes in the Levels of Mediators during the Measurement Interval in the OSA Treatment Group and OSA Untreated Group

Variable		*First blood sample*	*Second blood sample*	p
Thioredoxin (ng/ml)	OSA treated	43.6 ± 23.0	33.3 ± 20.8	**0.03**
	OSA untreated	35.9 ± 27.1	32.5 ± 15.8	0.64
Adiponectin (μg/ml)	OSA treated	3.55 ± 1.37	3.79 ± 1.14	**0.03**
	OSA untreated	4.40 ± 2.04	4.30 ± 2.06	0.29
IL-6 (pg/ml)	OSA treated	1.68 ± 2.87	0.63 ± 0.62	**0.0008**
	OSA untreated	1.33 ± 1.59	0.94 ± 0.58	0.78
CRP (mg/dl)	OSA treated	0.178 ± 0.156	0.120 ± 0.117	**0.01**
	OSA untreated	0.161 ± 0.130	0.119 ± 0.091	0.27

Data are expressed as mean ± SD.
OSA, obstructive sleep apnea.

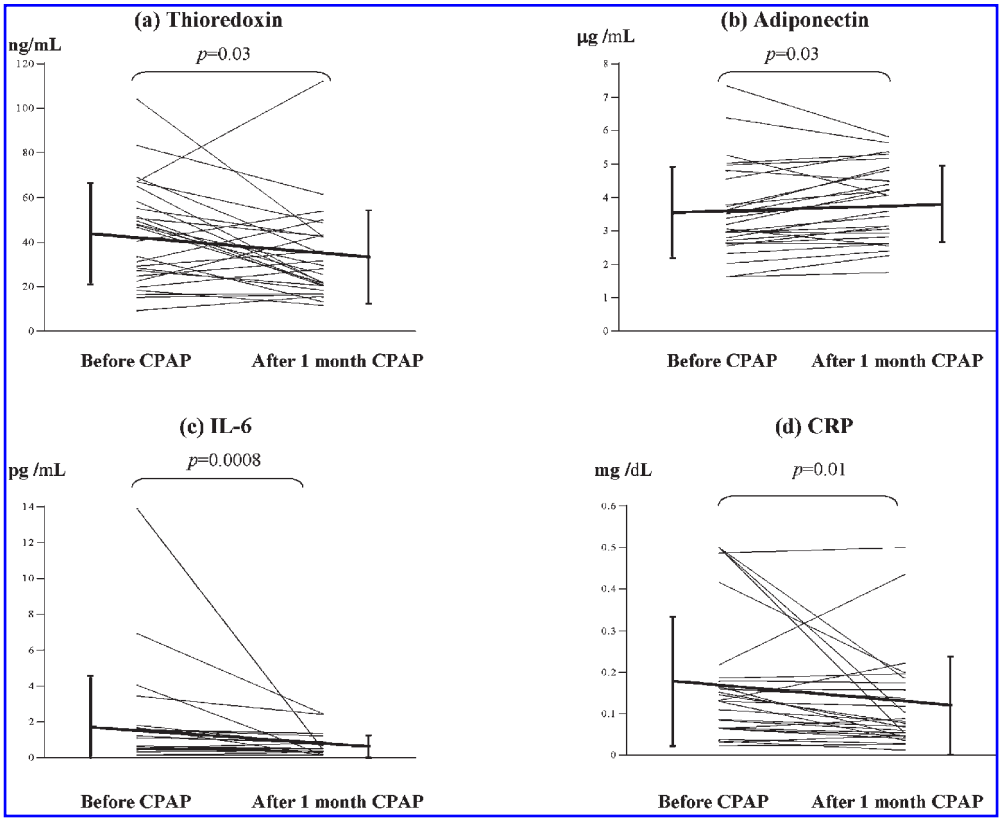

FIG. 6. Changes in the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels after 1 month of nasal CPAP use in the OSA treatment group. Nasal CPAP treatment significantly reduced the plasma thioredoxin level but increased the plasma adiponectin level. Nasal CPAP treatment significantly reduced the plasma IL-6 and serum CRP levels. OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein; CPAP, continuous positive airway pressure.

