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Association between the severity of obstructive sleep apnea and the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol

*Yoshiyuki Kawano**, *Akira Tamura*, *Junichi Kadota*

Internal Medicine 2, Faculty of Medicine, Oita University, Yufu 879-5593, Japan

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ABSTRACT

The positive association between the ratio of serum low-density lipoprotein cholesterol (LDL-C) to serum high-density lipoprotein cholesterol (HDL-C) and cardiovascular events has recently been receiving much attention. However, the association between the severity of obstructive sleep apnea (OSA) and this ratio has not yet been investigated. Accordingly, we sought to clarify this association and the effect of continuous positive airway pressure (CPAP) therapy on the ratio. We performed polysomnography and LDL-C/HDL-C measurements in 215 patients who were suspected of having OSA. Furthermore, LDL-C/HDL-C was again evaluated 6 months after polysomnography in 30 OSA patients for whom CPAP therapy was initiated and continued, and in 11 age- and sex-matched OSA patients for whom the therapy could not be initiated. The LDL-C/HDL-C correlated positively with apnea-hypopnea index ($\rho = 0.28$, $P < .001$) and negatively with the lowest arterial oxyhemoglobin saturation ($\rho = -0.30$, $P < .001$). Multivariate regression analysis revealed that ln apnea-hypopnea index (or ln lowest arterial oxyhemoglobin saturation) was independently associated with LDL-C/HDL-C. The LDL-C/HDL-C decreased after 6 months in the CPAP group (2.29 ± 0.67 to 2.11 ± 0.74, $P = .02$), whereas it did not change in the non-CPAP group (2.65 ± 0.82 to 2.62 ± 0.66, $P = .81$). The severity of OSA was independently associated with LDL-C/HDL-C, and LDL-C/HDL-C was significantly reduced at 6 months after CPAP therapy. These findings suggest that LDL-C/HDL-C increases in proportion to the severity of OSA, which may contribute partly to an increased risk for cardiovascular events in OSA patients.

1. Introduction

Dyslipidemia is a well-established risk factor for cardiovascular diseases [1-7]. Recently, much attention has been paid to the positive association between the ratio of serum low-density lipoprotein cholesterol (LDL-C) to serum high-density lipoprotein cholesterol (HDL-C) and cardiovascular events or progression of coronary atherosclerosis [8-12]. Analysis using data obtained from the Framingham Heart Study and the Coronary Primary Prevention Trial showed that the percentage change in LDL-C/HDL-C by lipid-lowering treatment was a more useful predictor of coronary events than the percentage

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* *Corresponding author*. Tel.: +81 97 586 5804; fax: +81 97 549 4245.
E-mail address: yoshi@oita-u.ac.jp (Y. Kawano).

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change in total cholesterol or LDL-C by lipid-lowering treatment [9]. In the Physician's Health Study, a 1-unit increase in LDL-C/HDL-C was associated with a 53% increase in the risk for myocardial infarction [10]. In post hoc analysis of the Treating to New Targets study, patients with LDL-C/HDL-C of at least 2.41 were at a higher risk for cardiovascular events than those with LDL-C/HDL-C less than 1.33 [11]. Moreover, a meta-analysis showed that the establishment of LDL-C/HDL-C less than 2.0 by treatment with lipid-lowering drugs leads to regression of coronary atherosclerosis assessed by intravascular ultrasonography in patients with coronary artery disease [12].

Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive episodes of upper airway collapse, apneas, and arousal during sleep. Previous studies have shown that OSA may promote dyslipidemia [13-25]. However, the association between the severity of OSA and LDL-C/HDL-C has not been investigated so far. Accordingly, we sought to examine this association and the effect of continuous positive airway pressure (CPAP) on LDL-C/HDL-C.

2. Subjects and methods

2.1. Subjects

The cross-sectional study: Between January 2006 and December 2009, 215 patients (177 men and 38 women; mean age, 55.0 ± 16.1 years) who were suspected of having OSA and who did not meet the following exclusion criteria were enrolled in this study: chronic heart failure, left ventricular ejection fraction less than 55%, hormone replacement therapy, nephritic syndrome, thyroid diseases, chronic hepatic diseases, the use of lipid-lowering agents, cerebrovascular diseases, neurological diseases, or chronic respiratory diseases. Patients with central sleep apnea were not included in this cohort. The patients underwent overnight polysomnography and serum lipid measurements.

