knew that plasma catecholamine levels were unstable and easily variable, the usefulness of which was difficult to understand, we measured plasma catecholamine levels. In the present study, urinary L-PGDS concentrations were also correlated with plasma adrenalin and noradrenalin. Therefore, sympathetic overactivity in OSA [40, 41] might also induce increases in urinary L-PGDS. The relationship between urinary catecholamine and L-PGDS should be studied in the future. We also found that HDL-C was a significant determinant of morning urinary L-PGDS. Miwa et al. reported that L-PGDS played a role in lipid transport [42]. Therefore, HDL-C might be a significant factor along with the arousal index or the AHI in determining the urinary L-PGDS levels.

The present study is the first to demonstrate the circadian variations in urinary L-PGDS concentrations in OSA. Urinary LPGDS values in both severe and non-to-moderate OSA were highest and at the same levels at 14:00, with the lowest values at 6:00 in both groups. However, only 6:00 urinary L-PGDS values significantly correlated with the AHI and were significantly higher in those with severe OSA compared with subjects with AHI < 30. In the current study, we showed that morning urinary L-PGDS concentrations were positively correlated with the AHI, 3% ODI, and arousal index. Through the circadian change in L-PGDS, we propose that L-PGDS might be a stress marker that increases during daytime and decreases during sleep, whereas the decrease in L-PGDS levels in OSA, especially severe OSA, during sleep is attenuated because intermittent or sustained hypoxia, sleep

fragmentation, and arousals caused by OSA lead to increased stress, including oxidative stress and sympathetic activation during sleep [39]. Additionally, occurrences of CVDs peak from morning to noon, while OSA patients have an increased risk of myocardial infarction between 0:00 and 6:00 compared with non OSA patients [43]. These circadian rhythms mimic the pattern of urinary L-PGDS in this study (Figure 4-A).

In the current study, we did not detect a significant relation between plasma L-PGDS and the AHI, whereas morning urinary L-PGDS levels were significantly positively correlated with the AHI. Although the reason for this discrepancy is unclear, Hirawa et al. reported that urinary protein excretion in the early stage of DM was correlated with urinary L-PGDS excretion, but not with plasma L-PGDS levels [44]. In addition, serum L-PGDS levels were not shown to be associated with the AHI [25]. The influence of OSA, such as intermittent hypoxemia, might have a significant effect on the renal system, which induced the differences in values between plasma and urinary L-PGDS. The differences in L-PGDS levels between plasma and urine should be studied in animal models. Furthermore, we did not collect peripheral blood samples at 22:00 in the current study. The night plasma L-PGDS concentrations or the differences between morning and night plasma L-PGDS may contribute to elucidating the relation between plasma L-PGDS and OSA.

This study had some limitations. Firstly, the sample size was small. However, the differences in the urinary L-PGDS values between control, moderate, and severe OSA

patients were large and therefore the results could be considered significant and definitive. Secondly, it is unclear whether the effect of CPAP on the PGD_2 system would persist over the long term. A long-term prospective study is needed to clarify this issue. Thirdly, we could not conduct a comparison between CPAP users and sham CPAP users. A future study that makes comparisons between CPAP users and sham CPAP users is warranted. Fourthly, we used spot urine samples for measurement of L-PGDS. There is a possibility that several factors such as reabsorption at tubules and physical activity influenced the urinary L-PGDS concentrations. However, use of overnight spot urine for measurement of L-PGDS has been validated because of the correlation between L-PGDS values of overnight urine and 24-hour collected urine [44]. Therefore, we believe overnight spot urine sampling is sufficient to evaluate the role of L-PGDS in OSA.

In conclusion, based on our results, in addition to circadian data, urinary L-PGDS might be a moderately useful marker for severe OSA. From this preliminary data, urine L-PGDS measurement may be a simple and cost-effective method to screen for and manage severe OSA. This method should be tested in unselected samples in the future because it is often difficult, costly, and time consuming to find patients with OSA while the number of OSA patients who should be treated is large.

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Tables

Table 1. Patients' characteristics, PSG data, and laboratory data according to severity of obstructive sleep apnoea (OSA)