> 0.27) between the 2 days of measurement (mean interval, 39.4 days) during which nasal CPAP treatment was not provided (see Table 3, Fig. 7).

DISCUSSION

In the OSA patient group ($n = 41$), the plasma TRX level, a marker of oxidative stress, was significantly increased before nasal CPAP treatment, but the plasma level of adiponectin, an adipocytokine, was significantly reduced. The plasma TRX level ($n = 53$: the 41 OSA subjects and the 12 non-OSA subjects) was positively correlated with RDI ($p = 0.001$) and percentage of time with $SaO_2 < 90\%$ ($p = 0.002$). Plasma TRX was strongly related to OSA independent of BMI, age, and current smoking habit ($p = 0.04$; $R = 0.38$). After nasal CPAP treatment, the plasma level of TRX decreased, as did the levels of other cardiovascular parameters, such as serum CRP and plasma IL-6, whereas the plasma level of adiponectin increased.

TRX expression is induced by oxidative stress, and this protein scavenges reactive oxygen radicals directly or together with TRX-dependent peroxiredoxin. Moreover, TRX is released from cells in the presence of oxidative stress, and the plasma/serum TRX levels are good markers of oxidative stress (12, 22). Several studies showed that the TRX level ranges from 10 to 30 ng/ml among normal subjects and that it is >40 ng/ml in patients with oxidative stress (20, 21, 35, 36). In the present study, the plasma TRX level was significantly higher in the 41 OSA subjects before nasal CPAP therapy than in the 12 non-OSA subjects (41.0 ± 24.4 *vs.* 23.9 ± 14.7 ng/ml; $p = 0.02$). Our results strongly support that OSA patients are subjected to hypoxia-induced oxidative stress every night. Some studies (3, 5) showed that patients with OSA have decreased antioxidant capacity. Indeed, a high concentration of TRX, such as 1,000 ng/ml, would be needed to scavenge reactive oxygen radicals completely and have antiinflammatory effects (24, 25). The mean TRX level of the OSA patients in this study was 41 ng/ml. Therefore, the TRX level in OSA patients may be insufficient to act as an antioxidant protein. Recently, Svatikova *et al.* (37) found that healthy OSA patients without any other comorbidities do not manifest evidence of higher oxidative stress by measuring the levels of oxidized products such as thiobarbituric acid–reactive substances, oxidized low-density lipoprotein, and isoprostanes, contrary to previous reports (3, 5, 15, 32, 41). Oxidative stress in OSA patients may be demonstrated more clearly by measuring the level of an antioxidant protein such as TRX. The plasma TRX level was positively correlated with both RDI and the percentage of time with $SaO_2 < 90\%$. The plasma TRX level was strongly related to OSA, independent of BMI, age, and current smoking habit. Plasma TRX may be a good marker of oxidative stress in OSA patients and may be a