The longitudinal study: Between January 2006 and June 2009, the following 41 untreated OSA patients with an apnea-hypopnea index (AHI) of at least 20 who did not have coronary artery disease and who did not meet the above-mentioned exclusion criteria were enrolled in this longitudinal study: 30 patients (26 men and 4 women; mean age, 59.9 ± 13.7 years) for whom CPAP therapy was initiated and continued and 11 age- and sex-matched patients (8 men and 3 women; mean age. 67.1 ± 12.0 years) for whom the therapy could not be initiated. Patients with dyslipidemia were recommended to undergo cholesterol-lowering dietary therapy according to the 2007 Japan Atherosclerosis Society guidelines for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese [26]. Lipid measurements were performed again after 6 months in the CPAP and non-CPAP groups, and follow-up polysomnography was performed after 6 months in the CPAP group. Lipid-lowering agents were not started during the study period in all patients.

The study protocol was approved by the ethics committee at our institutions, and informed consent was obtained from each patient before the study.

2.2. Polysomnography

All subjects underwent polysomnography (E-series; Compumedics, Abbotsford, Australia), including electroencephalography, electrooculography, submental electromyography, electrocardiography, measurements of oronasal airflow by a nasal pressure transducer and an oronasal thermistor, measurements of thoracoabdominal excursions by a piezo belt, and pulse oximetry. *Obstructive apnea* was defined as the absence of oronasal airflow for at least 10 seconds associated with continued or increased inspiratory effort. *Central apnea* was defined as the absence of oronasal airflow for at least 10 seconds associated with an absent inspiratory effort [27]. *Hypopnea* was defined as at least 50% reduction in oronasal airflow for at least 10 seconds associated with at least 3% fall in oxygen saturation or an arousal [27]. The AHI was calculated as the mean number of apneas and hypopneas per hour of sleep. The obstructive and central apnea indexes were calculated as the mean number of obstructive and central apneas per hour of sleep, respectively. *Arousal* was defined as follows: an abrupt shift in encephalogram frequency including α, θ, and/or frequencies greater than 16 Hz (but not spindle) that lasted for at least 3 seconds, with at least 120 seconds of stable sleep preceding the changes during the sleep stages N1, N2, N3, or R; furthermore, arousal during stage R required a concurrent increase in the submental electromyogram lasting for at least 1 second [27]. The arousal index (ArI) was calculated as the mean number of arousals per hour of sleep.

2.3. CPAP titration

An AutoSet System (ResMed, Sydney, Australia) was used for CPAP therapy. The data recorded under an autoadjusting CPAP mode were analyzed, and the fixed pressure level for each patient was determined based on the 95th percentile pressure [28,29].

Table 1 – Patient characteristics

No. of patients	215
Age (y)	55.0 ± 16.1
Male sex	82.3%
BMI (kg/m^2)	24.6 (22.8-27.2)
Hypertension	56.3%
Dyslipidemia	57.7%
Diabetes mellitus	13.5%
Current smoker	24.2%
Coronary artery disease	7.0%
LDL-C (mg/dL)	118.7 ± 30.7
HDL-C (mg/dL)	53.2 ± 15.6
TG (mg/dL)	121.0 (90.0-172.0)
LDL-C/HDL-C	2.4 ± 0.9
Medications	
Calcium antagonists	34.4%
ACEIs/ARBs	29.8%
α-Blockers	4.7%
β-Blockers	14.9%

Data are presented as mean ± SD, median (first-third quartiles), or percentages. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2 – Overnight polysomnographic findings

No. of patients	215
Sleep period time (min)	556 ± 85
Total sleep time (min)	414 ± 109
AHI	24.1 (11.4-45.7)
Obstructive apnea index	6.5 (1.9-18.0)
Central apnea index	0.2 (0.0-1.0)
ArI	33.5 (20.9-49.9)
L-SpO_2 (%)	85.0 (79.0-89.0)
Total time of SpO_2 <90% (min)	2.7 (0.2-16.4)

Data are presented as mean ± SD or median (first-third quartiles).

2.4. *Lipid measurements*

Blood samples were collected in the overnight fasting state after polysomnography. Serum LDL-C levels were measured by a liquid selective detergent method (Sekisui Medical, Tokyo, Japan) [30]. Serum HDL-C levels were measured by an accelerator selective detergent method (Sekisui Medical) [31]. Serum triglycerides (TG) levels were measured by a glycerol elimination method (Sekisui Medical) [32]. In a preliminary study, serum LDL-C measured by a liquid selective detergent method and that calculated by the Friedewald equation showed excellent correlation (489 men and 374 women; mean age, 51.3 ± 9.6 years; $r = 0.98$; $P < .0001$).

