L-PGDS (ng/mg · Cre)

Abbreviations: L-PGDS, lipocalin-type prostaglandin D synthase; RH-PAT, reactive hyperemia peripheral arterial tone; PSG, polysomnography; BMI, body mass index; BP, blood pressure; ESS, Epworth sleepiness scale, TST, total sleep time; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; Min SpO_2, minimum percutaneous oxygen saturation; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C reactive protein. *<0.05

Table 3. Multivariate liner regression analysis for morning urinary L-PGDS

Model 1.				
	β	r	P value	R^2 (%)
AHI, events/h	0.326	0.426	0.02	13.9
HDL-C (mg/dl)	0.297	0.214	0.02	6.4
Cumulative R^2				20.3

Model 2.				
	β	r	P value	R^2 (%)
Arousal, events/h	0.411	0.472	0.001	19.4
HDL-C (mg/dl)	0.290	0.214	0.01	6.2
Cumulative R^2				25.6

Model 3.				
	β	r	P value	R^2 (%)
3% ODI, events/h	0.291	0.384	0.03	11.2
HDL-C (mg/dl)	0.280	0.214	0.02	6.0
Cumulative R^2				17.2

Abbreviations: L-PGDS, lipocalin-type prostaglandin D synthase; β, standard regression coefficient; r, correlation coefficient; R^2, contribution rate; AHI, apnoea-hypopnoea index; HDL-C, high-density lipoprotein cholesterol; ODI, oxygen desaturation index.

Table 4. Effects of CPAP on RH-PAT index, various parameters, and L-PGDS

	Before CPAP	After 2 days of CPAP	P value
BMI	25.2 (21.0 to 39.9)	24.8 (20.8 to 39.9)	0.11
Morning systolic BP (mmHg)	126 (102 to 138)	121 (103 to 138)	0.15
Morning diastolic BP (mmHg)	80 (69 to 94)	79 (63 to 94)	0.44
Arousal index, events/h	31.6 (10.8 to 54.8)	16.8 (8.6 to 42.8)	0.0005
AHI, events/h	33.6 (20.3 to 59.6)	4.4 (0 to 8.8)	< 0.0001
3% ODI, events/h	27.9 (16.2 to 61.3)	3.5 (0 to 7.6)	< 0.0001
RH-PAT index	1.75 (1.46 to 3.91)	1.82 (1.41 to 2.83)	0.61
Blood			
Creatinine (mg/dl)	0.8 (0.6 to 1.0)	0.8 (0.6 to 1.0)	0.41
TC (mg/dl)	189 (130 to 299)	184 (132 to 293)	0.78
HDL-C (mg/dl)	53 (41 to 66)	52 (38 to 68)	0.13
TG (mg/dl)	95 (44 to 215)	98 (58 to 304)	0.30
CRP (mg/dl)	0.1 (0.0 to 0.5)	0.0 (0.0 to 0.4)	0.07
Glucose (mg/dl)	96 (75 to 133)	96 (83 to 140)	0.23
Adrenaline (pg/ml)	16 (5 to 45)	16 (5 to 36)	0.38
Noradrenaline (pg/ml)	257 (82 to 521)	216 (113 to 529)	0.31
L-PGDS (ng/ml)	480.4 (323.2 to 567.4)	466.0 (323.9 to 599.2)	0.92
Urine			
Morning L-PGDS (ng/mg・Cre)	591.2 (227 to 3274.1)	317.8 (130.3 to 1587.6)	0.007

Data are median (range).

Abbreviations: CPAP, continuous positive airway pressure; RH-PAT, reactive hyperemia peripheral arterial tone; L-PGDS, lipocalin-type prostaglandin D synthase; BMI, body mass index; BP, blood pressure; AHI, apnoea-hypopnoea index; ODI, oxygen desaturation index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C reactive protein.

FIGURE LEGENDS

Figure 1.

Comparison of morning urinary L-PGDS concentrations (A) and RH-PAT index (B) between control, moderate, and severe OSA patients. Data are shown as mean ± standard error (SE).

Abbreviations: L-PGDS, lipocalin-type prostaglandin D synthase; RH-PAT, reactive hyperemia peripheral arterial tone.

Figure 1.