	Control (n=16)	Moderate OSA (n=25)	Severe OSA (n=23)	P value
Age	47.5 (21 to 76)	55 (31 to 74)	55 (27 to 78)	0.12
Male	12 (75.0)	21 (84.0)	21 (91.3)	0.39
BMI	26.0 (20.4 to 35.8)	24.5 (20.2 to 34.8)	26.6 (21.6 to 39.9)	0.10
Waist circumference (cm)	87 (76 to 118)	90 (78 to 113)	94 (82 to 120)	0.13
Morning systolic BP (mmHg)	114 (95 to 136)	118 (99 to 139)	127 (96 to 150)[a,b]	0.003
Morning diastolic BP (mmHg)	70 (58 to 91)	74 (57 to 96)	80 (69 to 97)[a,b]	0.0004
Ex-smoker	9 (56.3)	12(48.0)	17 (73.9)	0.18
ESS	14 (1 to 24)	12 (2 to 19)	12 (4 to 20)	0.13
Comorbidity				
Hypertension	3 (18.8)	10 (40.0)	10 (47.8)	0.25
Dyslipidemia	9 (56.3)	17 (68.0)	15(65.2)	0.74
Diabetes mellitus	2 (12.5)	2 (8.0)	2 (8.7)	0.88
PSG data				
TST, min	408.5 (256.5 to 510)	389.0 (205.5 to 515.5)	378.0 (240.5 to 499)	0.56
Sleep efficiency, %	81.1 (63.3 to 94.4)	76.6 (42.9 to 94.2)	72.9 (50.4 to 96.4)	0.50
Arousal index, events/h	17.8 (9.5 to 26.7)	22.2 (10.8 to 46.5)	44.3 (12.6 to 61.2)[a,b]	< 0.0001
AHI, events/h	7.3 (1.2 to 14.8)	22.7 (15.2 to 29.8)[a]	47.2 (31.9 to 85.4)[a,b]	< 0.0001
3% ODI, events/h	5.3 (0.5 to 14.1)	17.4 (10.1 to 27.2)[a]	48.0 (26.9 to 86.4)[a,b]	< 0.0001
Min SpO_2, %	90.5 (81 to 97)	81.5 (73 to 90)[a]	75.0 (61 to 86)[a,b]	< 0.0001
SpO_2 < 90%, %TST	0 (0 to 5.0)	2.5 (0 to 8.1)	11.9 (1.2 to	< 0.0001

			87.7)[a,b]	
RH-PAT index	1.91 (1.30 to 2.87)	2.00 (1.32 to 3.91)	1.65 (1.42 to 3.23)[b]	0.02
Blood				
Creatinine (mg/dl)	0.8 (0.4 to 1.0)	0.8 (0.6 to 1.1)	0.8 (0.6 to 1.1)	0.49
TC (mg/dl)	204 (125 to 241)	197 (130 to 255)	199 (141 to 299)	0.58
HDL-C (mg/dl)	51 (35 to 86)	53 (40 to 93)	49 (30 to 82)	0.30
TG (mg/dl)	103 (54 to 245)	100 (44 to 334)	132 (70 to 286)	0.21
CRP (mg/dl)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.5)[a,b]	0.004
Glucose (mg/dl)	87 (81 to 114)	95 (75 to 146)	96 (85 to 121)	0.07
Adrenaline (pg/ml)	14 (5 to 31)	16 (5 to 30)	16 (5 to 45)	0.65
Noradrenaline (pg/ml)	241 (67 to 465)	252 (91 to 398)	261 (82 to 569)	0.52
L-PGDS (ng/ml)	422.0 (291.7 to 588.6)	469.3 (270.3 to 657.0)	491.4 (343.3 to 726.0)	0.09
Urine				
Morning L-PGDS (ng/mg・Cre)	262.1 (21.3 to 1178.6)	371.7 (92.3 to 2378.2)	784.7 (124.4 to 3274.1)[a,b]	0.0009
Night L-PGDS (ng/mg・Cre)	745.8 (30.5 to 1754.0)	659.5 (78.9 to 2937.9)	958.3 (221.0 to 5621.8)	0.19

Data are median (range) or number (%)

[a] $p < 0.0167$ versus control, [b] $p < 0.0167$ versus moderate OSA

Abbreviations: 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; RH-PAT, reactive hyperemia peripheral arterial tone; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C reactive protein; L-PGDS, lipocalin-type prostaglandin D synthase.

Table 2. Associations of L-PGDS level and RH-PAT index with patients' characteristics, PSG data, and biomarkers

	Morning urinary L-PGDS (ng/mg · Cre)		Plasma L-PGDS (ng/ml)		RH-PAT index	
	r	P value	r	P value	r	P value
Age (years)	0.164	0.20	0.362	0.003	0.074	0.56
Gender (Male)	-0.013	0.92	0.048	0.71	-0.160	0.21
BMI (kg/m^2)	-0.060	0.64	-0.132	0.31	-0.135	0.29
Waist circumference (cm)	-0.062	0.63	-0.076	0.55	-0.081	0.53
Morning systolic BP (mmHg)	0.394	0.001*	0.279	0.03*	-0.150	0.24
Morning diastolic BP (mmHg)	0.323	0.009*	0.274	0.03*	0.001	0.99
ESS	-0.139	0.27	-0.035	0.78	0.075	0.56
Arousal, events/h	0.472	< 0.0001*	0.220	0.08	-0.268	0.03*
AHI, events/h	0.426	0.0005*	0.180	0.16	-0.241	0.06
3% ODI, events/h	0.384	0.002*	0.173	0.18	-0.244	0.054
Mini SpO_2, %	-0.112	0.38	0.099	0.44	0.046	0.72
SpO_2 < 90%, %TST	0.128	0.31	0.017	0.90	-0.190	0.14
RH-PAT index	-0.068	0.59	0.030	0.82	-	-
Creatinine (mg/dl)	0.052	0.68	0.256	0.04	-0.067	0.60
TC (mg/dl)	0.189	0.14	0.233	0.07	-0.003	0.98
HDL-C (mg/dl)	0.214	0.09	0.045	0.73	0.079	0.54
TG (mg/dl)	-0.067	0.60	0.170	0.18	0.134	0.30
CRP (mg/dl)	0.071	0.58	0.083	0.52	-0.132	0.30
Glucose (mg/dl)	0.158	0.22	-0.161	0.21	-0.143	0.27
Adrenaline (pg/ml)	0.310	0.02*	0.220	0.10	0.018	0.89
Noradrenaline (pg/ml)	0.329	0.008*	0.149	0.25	0.128	0.32
Plasma L-PGDS (ng/ml)	0.228	0.07	-	-	0.030	0.82
Morning urinary L-PGDS (ng/mg · Cre)	-	-	0.228	0.07	-0.068	0.59
Night urinary	0.868	< 0.0001*	0.090	0.51	0.050	0.71