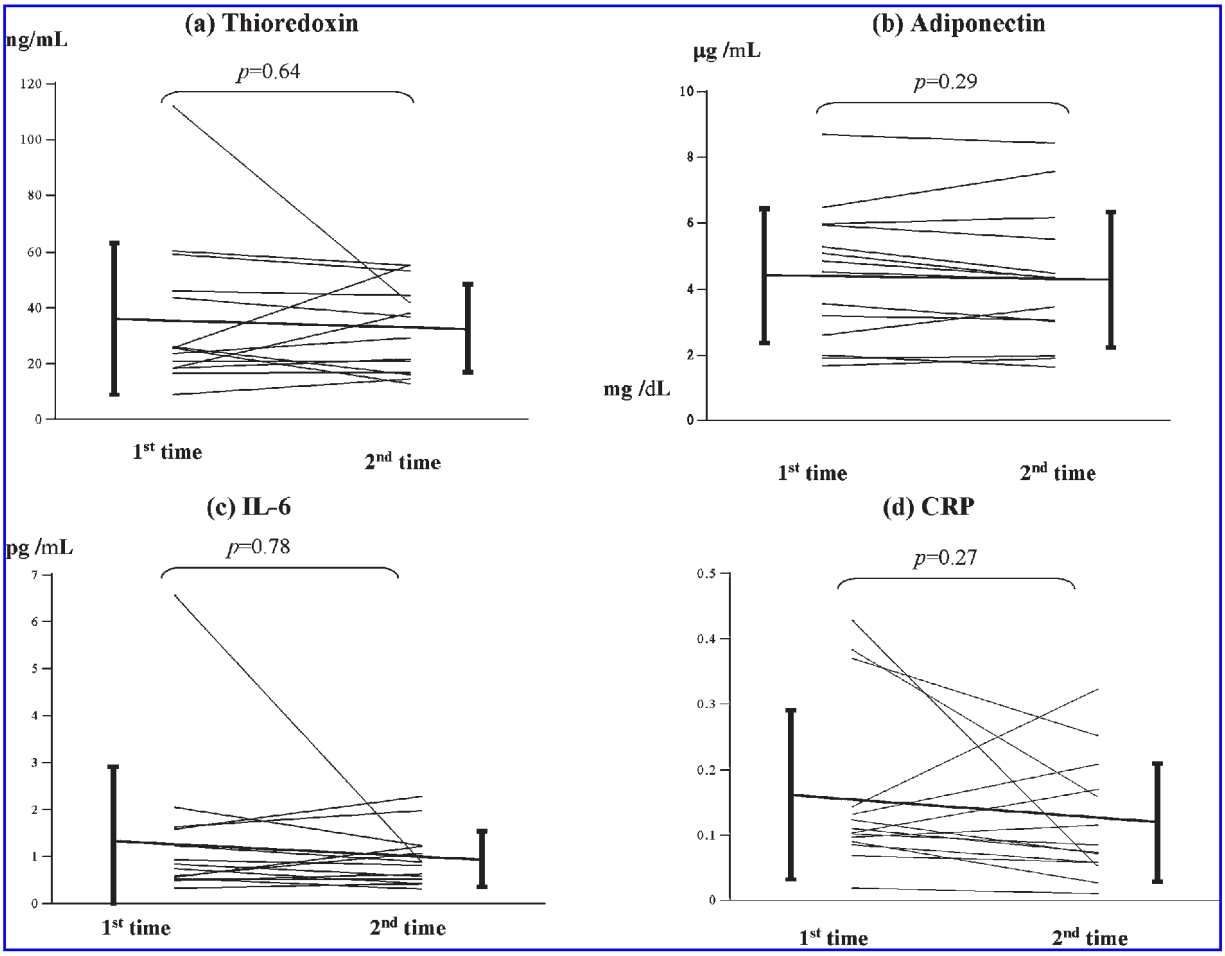

FIG. 7. Changes in the plasma thioredoxin, adiponectin, IL-6, and serum CRP levels between the 2 measurement days (mean interval, 39.4 days) during which nasal CPAP treatment was not provided in the OSA untreated group. The plasma thioredoxin, adiponectin, IL-6, and serum CRP levels did not significantly differ between the two measurement days. OSA, obstructive sleep apnea; IL-6, interleukin 6; CRP, C-reactive protein; CPAP, continuous positive airway pressure.

sensitive barometer of the effectiveness of nasal CPAP treatment. Because the number of subjects in our study was small, further studies are needed to investigate the precise role of TRX in OSA.