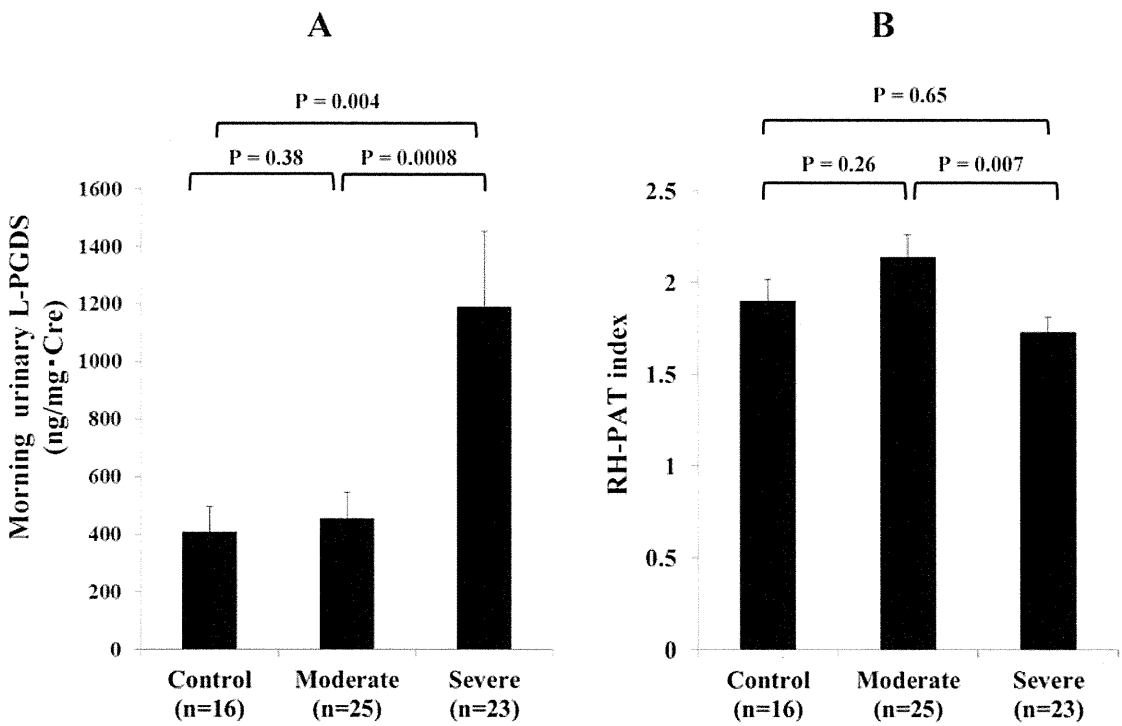


Figure 2.

Receiver operating characteristic curve analysis to assess the diagnostic validity of morning urinary lipocalin-type prostaglandin D synthase concentrations to detect severe OSA.

Figure 2.

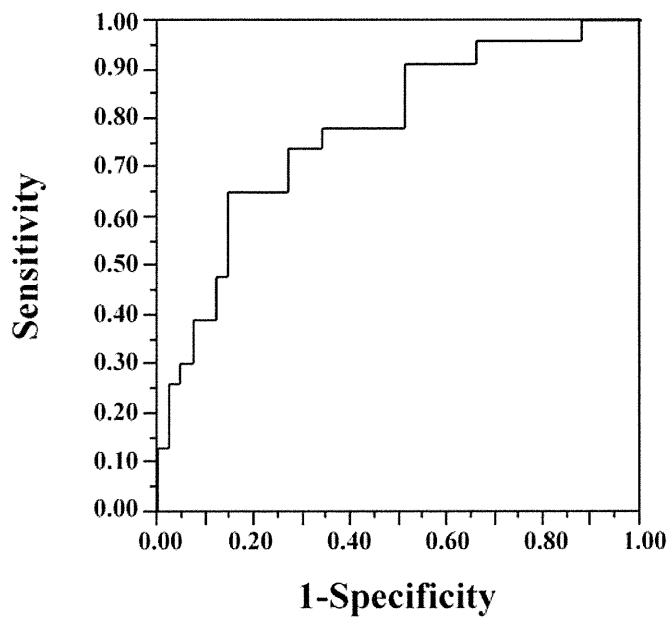


Figure 3.

Relationship between AHI (x axis) and morning urinary L-PGDS concentrations (y axis). β and *P were values after adjustment for age, gender, body mass index, and morning systolic and diastolic blood pressure.

Abbreviations: AHI, apnoea-hypopnoea index; L-PGDS, lipocalin-type prostaglandin D synthase.

Figure 3.

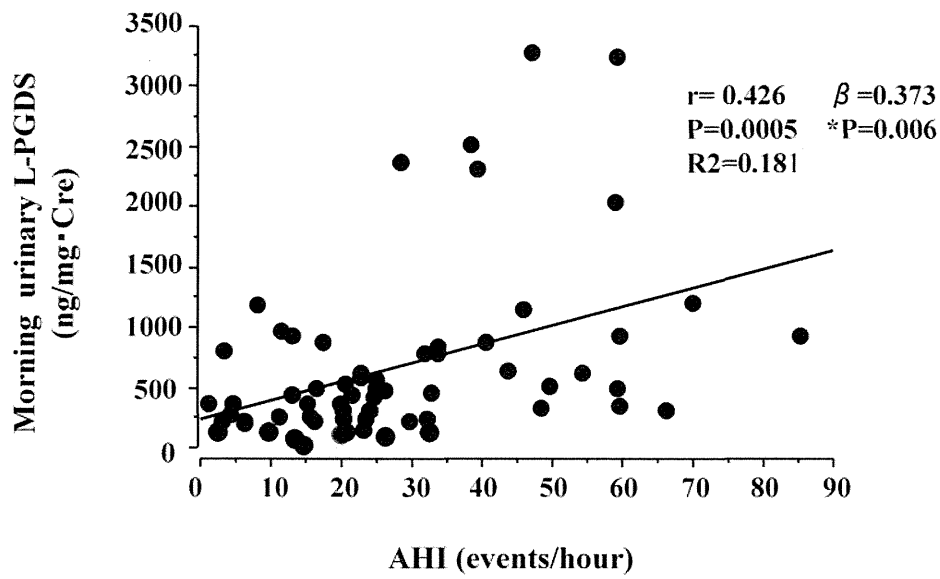


Figure 4.

Change in morning urinary L-PGDS concentrations (A) and RH-PAT index (B) before and after 2 days of CPAP. Individual data are presented.