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.

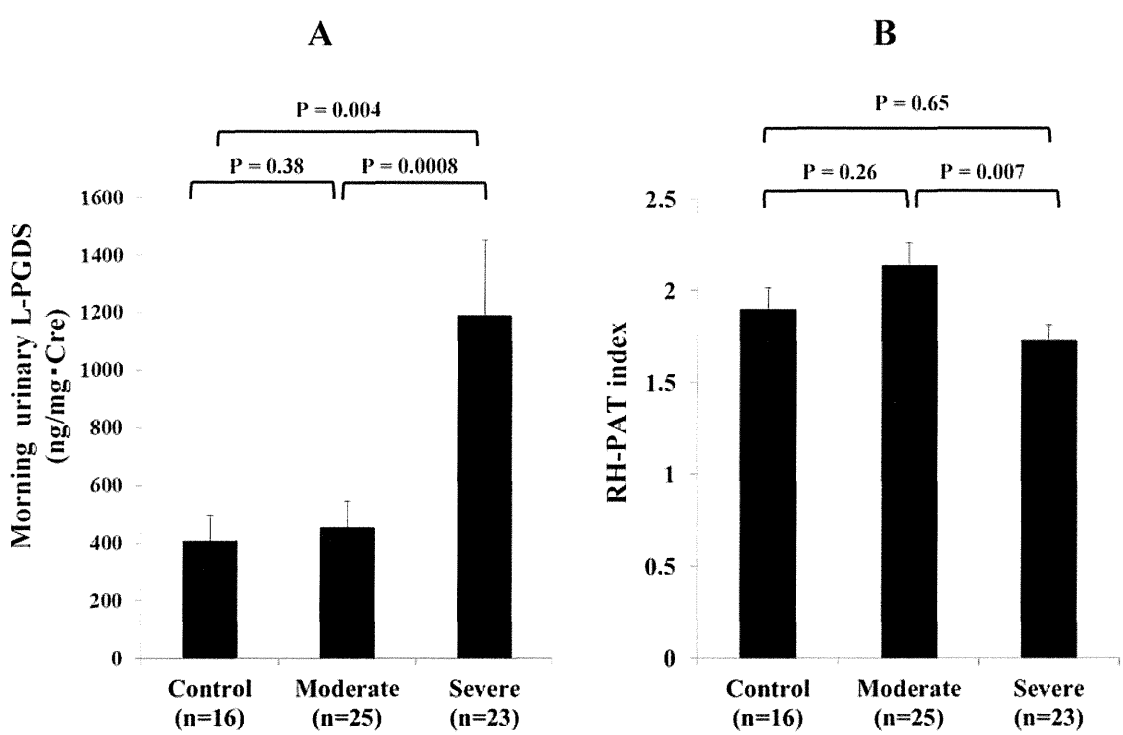

Figure 2.

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.

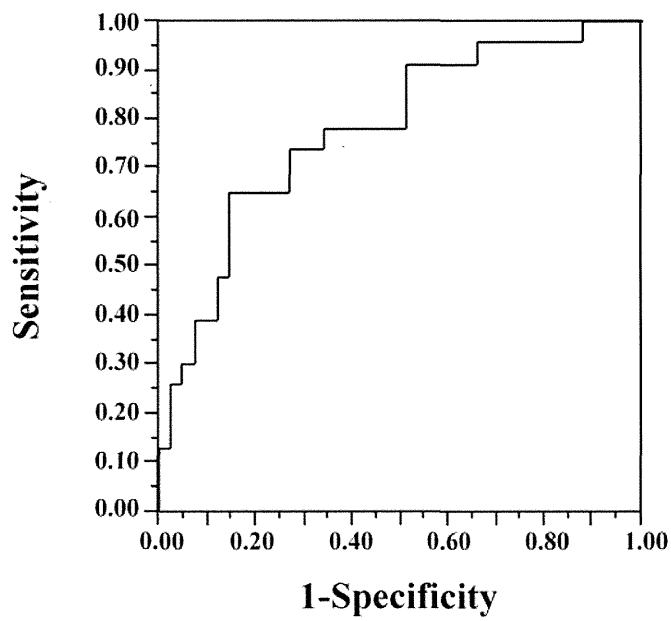

Figure 3.

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.