Characteristics of sleep–wake cycle and sleep duration in Japanese type 2 diabetes patients with visceral fat accumulation

Shiro Fukuda, Ayumu Hirata, Hitoshi Nishizawa, Hirofumi Nagao, Takekazu Kimura, Yuya Fujishima, Masaya Yamaoka, Junji Kozawa, Akihisa Imagawa, Tohru Funahashi, Norikazu Maeda, Ichiro Shimomura

Departments of 1Metabolic Medicine, and 2Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University, Osaka, Japan

INTRODUCTION
The prevalence of obesity-related type 2 diabetes mellitus has been increasing worldwide, especially in Asia. It is known that Asian diabetes patients have lower body mass indexes (BMI) compared with those of Caucasians. Irrespective of BMI (< or ≥25 kg/m²), visceral fat accumulation leads to dysregulation of adipocytokines, such as hypoadiponectinemia, and results in type 2 diabetes mellitus and metabolic syndrome. Recently, we reported that Japanese type 2 diabetes mellitus patients with visceral fat accumulation showed a higher prevalence of dyslipidemia and hypertension, lower plasma adiponectin, and more advanced systemic arteriosclerosis than those without.

Sleep duration has decreased in the modern lifestyle. Several researchers showed that shorter or longer sleep durations were associated with type 2 diabetes mellitus and metabolic syndrome. Recently, we reported that sleep–wake cycle irregularities (later bedtime and later waking time) existed in type 2 diabetes mellitus patients compared with non-type 2 diabetes mellitus patients, although sleep duration was not different. However, there is no report to compare sleep duration or sleep–wake cycle irregularities between type 2 diabetes mellitus patients with visceral fat accumulation and those without.

Here, we show the difference in bedtime, waking time and estimated sleep duration in type 2 diabetes mellitus patients with or without visceral fat accumulation, using a questionnaire on sleep patterns.

ABSTRACT
Sleep pattern has been shown to be associated with type 2 diabetes mellitus. Here, we investigated the difference in bedtime, waking time and estimated sleep duration in type 2 diabetes mellitus patients with or without visceral fat accumulation, using a questionnaire on sleep patterns. The study participants were 59 Japanese type 2 diabetes mellitus patients (men/women 34/25, age 64.5 ± 12.1 years). Visceral fat accumulation was defined as estimated visceral fat area ≥100 cm². The patients with visceral fat accumulation (n = 40) showed significantly later bedtime (23.51 ± 01.23 h in the [+ group vs 22.49 ± 01.23 h in the [-] group) and shorter estimated sleep duration (6.6 ± 1.4 h in the [+ group vs 7.9 ± 1.0 h in the [-] group) on weekdays, compared with those without (n = 19). Later bedtime and shorter estimated sleep duration existed in the type 2 diabetes mellitus patients with visceral fat accumulation, compared with those without.

METHODS
Participants
The present study was a subanalysis of our previous report. The study participants with type 2 diabetes were enrolled from April 2012 to December 2012 among the patients hospitalized for the control of diabetes at the Division of Endocrinology and Metabolism of Osaka University Hospital, Osaka, Japan, and the patients who visited the ‘Diabetes & Metabolic Station’ outpatient clinic of Osaka University Hospital. Patients excluded were those whose questionnaires on sleep habits were not completed. All participants were Japanese, and there were no shift-workers in this study. Written consent was obtained. This study complied with the Guidelines of the Ethical Committees of Osaka University.
Clinical examinations and laboratory tests
Duration of diabetes, weekly alcohol consumption and medications were retrieved through medical interview. The bioelectrical impedance analysis method was used to measure estimated visceral fat area (eVFA). Serum levels of total adiponectin were measured by enzyme-linked immunosorbent assay (human adiponectin ELISA kit; Otsuka Pharmaceutical Co. Tokushima, Japan). The systemic arteriosclerosis was assessed with vascular ultrasonography, described previously. The score, ≥2 points, means that the participants had arteriosclerotic lesions in two or more arteries, which significantly predicts the existence of coronary artery disease. The definitions of visceral fat accumulation (eVFA ≥100 cm²), diabetic retinopathy, diabetic nephropathy, hypertension, dyslipidemia and metabolic syndrome were the same as previously reported.