Abbreviations: L-PGDS, lipocalin-type prostaglandin D synthase; CPAP, continuous positive airway pressure; RH-PAT, reactive hyperemia peripheral arterial tone.

Figure 4.

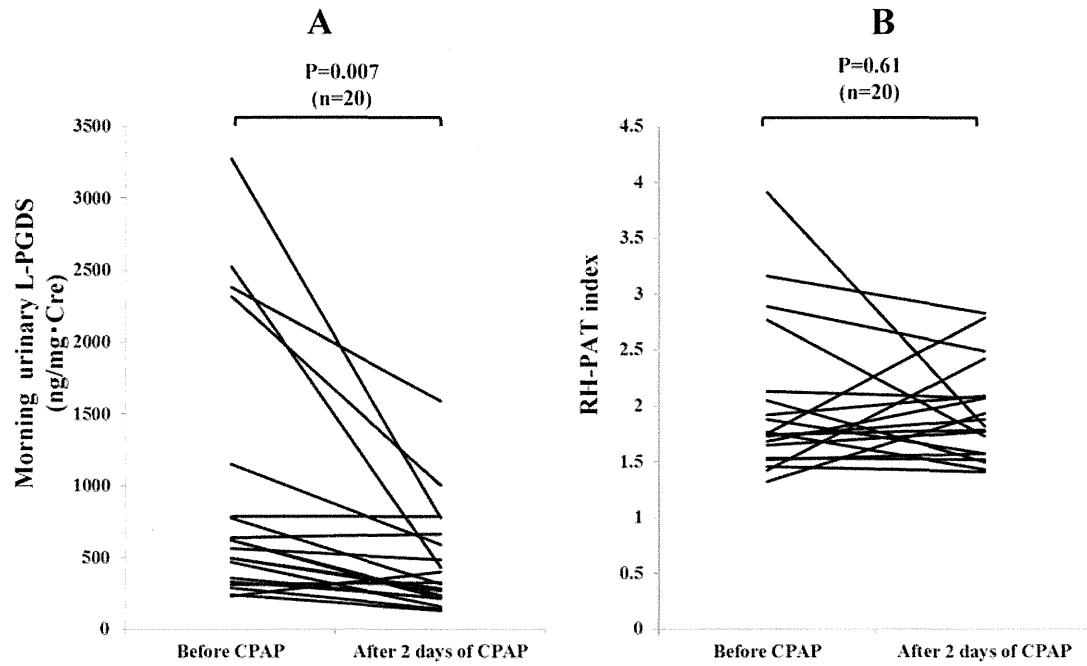
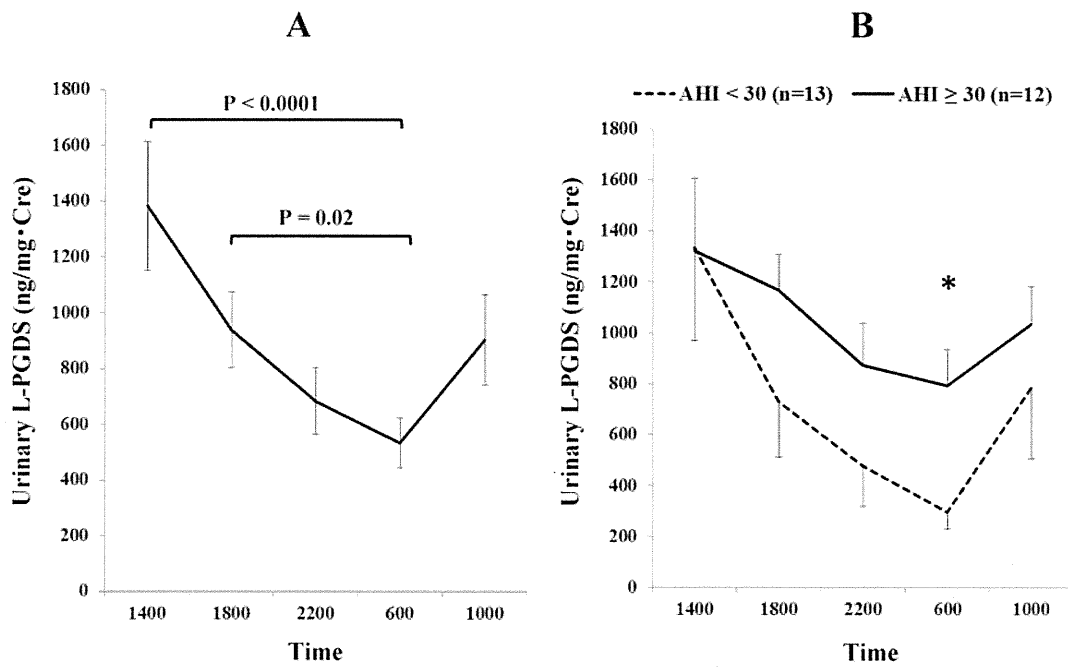


Figure 5.

Urinary L-PGDS concentrations in 25 study patients at 4-hour intervals within a day (except midnight) (A). Figure 3-B shows the comparison of circadian variations in urinary L-PGDS between patients with AHI $\geqq$ 30 (n=12) and patients with AHI < 30 (n=13). Data are shown as mean ± standard error (SE). Single asterisk indicates $p < 0.01$ between patients with AHI $\geqq$ 30 and those with AHI < 30.