2.5. *Statistical analysis*

Continuous data are expressed as mean ± SD or median (first-third quartiles). Continuous data between the 2 groups were compared using the unpaired *t* test or the Mann-Whitney *U* test. Categorical data between the 2 groups were compared using the Fisher exact test or the χ^2 test. Spearman rank correlations were used to examine correlations between the 2 continuous variables. Data at baseline and after 6 months were compared using the paired *t* test or the Wilcoxon signed rank test. Univariate and multiple regression analyses were performed to determine variables associated with LDL-C/HDL-C. Because body mass index (BMI), TG, AHI, lowest arterial oxyhemoglobin saturation (L-SpO_2), and ArI were not normally distributed, logarithmically transformed values of these variables were used in the analyses. Multiple regression analysis was performed using explanatory variables that showed $P < .2$ on univariate analysis. A $P < .05$ was considered to be

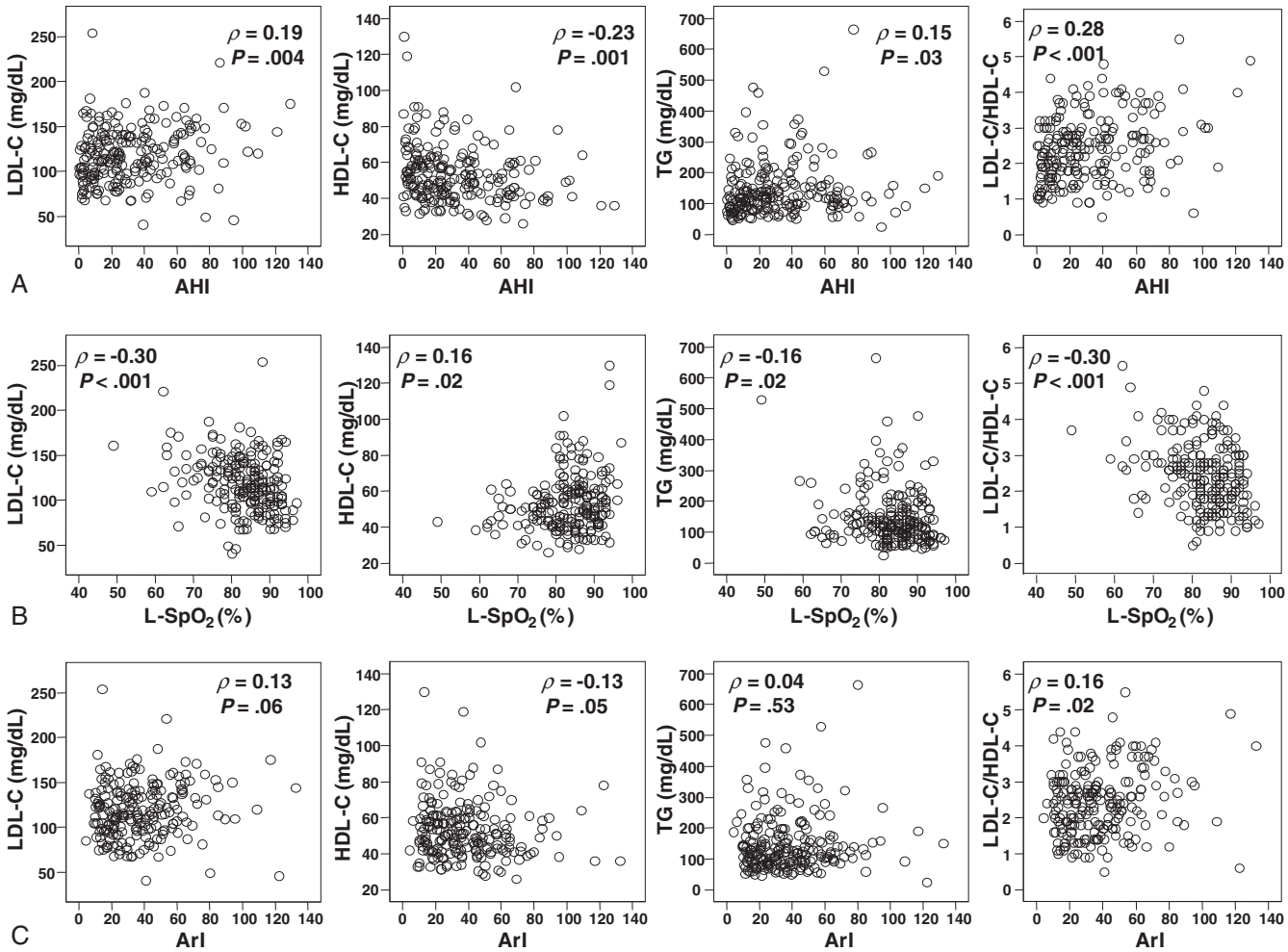

Fig. 1 – Associations of serum LDL-C, HDL-C, TG, or LDL-C/HDL-C with AHI (A), L-SpO_2 (B), or ArI (C). Spearman rank correlations were used to examine correlations between the 2 continuous variables.

Table 3 – Univariate regression analysis to determine variables associated with LDL-C/HDL-C

Variables	Standard regression coefficient	P value
Age	−0.06	.36
Male sex	0.20	.004
Ln BMI	0.40	<.001
Hypertension	0.07	.31
Diabetes mellitus	−0.01	.92
Current smoker	0.13	.06
Coronary artery disease	−0.07	.31
Calcium antagonists	−0.06	.42
ACEIs/ARBs	−0.03	.62
α-Blockers	−0.10	.16
β-Blockers	−0.02	.78

statistically significant. Statistical analyses were performed using a statistical software package (SPSS, version 12.0J; SPSS, Tokyo, Japan).

3. Results