In this study, the plasma adiponectin level was significantly reduced in the OSA treatment group before nasal CPAP treatment, and it increased after nasal CPAP treatment for 1 month. The plasma adiponectin level was negatively correlated with the plasma TRX level. Adiponectin is an adipocyte-specific cytokine. In clinical studies, a low adiponectin level has been associated with insulin resistance (10), atherosclerosis (18), and cardiovascular diseases (28). Moreover, the increased oxidative stress in patients with obesity has a significant impact on the low adiponectin level (7). OSA is clearly associated with obesity and is also linked to the risk of insulin resistance (11) and cardiovascular diseases (34). However, the linkage between OSA and adiponectin has been equivocal (9, 40). This ambiguity may be due to the complexity of regulation of adiponectin. For example, obesity itself results in a low adiponectin level (2), as well as in our data: the plasma adiponectin level in this study was negatively correlated with BMI ($p = 0.02$; $r = -0.32$).

In addition to plasma TRX and adiponectin levels, we measured the levels of inflammatory markers that have been considered to be elevated in oxidative stress. It has been reported that the levels of inflammatory markers such as CRP and IL-6 were elevated in patients with OSA, and they were reduced by nasal CPAP therapy (33, 42). In our data, the CRP level was significantly elevated, although the IL-6 level was not significantly elevated in the untreated OSA patients. However, when CPAP was administered to OSA patients, the CRP and IL-6 levels significantly decreased. A recent study (8) showed that CRP in OSA patients may be associated with obesity rather than with OSA itself. In our data, the difference in CRP level between the OSA and non-OSA subjects disappeared after adjusting for BMI. The inflammatory pathway can be initiated by oxidative stress (14). Because many confounding factors participate in the inflammatory pathway, it is difficult to show a clear association between OSA and inflammation. However, considering that the plasma TRX level was positively correlated with the plasma IL-6 and serum CRP levels and that CPAP treatment improved the serum CRP and plasma IL-6 levels, oxidative stress may be one mechanism of inflammation in OSA patients. Oxidative stress markers such as TRX are directly as-

sociated with the pathogenesis of OSA and may be more sensitive markers of OSA than inflammatory markers.

This study has some limitations. The first limitation was that a significant difference in BMI was found between the non-OSA group and the OSA patient group. The serum CRP level is increased in patients with obesity, whereas the plasma adiponectin level is decreased (2, 10). In this study, the plasma TRX level was not correlated with BMI. In addition, BMI was not a significant variable in the multiple regression analysis with plasma TRX level as the dependent variable. Therefore, the difference in BMI between the non-OSA group and the OSA patient group would not have significant effects on the plasma TRX level.

Another limitation of this study is that polysomnography was not performed in the non-OSA volunteers. The volunteers were not heavy snorers. It was recently reported that the best agreement between AHI and 3%ODI values was found among individuals with AHI values <15, where the difference between the estimated AHI and 3%ODI values was only -0.4 among 49 subjects (26). Therefore, although sleep-disordered breathing in the non-OSA volunteers in this study was measured by oximetry and not polysomnography, this would not have a significant effect on the overall results.

The last limitation is that the effects of nasal CPAP were not examined in a randomized, placebo-controlled design because of the difficulty in implementing placebo nasal CPAP treatment under the official medical insurance system in Japan. However, in the OSA-untreated group, who did not receive nasal CPAP treatment, the levels of the mediators did not change significantly during the interval between the measurement points. Therefore, we could reveal the effects of nasal CPAP.

In conclusion, we demonstrated that the plasma TRX level was elevated in patients with OSA independent of BMI and comorbidities, but that it is reduced by nasal CPAP. TRX has the potential to be a good marker to evaluate oxidative stress in OSA patients and to monitor the effectiveness of CPAP therapy.

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ABBREVIATIONS

AHI, apnea hypopnea index; BMI, body mass index; CPAP, continuous positive pressure; CRP, C-reactive protein; IL-6, interleukin-6; nCPAP, nasal CPAP; OSA and ObA, obstructive sleep apnea; 3%ODI, 3% oxygen desaturation index; RDI, respiratory disturbance index; SaO_2, arterial oxygen saturation; TRX, thioredoxin.

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