Abbreviations: L-PGDS, lipocalin-type prostaglandin D synthase; AHI, apnoea-hypopnoea index.

Figure 5.


A
B
P < 0.0001
P = 0.02
AHI < 30 (n=13)
AHI ≥ 30 (n=12)
Urinary L-PGDS (ng/mg·Cre)
Time
1400
1800
2200
600
1000
0
200
400
600
800
1000
1200
1400
1600
1800
*

Original Research | March 2013

Association Between Sleep Apnea, Sleep Duration, and Serum Lipid Profile in an Urban, Male, Working Population in Japan

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Abstract

Background: Dyslipidemia is often comorbid with obstructive sleep apnea (OSA), but few population-based studies have investigated their relationship. Short sleep duration is associated with hypertension and diabetes; however, its association with dyslipidemia is not well known. We investigated relationships among OSA, sleep duration, and the lipid profile in a community-based study.

Methods: We measured the respiratory disturbance index (RDI) and sleep duration by a type 3 portable device and actigraph in 275 men in a Japanese company. Fasting blood parameters were obtained from periodic inspection data.

Results: According to Japanese criteria, 143 subjects had dyslipidemia. Percent sleep time of oxygen saturation as measured by pulse oximetry (SpO_2) < 90% and prevalence of severe OSA were greater and sleep duration and mean SpO_2 during sleep were lower in subjects with dyslipidemia than in those without. Univariate analysis showed that the RDI was positively correlated with serum triglyceride (TG) levels ($\rho = 0.20$, $P < .01$), and sleep duration was negatively correlated with serum total cholesterol (TC) levels ($\gamma = -0.13$, $P = .03$) and serum low-density lipoprotein cholesterol levels ($\gamma = -0.12$, $P = .04$). Stepwise multiple regression analysis revealed that TG was correlated with RDI ($\beta = 0.14$, $P = .02$), BMI ($\beta = 0.20$, $P < .01$), and alcohol intake ($\beta = 0.20$, $P < .01$), and that TC was correlated with sleep duration ($\beta = -0.13$, $P = .03$), age ($\beta = 0.15$, $P = .02$), and waist/hip ratio ($\beta = 0.15$, $P = .02$).

Conclusions: Short sleep duration was associated with TC levels and RDI was positively associated with TG levels among working-aged men in an urban Japanese company. Correcting the status of OSA and/or short sleep duration might improve the lipid profile and cardiovascular consequences.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of apnea and hypopnea during sleep, which cause intermittent hypoxia and frequent arousals. Many studies have shown that OSA is a risk factor for hypertension, cardiovascular consequences,[1] diabetes mellitus (DM),[2,3] and metabolic syndrome.[4,5] A relationship between OSA and lipid metabolism was shown in animal models, in which intermittent hypoxia aggravated lipid metabolism.[6,7]

In human studies, most of which were clinic based, dyslipidemia (DL) was found more frequently in patients with OSA than in

subjects without OSA. However, it is still controversial whether OSA correlates independently with the serum lipid profile or what components of the lipid profile are associated with OSA.[4,9-15]

Similar to findings for OSA, a large number of studies demonstrated that short sleep duration is associated with hypertension,[16,17] cardiovascular consequences,[18] DM,[19,20] and metabolic syndrome.[21,22] On the other hand, the results of studies about relationships between sleep duration and the serum lipid profile were inconsistent.[21-27] It should be noted that all but one of these studies evaluated sleep duration by questionnaire, which is unacceptable as an objective measurement.[28]

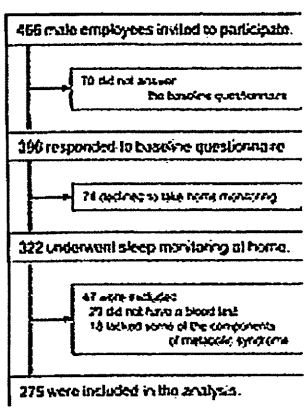
Thus, the relationships between lipid metabolism and OSA or sleep duration are not well known. We previously reported that sleep duration was significantly shorter in subjects with severe OSA than in those with mild or no OSA.[29] To our knowledge, however, the associations among sleep duration, OSA, and lipid metabolism have not been evaluated simultaneously. We hypothesized that OSA and sleep duration affect the lipid profile independently of other confounding factors. To test this hypothesis, we analyzed data from a cross-sectional epidemiologic health survey of middle-aged male employees in Japan, in whom we measured sleep duration and the respiratory disturbance index (RDI) by portable home-monitoring devices.[30]

Materials And Methods

Study subjects were male employees of an urban wholesale company in Japan as described elsewhere in detail.[30] All of the male employees were invited to participate in the study between January 2004 and December 2005. Of the 466 male subjects who were invited to participate, 396 answered the baseline questionnaire (85.0% of eligible subjects).

Of the questionnaire responders, 322 (69.1%) underwent monitoring with home-based portable monitors. There were no significant differences in characteristics (such as age, BMI, Epworth sleepiness scale scores, and numbers of current smokers, habitual snorers, alcohol drinkers, and subjects with hypertension) between eligible subjects and participants.[30] Of those 322 employees, 47 were further excluded from the analysis either because blood parameters were not measured (n = 29) or because some of the components of metabolic syndrome, such as blood parameters and waist circumference, were not determined (n = 18) (Fig 1). There was no shift worker in this population. The prevalence of DL, distribution of OSA severity, and mean duration of weekly sleep did not differ significantly between the included subjects and the excluded subjects ($P = .69$ and 0.85 by χ^2 tests and $P = .63$ by unpaired t test, respectively).