Patient characteristics and biochemical markers in the cross-sectional study are shown in Table 1. Overnight polysomnographic findings are shown in Table 2. Of 215 patients, 189 (87.9%) had an AHI of at least 5. The associations of serum LDL-C, HDL-C, TG, or LDL-C/HDL-C with AHI, L-SpO_2, or ArI are shown in Fig. 1. Serum LDL-C, TG, and LDL-C/HDL-C correlated positively with AHI; and serum HDL-C correlated negatively with AHI. Serum LDL-C, TG, and LDL-C/HDL-C correlated negatively with L-SpO_2; and serum HDL-C correlated positively with L-SpO_2. The LDL-C/HDL-C correlated positively with ArI. Univariate regression analysis revealed that male sex and ln BMI were also significantly associated with LDL-C/HDL-C (Table 3). Multiple regression analysis revealed that ln BMI, ln AHI, and α-blocker use were independently associated with LDL-C/HDL-C (Table 4). When ln L-SpO_2 was entered into multiple regression analysis as an explanatory variable instead of ln AHI, ln BMI, ln L-SpO_2, and α-blocker use were independently associated with LDL-C/HDL-C (Table 4). When ln ArI was entered into multiple regression analysis as an explanatory variable instead of ln AHI, ln BMI and α-blocker use were independently associated with LDL-C/HDL-C (Table 4).

Patient characteristics in the longitudinal study are shown in Table 5. Patient characteristics did not differ significantly between the 2 groups. In the CPAP group, the average pressure level was 8.0 ± 1.6 cmH_2O. The average usage time was 7.0 ± 2.2 h/d. The LDL-C/HDL-C decreased significantly in the CPAP group (2.29 ± 0.67 to 2.11 ± 0.74, $P = .02$), whereas it did not change significantly in the non-CPAP group (2.65 ± 0.82 to 2.62 ± 0.66, $P = .81$) (Table 6).

4. Discussion

The main findings of the present study were as follows: (1) LDL-C/HDL-C correlated positively with AHI and ArI and correlated negatively with L-SpO_2; (2) multiple regression analysis showed that AHI (or L-SpO_2) was independently associated with LDL-C/HDL-C; and (3) LDL-C/HDL-C decreased significantly in the CPAP group, whereas LDL-C/HDL-C did not change significantly in the non-CPAP group. To the best of our knowledge, this is the first study that shows a positive association between the severity of OSA and LDL-C/HDL-C and the favorable effect of CPAP therapy on LDL-C/HDL-C.