Figure 1. Flowchart of study subjects.



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We analyzed data on the remaining 275 subjects regarding the relationships among the lipid profile, sleep duration, and OSA. Written informed consent was obtained from all subjects. The study protocol was approved by the University Graduate School and Faculty of Medicine Ethics Committee, institutional review board approval number E-37.

Trained research staff performed measurements of weight, waist circumference, and BP. BP was decided based on the average of

the last three of seven measurements made after the subjects rested a few minutes in a sitting position. Height and fasting blood parameters, including fasting blood glucose (FBG), serum triglyceride (TG) levels, serum total cholesterol (TC) levels, and serum high-density lipoprotein cholesterol (HDL-C) levels, were obtained retrospectively from periodic inspection data. When TG levels were < 400 mg/dL, serum low-density lipoprotein cholesterol (LDL-C) levels were calculated by the Friedewald formula (LDL-C = TC − HDL-C − TG/5).

According to diagnostic criteria of DL for Japanese people,[31] DL was defined by LDL-C ≥ 140 mg/dL, HDL-C < 40 mg/dL, and/or TG ≥ 150 mg/dL, or by the current use of lipid-lowering drugs. Hypertension was defined by BP ≥ 140/90 mm Hg or by the current use of antihypertensive drugs. DM was defined by FBG ≥ 126 mg/dL or by use of glucose-lowering drugs.

Each subject wore an actigraph (Actiwatch AW-Light; Koninklijke Philips Electronics N.V.) for 7 days to estimate sleep-wake time[32] and a type 3 portable monitor (PM) (Morpheus; Teijin Pharma Ltd, which is the same as Somté; Compumedics Ltd) for two nights at home as an alternative to polysomnography in the diagnosis of OSA.[33] Sleep duration was estimated from analysis of actigraphy tracings in conjunction with a sleep diary. RDI (number of apnea and hypopnea episodes per hour of the analyzed time) was calculated from data acquired from the actigraph and the PM. PM records were inspected visually and scored by at least two medical doctors specialized in respiratory medicine. Apnea (cessation of breathing for at least 10 s) and hypopnea (> 50% reduction in the amplitude of nasal pressure or respiratory effort associated with > 3% reduction in oxygen saturation as measured by pulse oximetry (SpO_2) for ≥ 10 s) were scored while assessors were blinded to other information except for sleep-wake time by actigraphy. Data without SpO_2 values, illegible recordings, and data from recordings of < 2 h were excluded from analysis. When data from both recorded nights were available, records from the second night were analyzed further. No OSA and mild, moderate, and severe OSA were defined by RDI < 5, 5 to < 15, 15 to < 30, and ≥ 30, respectively. The modified Japanese version of the Epworth Sleepiness Scale (ESS) was used to assess subjective sleepiness. A separate sleep diary was also completed during the survey period.

Results are expressed as the mean plus or minus SD or the number of subjects. We compared the differences in characteristics between the subjects with DL and those without DL. Following testing for normality and equality of variance, continuous variables were compared by unpaired *t* tests, the Welch test, or the Mann-Whitney *U* test, and categorical variables were compared by χ^2 tests. It has been reported that the prevalence of DL and that of severe OSA were approximately 50%[34] and 7%,[35] respectively, among adult men in the general population and that the rate of DL among subjects with severe OSA was 70%.[5] Based on these data, the sample size was set to achieve 80% power at a 5% significance level, and it was determined that there should be a sample size of 40 patients with severe OSA. Subjects were also categorized into four groups by weekly, mean sleep duration as follows: sleep duration < 5 h, 5 to < 6 h, 6 to < 7 h, and ≥ 7 h; two subjects slept longer than 8 h. The significance of an intergroup difference was determined by an analysis of variance, Welch test, or Wilcoxon rank-sum test for the continuous variables following testing for normality and equality of variance. When a significant difference was observed, the Tukey-Kramer test or Steel-Dwass test was performed. For categorical variables, the significance of an intergroup difference was determined by χ^2 tests.

To test our hypothesis that the serum lipid profile was associated with OSA and sleep duration, we performed univariate and multivariate analyses. First, relationships between each serum lipid level and the other variables were analyzed by Pearson correlation coefficients or Spearman rank correlation coefficients following testing for normality and equality of variance. Next, to identify those variables that could best predict each serum lipid level, stepwise multiple regression analyses were performed and coefficients of determination were calculated. The variables entered in these analyses were those yielding a *P* value < .10 by univariate analysis, and when two independent variables had very strong collinearity ($\gamma > 0.70$), one was selected. Cutoff values set in the stepwise analysis were *P* = .05 for both the forward and backward processes. Interactions between any two sets of the variables remaining in the stepwise models were assessed by centered cross terms. *P* values < .05 were considered statistically significant. All analyses were performed using JMP, version 9.0.0 (SAS Institute, Inc).

Results

Characteristics of study subjects with and without DL are shown in Table 1. There were only four subjects whose LDL-C could not be calculated because of TG ≥ 400 mg/dL. Of the 275 subjects, 148 (53.8%) had DL. Besides values for the lipid profile and anthropometric parameters related to obesity, percent sleep time of SpO_2 <90% (%T < 90), systolic BP, diastolic BP, FBG, prevalence of severe OSA, and rate of current smoking were significantly greater, mean SpO_2 during sleep and sleep duration were significantly lower, and RDI tended to be greater in the subjects with DL than in those without DL. Thirteen subjects with DL (8.8%)

were being treated with lipid-lowering drugs. While they had significantly higher TG levels than the others (mean ± SD, 215.1 ± 126.7 mg/dL vs 118.2 ± 75.9 mg/dL; $P < .001$), TC, HDL-C, and LDL-C levels did not differ. Characteristics of the four groups categorized by sleep duration are presented in Table 2. TC level was greater in the subjects who slept 5-< 6 h than in those who slept ≥ 7 h. LDL-C levels tended to differ among the categories. All subjects with moderate to severe OSA slept < 7 h, and 7 (44%) of the 16 patients with severe OSA slept < 5 h. On the other hand, 14 of the 19 subjects (73.7%) who slept ≥ 7 h did not have OSA (Table 2).

Table 1 —Characteristics of Study Subjects With and Without Dyslipidemia

View Large | Save Table

Table 2 —Characteristics of Study Subjects Categorized by Sleep Duration

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The associations between serum lipid levels and the other variables examined are summarized in Table 3. TG level was positively and significantly correlated with BMI, neck circumference, waist/hip ratio, RDI, %T < 90, FBG, diastolic BP, and alcohol intake, negatively with mean SpO_2 during sleep and lowest SpO_2 during sleep, and tended to be correlated with current smoking. TC level was positively and significantly correlated with age, BMI, neck circumference, waist/hip ratio, RDI, FBS, systolic BP, and diastolic BP, negatively with sleep duration, and tended to be correlated with the lowest SpO_2 during sleep and a history of cardiovascular disease (CVD). HDL-C was negatively correlated with BMI, neck circumference, waist/hip ratio, and current smoking, positively with mean SpO_2 during sleep and with alcohol intake, and tended to be correlated with %T < 90. LDL-C was positively correlated with age, BMI, neck circumference, and waist/hip ratio, negatively with sleep duration and alcohol intake, and tended to be correlated with RDI and FBS.

Table 3 —Correlation Coefficients With Serum Lipid Levels

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With the exception of neck circumference and diastolic BP, these variables were entered into stepwise multiple regression analysis for predicting each serum lipid level for strong collinearity with BMI or systolic BP. These analyses identified BMI ($\beta = 0.20$, $P = .002$), RDI ($\beta = 0.14$, $P = .024$), and alcohol intake ($\beta = -0.20$, $P < .001$) as independent explanatory variables for TG level; age ($\beta = 0.15$, $P = .019$), waist/hip ratio ($\beta = 0.15$, $P = .019$), and sleep duration ($\beta = -0.13$, $P = .030$) for TC level; and BMI ($\beta = -0.36$, $P < .001$), alcohol intake ($\beta = 0.13$, $P = .026$), and current smoking ($\beta = -0.22$, $P < .001$) for HDL-C level (Tables 4-8). Stepwise analysis gave no multivariate model that showed statistical significance for LDL-C, but sleep duration ($\beta = -0.12$, $P = .052$) tended to correlate with LDL-C level (Table 9). The results of analysis using neck circumference instead of BMI are shown in Tables 5 and 8. Almost none of the results changed when systolic BP was changed to diastolic BP. There was no significant interaction between any of two sets of the variables in each stepwise model. Even excluding the 13 subjects who used lipid-lowering drugs, the results of stepwise regression analysis did not change except that current smoking became correlated with TG level.

Table 4 —Stepwise Linear Regression Model to Predict Serum Triglyceride Levels: Model 1

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Table 5 —Stepwise Linear Regression Model to Predict Serum Triglyceride Levels: Model 2

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Table 6 —Stepwise Linear Regression Model to Predict Serum Total Cholesterol Levels

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Table 7 —Stepwise Linear Regression Model to Predict Serum HDL Cholesterol Levels: Model 1

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Table 8 —Stepwise Linear Regression Model to Predict Serum HDL Cholesterol Levels: Model 2

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Table 9 —Stepwise Linear Regression Model to Predict Serum LDL Cholesterol Levels

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Discussion

This was a cross-sectional epidemiologic survey that used portable home-monitoring devices for assessment of sleep duration and OSA, and, to our knowledge, is the first study to evaluate the relationship among the lipid profile, OSA, and sleep duration simultaneously. This study of middle-aged men demonstrated that TG level was correlated with RDI ($P = .02$), BMI ($P < .01$), and alcohol intake ($P < .01$), and that TC level was correlated with sleep duration ($P = .03$), age ($P = .02$), and waist/hip ratio ($P = .02$).