It has been shown that LDL-C/HDL-C is a useful marker for predicting cardiovascular events and progression of coronary atherosclerosis [8-12]. The association between the severity of OSA and LDL-C/HDL-C has not been investigated so far. In the present study, AHI (or L-SpO_2) was independently associated with LDL-C/HDL-C. Furthermore, 6-month CPAP treatment significantly reduced LDL-C/HDL-C. These results suggest that OSA itself increases LDL-C/HDL-C in proportion to the severity of OSA. In the present study, serum HDL-C correlated negatively with AHI and positively with L-SpO_2. Previous large population studies have shown that OSA is independently associated with a decreased level of serum HDL-C [16,23]. Börgel et al [16], whose study had the largest sample size among the previous studies [13,16,21,24,25] that investigated the effect of CPAP on serum HDL-C, showed that bilevel positive airway pressure or CPAP therapy significantly increased serum HDL-C. A significant decrease in serum HDL-C caused by OSA might lead to an increase in LDL-C/HDL-C in proportion to the severity of OSA. In the present study, serum LDL-C correlated positively with AHI and negatively with L-SpO_2. A previous large population study failed to show an independent association between the

Table 4 – Multiple regression analysis to determine variables associated with LDL-C/HDL-C

Variables	Standard regression coefficient	P value	Ln L-SpO_2 was entered instead of ln AHI		Ln ArI was entered instead of ln AHI	
			Standard regression coefficient	P value	Standard regression coefficient	P value
Male sex	0.10	.13	0.14	.03	0.12	.06
Ln BMI	0.32	<.001	0.29	<.001	0.37	<.001
Current smoker	0.07	.24	0.05	.42	0.07	.27
Ln AHI	0.18	.01				
Ln L-SpO_2			−0.19	.006		
Ln ArI					0.07	.27
α-Blockers	−0.15	.01	−0.15	.01	−0.14	.03

Table 5 – Patient characteristics at baseline in the CPAP and non-CPAP groups

Variables	CPAP group (n = 30)	Non-CPAP group (n = 11)	P value
Age (y)	59.9 ± 13.7	67.1 ± 12.0	.13
Male sex	86.7%	63.6%	.18
BMI (kg/m^2)	26.4 ± 3.5	27.4 ± 3.0	.44
Hypertension	70%	100%	.08
Dyslipidemia	70%	81.8%	.69
Diabetes mellitus	23.3%	18.2%	.99
Current smoker	16.7%	18.2%	.99
LDL-C (mg/dL)	119.0 ± 25.2	125.1 ± 25.3	.50
HDL-C (mg/dL)	53.8 ± 9.3	49.7 ± 11.6	.24
TG (mg/dL)	141.8 ± 35.4	102.8 ± 34.6	.003
LDL-C/HDL-C	2.29 ± 0.67	2.65 ± 0.82	.15
Medications			
Calcium antagonists	46.7%	72.7%	.17
ACEIs/ARBs	46.7%	36.4%	.73
α-Blockers	20%	27.3%	.68
β-Blockers	13.3%	36.4%	.18

Data are presented as mean ± SD or percentages. Continuous data between the 2 groups were compared using the unpaired *t* test or the Mann-Whitney *U* test. Categorical data between the 2 groups were compared using the Fisher exact test or the χ^2 test.

severity of OSA and serum LDL-C [23]. Börgel et al [16], whose study had the largest sample size among the previous studies [13,16,21,24,25] that investigated the effect of CPAP on serum LDL-C, showed that bilevel positive airway pressure or CPAP therapy tended to increase serum LDL-C (P = .15). Further studies with a large sample size are needed to clarify whether OSA itself can increase serum LDL-C, leading to an increase in LDL-C/HDL-C.

We speculate the following explanations for the positive association between the severity of OSA and LDL-C/HDL-C. First, chronic sympathetic nervous activation caused by OSA [33-37] could increase the synthesis of very low-density lipoprotein in the liver and suppress the catabolism of LDL in the liver through the stimulation of α_1 receptors [38], leading to a decrease in serum HDL-C and an increase in serum LDL-C and thereby an increase in LDL-C/HDL-C. It has been shown that α_1-blockers activate lipoprotein lipase [38], which plays a key role in the synthesis of HDL-C [39], and increase lecithin cholesterol acyltransferase activity [40], leading to a decrease in serum very low-density lipoprotein and an increase in serum HDL-C and thereby a decrease in LDL-C/HDL-C. Second, intermittent hypoxia, activated sympathetic nervous system, and activated hypothalamus-pituitary-adrenal axis, all of which are observed in OSA [36,41], could modify the expression of the lipoprotein lipase, leading to a decrease in serum HDL-C and thereby an increase in LDL-C/HDL-C. In the present study, L-SpO_2 was independently associated with LDL-C/HDL-C. This result suggests that OSA-induced hypoxia contributes to the increase in LDL-C/HDL-C. In contrast, ArI was not independently associated with LDL-C/HDL-C. Although recurrent arousals can cause sympathetic nervous activation [42], hypoxia and inhibition of pulmonary expansion may play a more important role in sympathetic nervous activation [43] and resultant exaggeration of lipid metabolism [44] than recurrent arousals in OSA.