DL is one of the major risk factors for CVD. Among lipid levels clinically measured, LDL-C has been shown to be the strongest risk factor for CVD and TG is also believed to advance atherosclerotic change.[36-38] Recently, two randomized, placebo-controlled studies reported improvements in the serum lipid profile of patients with OSA by CPAP therapy. Phillips et al[39] reported that 8 weeks of CPAP therapy for severe OSA decreased postprandial TG and TC levels, but that fasting TG levels did not change significantly with such treatment. However, Sharma et al[40] reported improvements in fasting TG, TC, and LDL-C levels after 3 months of CPAP therapy for OSA of moderate or greater severity. Therefore, it is still controversial how the lipid profile is affected by CPAP therapy in patients with OSA. On the other hand, severe OSA was related to short sleep duration (Table 2). It has been reported that sleep duration lengthened after adoption of CPAP therapy for OSA.[41] Therefore, the improvements in TC and/or LDL-C levels by CPAP therapy might be partly caused by extension of sleep duration. Indeed, daily use of CPAP for > 5 h in the subanalysis in the Sharma et al study induced improvements in fasting TG, LDL-C, and TC levels[40]; however, these values did not change significantly with 4.4 h of CPAP treatment per day in the report by Phillips et al.[39]

Besides obesity, increases in serum free-fatty-acid (FFA) levels by sympathetic nervous tone,[42] activation of TG biosynthesis in liver through a pathway from hypoxia-inducible factor-1,[6,7,14] and decreases in lipoprotein lipase activity[43] have been advocated as possible mechanisms for the elevation of serum TG levels in OSA patients. Barceló et al[44] reported that patients with OSA had higher serum FFA levels than control subjects, and that this increase in serum FFAs may result in elevated TG levels. Several studies have reported associations between TG level and OSA, but most were clinically based.[4,9,11,14,15] Newman et al[10] reported that in an epidemiologic survey, a correlation between TG level and apnea-hypopnea index was seen only among female patients. Therefore, our study is the first to report a relationship between TG level and OSA in a general male population.

To our knowledge, seven studies have reported associations between the lipid profile and sleep duration,[21-27] but their results were inconsistent. In addition, six of the seven studies estimated sleep duration only by a questionnaire. Our study population was comparable in age to that of Bjorvan et al[23] and relatively close to that of Choi et al.[21] Considering that the subjects in our study included few long sleepers (≥ 8 h), our findings were consistent with the findings of those reports. Two of the seven studies analyzed data specifically according to sex[24,25] and both reported a relationship between sleep duration and HDL-C levels in a female population. It is known that features of the lipid profile differ according to sex[45]; the influence of sleep duration on lipid metabolism may also differ between men and women. Katano et al[27] studied 4,356 healthy workers (including 800 women) from Japan. They studied the correlation between sleep duration and DL and found that those with the lowest sleep duration (< 6 h/night) had DL, which supports our results.

There have been several reports of close relationships between OSA and metabolic syndrome, including several factors that compose metabolic syndrome.[4,5,8,15] Data showed that 3 months of CPAP therapy lowers BP and partially reverses metabolic abnormalities and metabolic syndrome in patients with OSA.[40] In that subanalysis, subjects with mean adherence to CPAP for ≥ 5 h had superior improvements in metabolic parameters to those with mean adherence to CPAP of < 5 h.

Thus, considering previous reports, OSA[4,9,10,12-15] and sleep duration,[21-27] including the treatment duration for OSA,[40] may have significant effects on metabolic parameters, including blood lipid levels. In addition to relationships with metabolic syndrome,[29] BP,[46]

and blood glucose, we have reported relationships among sleep apnea, sleep duration, and lipidemia in this study. Thus, we propose that sleep duration should be considered for relationships between OSA and metabolic parameters whether these conditions are treated or untreated.

In this study, mean sleep duration in urban subjects in Japan was 6.0 h. It was reported that the average sleep duration by self report was 7.2 h/d among middle-aged Japanese people.[48] Actigraph-measured sleep duration was reported to be shorter than self-reported sleep.[28] In addition, recently it was reported that 30% of employed civilian workers in the United States were short sleepers (sleep duration < 6 h/d).[49] Although it is said that the sleep duration among Japanese is one of the shortest in the world,[50] subjects in Western countries might also have developed sleep patterns similar to those shown in the present study. Therefore, our results might apply to urban subjects in Western countries.

Limitations of this study should be mentioned. First, we cannot know causality or the mechanisms of our findings because this was a cross-sectional study. Results of the present study were simple epidemiologic data. Second, the study population was limited to working-age men from an urban company in Japan and included few long sleepers (≥ 8 h). This bias of the study population could have affected the results and they cannot be generalized to women, the elderly, long sleepers, or other ethnic groups. However, limiting the characteristics of study subjects might have enabled us to more clearly identify the relationships under study because lipid metabolism would likely differ considerably in study subjects with a more heterogeneous background. Third, we could not estimate the lifestyles of the participants, namely, dietary habits, exercise habits, and so forth, which are believed to influence lipid metabolism. It is very difficult to evaluate these factors quantitatively by a questionnaire alone. Subjects of the present study, however, were limited to those employed by one company in the service industry, so we might think that their lifestyles, physical workload, and socioeconomic status were relatively similar compared with subjects in previous epidemiologic cohort studies. In addition, the indices associated with obesity, which are usually believed to strongly reflect a daily energy balance, did not differ according to sleep duration. Fourth, the study population was small, especially regarding the number of patients with severe OSA, because this was an exhaustive survey and the number of company employees that we surveyed was smaller than the calculated sample size. Therefore, future testing should include many more subjects among which there is a sufficient number of patients with severe OSA that would correspond to the estimated sample size. Finally, we did not perform polysomnography. However, the interscorer and night-to-night reliability of the RDI were excellent (interclass correlation coefficients of 0.98 and 0.95, respectively).[30] In addition, it has been reported that the nonattached PM is reliable under the specified conditions in which our study was conducted.[33]

In conclusion, we showed that sleep duration was negatively associated with TC levels and that RDI was positively associated with TG levels in middle-aged men working in an urban Japanese company. For working-age men with DL, CPAP therapy for severe OSA may improve the lipid profile and subsequently reduce risk of cardiovascular events. Further study is needed to determine the association among lipid metabolism, OSA, and sleep duration. This will require surveys of various populations with different backgrounds.