The present study has an important clinical implication. Because it has been shown that elevated LDL-C/HDL-C is associated with increased cardiovascular events [8-11] and progression of coronary atherosclerosis [12], the increase in LDL-C/HDL-C in proportion to the severity of OSA may partly explain why patients with OSA, especially those with severe OSA, are at an increased risk for cardiovascular events [45]. Furthermore, a significant, although small, reduction in LDL-C/HDL-C by CPAP therapy may partly contribute to the prevention of cardiovascular events in patients with OSA.

The present study has several limitations. First, the longitudinal study was not randomized. In addition, the non-CPAP group consisted of patients for whom CPAP therapy could not be initiated, which raises the possibility that the non-CPAP group might have been less aggressive for cholesterol-lowering dietary therapy than the CPAP group. Second, the present study included patients who were taking α- and/or β-blockers, both of which can affect LDL-C/HDL-C. However, when we analyzed the data of 176 patients who were not taking these drugs, AHI (or L-SpO_2) was independently associated with LDL-C/HDL-C (data not shown). Third, we did not assess physical activity and daily alcohol consumption, both of which can affect LDL-C/HDL-C [46,47]. Finally, in

Table 6 – Data at baseline and after 6 months in the CPAP and non-CPAP groups

Variables	CPAP group (n = 30)			Non-CPAP group (n = 11)		
	At baseline	After 6 mo	P value	At baseline	After 6 mo	P value
BMI (kg/m^2)	26.4 ± 3.5	27.0 ± 3.2	.21	27.4 ± 3.0	26.9 ± 3.3	.16
Total sleep time (min)	388.2 ± 102.5	439.1 ± 108.3	.02	375.5 ± 86.0	–	–
AHI	50.2 ± 17.9	4.8 ± 3.7	<.001	44.2 ± 23.0	–	–
Obstructive apnea index	20.8 ± 13.3	0.3 ± 0.7	<.001	14.1 ± 13.5	–	–
Central apnea index	2.1 ± 3.1	0.4 ± 0.7	.002	0.7 ± 0.9	–	–
L-SpO_2 (%)	78.6 ± 6.3	90.3 ± 3.4	<.001	81.9 ± 8.3	–	–
Total time of SpO_2 <90% (min)	18.4 (5.4-48.4)	0.0 (0.0-0.4)	<.001	5.2 (0.8-48.1)	–	–
LDL-C (mg/dL)	119.0 ± 25.2	112.9 ± 25.7	.05	125.1 ± 25.3	113.3 ± 12.9	.10
HDL-C (mg/dL)	53.8 ± 9.3	56.8 ± 14.7	.20	49.7 ± 11.6	46.1 ± 13.6	.35
TG (mg/dL)	141.8 ± 35.4	134.3 ± 52.8	.43	102.8 ± 34.6	94.7 ± 24.3	.48
LDL-C/HDL-C	2.29 ± 0.67	2.11 ± 0.74	.02	2.65 ± 0.82	2.62 ± 0.66	.81

Data are presented as mean ± SD or median (first-third quartiles). Data at baseline and after 6 months were compared using the paired *t* test or the Wilcoxon signed rank test.

the present study, we did not evaluate the sympathetic nervous activity. Further studies are needed to clarify the association between LDL-C/HDL-C and the magnitude of the sympathetic nervous activity in OSA patients.

In conclusion, LDL-C/HDL-C was independently associated with the severity of OSA; and 6-month CPAP treatment significantly reduced LDL-C/HDL-C. These findings suggest an increase in LDL-C/HDL-C in proportion to the severity of OSA, which may contribute partly to the increased risk for cardiovascular events in OSA patients.

Conflict of Interest

The authors have reported no potential conflicts of interest with any companies/organizations.

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