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Author contributions: Dr Chin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Toyama: contributed to data analysis and interpretation, drafted the manuscript, and served as principal author.

Dr Chin: contributed to the design and supervision of the study.

Dr Chihara: contributed to drafting the manuscript and approved the manuscript.

Ms Takegami: performed the primary statistical analysis and approved the manuscript.

Dr Takahashi: evaluated records of portable devices visually and clinically and approved the manuscript.

Dr Sumi: evaluated records of portable devices visually and clinically and approved the manuscript.

Dr Nakamura: evaluated records of portable devices visually and clinically, and approved the manuscript.

Ms Nakayama-Ashida: contributed to data acquisition and approved the manuscript.

Dr Minami: contributed to data acquisition and approved the manuscript.

Ms Horita: contributed to data acquisition and approved the manuscript.

Dr Oka: contributed to data acquisition and approved the manuscript.

Dr Wakamura: contributed to data acquisition and approved the manuscript.

Dr Fukuhara: performed the primary statistical analysis and approved the manuscript.

Dr Mishima: contributed to the study design, and approved the manuscript.

Dr Kadotani: contributed to the study design and data acquisition and approved the manuscript.

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CVD	cardiovascular disease
DL	dyslipidemia
DM	diabetes mellitus
ESS	Epworth sleepiness scale
FBG	fasting blood glucose
FFA	free fatty acid
HDL-C	serum high-density lipoprotein cholesterol
LDL-C	serum low-density lipoprotein cholesterol
OSA	obstructive sleep apnea
%T < 90	percent sleep time of oxygen saturation as measured by pulse oximetry < 90%
PM	type 3 portable monitor
RDI	respiratory disturbance index
SpO_2	oxygen saturation as measured by pulse oximetry
TC	serum total cholesterol
TG	serum triglyceride

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Association between Plasma Neutrophil Gelatinase Associated Lipocalin Level and Obstructive Sleep Apnea or Nocturnal Intermittent Hypoxia

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Abstract

Background: Both obstructive sleep apnea (OSA) and a novel lipocalin, neutrophil gelatinase associated lipocalin (Ngal), have been reported to be closely linked with cardiovascular disease and loss of kidney function through chronic inflammation. However, the relationship between OSA and Ngal has never been investigated.

Objectives: To evaluate the relationship between Ngal and OSA in clinical practice.

Methods: In 102 patients, polysomnography was performed to diagnose OSA and plasma Ngal levels were measured. The correlations between Ngal levels and OSA severity and other clinical variables were evaluated. Of the 46 patients who began treatment with continuous positive airway pressure (CPAP), Ngal levels were reevaluated after three months of treatment in 25 patients.

Results: The Ngal level correlated significantly with OSA severity as determined by the apnea hypopnea index ($r = 0.24$, $p = 0.01$) and 4% oxygen desaturation index (ODI) ($r = 0.26$, $p = 0.01$). Multiple regression analysis showed that the Ngal level was associated with 4%ODI independently of other clinical variables. Compliance was good in 13 of the 25 patients who used CPAP. Although the OSA (4%ODI: 33.1 ± 16.7 to 1.1 ± 1.9/h, $p < 0.01$) had significantly improved in those with good compliance, the Ngal levels were not significantly changed (60.5 ± 18.1 before CPAP vs 64.2 ± 13.9 ng/ml after CPAP, $p = 0.27$).

Conclusions: Plasma Ngal levels were positively associated with the severity of OSA. However, the contribution rate of OSA to systemic Ngal secretion was small and changes in Ngal levels appeared to be influenced largely by other confounding factors. Therefore, it does not seem reasonable to use the Ngal level as a specific biomarker of OSA in clinical practice.

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Introduction

Neutrophil gelatinase associated lipocalin (Ngal), also known as lipocalin 2, is a 25-kDa secretory glycoprotein that was originally identified in human neutrophils. This protein was originally known as an innate immunity antibacterial factor released by activated neutrophils. [1,2] It has also become known to be produced by renal tubular cells in response to different types of injury. [3] Based on experimental and clinical findings, Ngal is widely considered as an excellent indicator of acute and chronic kidney injury.[3–7] Moreover, because this protein is also released by endothelial cells and failing myocardium, a close relationship between blood Ngal levels and heart failure or cardiovascular diseases has been suggested.[8–10].

Obstructive sleep apnea (OSA) is a highly prevalent disorder, affecting about 4–20% of adults and is characterized by repetitive episodes of partial or complete obstruction of the upper airway during sleep associated with transient oxygen desaturation.[11–13] Accumulating clinical evidence suggests that OSA is an independent risk factor for cardiovascular disease and loss of kidney function through nocturnal hypoxia and chronic inflammation.[14–17] From an in vitro model of OSA, it was suggested that the pro-inflammatory transcription factor, nuclear factor-kappa B (NF-κB), plays an important role in the inflammatory