Questionnaire on sleep patterns
Using the questionnaire as shown in Figure 1, usual bedtime and waking time (at 1-h intervals) were retrieved. Estimated sleep duration (hours) was calculated as waking time and waking time (at 1-h intervals) were retrieved. Estimated sleep duration was calculated as the difference between ‘bedtime’ and ‘waking time.’

Statistical analysis
The differences between the two groups were compared by Welch’s t-test (for continuous variables with normal distribution), Mann–Whitney’s U-test (for continuous variables with skewed distribution or non-continuous variables) or Fisher’s exact test (for frequencies). P-values of <0.05 were considered statistically significant. All analyses were carried out with the JMP Pro 11.2.0 (64 bit) for Windows (SAS Institute, Cary, North Carolina, USA).

RESULTS
Participant characteristics
Of the 75 Japanese type 2 diabetes mellitus patients (58 inpatients and 17 outpatients; all patients had eVFA data) enrolled in our previous study, we excluded 16 patients (9 inpatients and 7 outpatients) who did not answer the questionnaire on sleep patterns, and finally enrolled 59 patients (49 inpatients and 10 outpatients) in the present study (Table 1). The participants were divided into two groups based on eVFA. We defined 40 participants with an eVFA ≥100 cm² as the visceral fat accumulation (+) group, and the 19 remaining participants as the visceral fat accumulation (−) group.

Compared with the visceral fat accumulation (−) group, the (+) group had a significantly higher prevalence of dyslipidemia, higher serum C-peptide and triglyceride, and lower high-density lipoprotein cholesterol. Furthermore, the (+) group showed lower serum adiponectin levels and a higher percentage of participants with systemic vascular score ≥2 points than those of the (−) group, as seen in our previous reports, whereas there were no significant differences in sex and age.

Assessment of sleep pattern: bedtime, waking time and estimated sleep duration
Figure 2 shows the distribution of bedtime, waking time, and estimated sleep duration on weekdays and holidays in each group. On weekdays, the bedtime was significantly later in the visceral fat accumulation (+) group, compared with the (−) group (23.51 ± 0.27 h in the [+ group vs 22.49 ± 0.23 h in the [−] group; Figure 2a). There was no significant difference in the waking time between the two groups. The estimated sleep duration was significantly shorter in the (+) group than in the (−) group (6.6 ± 1.4 h in the [+ group vs 7.9 ± 1.0 h in the [−] group). Similar results were obtained in the sleep pattern on holidays (Figure 2b). Age in the visceral fat accumulation (−) group tended to be slightly higher than that of the visceral fat accumulation (+) group, although not statistically significant (Table 1). Then, we carried out multivariate analysis, and confirmed a significant correlation between eVFA and estimated sleep duration after adjustment of age (data not shown).

DISCUSSION
In the present study, we showed that type 2 diabetes mellitus patients with visceral fat accumulation had significantly later bedtime and shorter estimated sleep duration compared with those without. Various studies have shown that short sleep duration is an independent risk factor for weight gain.
### Table 1 | Baseline characteristics of participants

|                      | All                  | Visceral fat accumulation | P-value |
|----------------------|----------------------|---------------------------|---------|
|                      | (+) Group            | (-) Group                |         |
| Total n (men/women)  | 59 (34/25)           | 40 (25/15)               | 19 (9/10)| NS*      |
| Age (years)          | 64.5 ± 12.1          | 62.4 ± 13.6              | 69.1 ± 6.5| NS*      |
| Body mass index (kg/m²) | 260 ± 6.2         | 285.5 ± 6.0              | 208.8 ± 4.1| <0.001†   |
| Waist circumferences (cm) | 93.2 ± 13.8     | 99.3 ± 11.9              | 803.6 ± 6.6| <0.001†   |
| eGFR (mL/min/1.73 m²) | 133.8 ± 70.2        | 165.4 ± 62.8             | 67.4 ± 21.2| <0.001†   |
| Duration of diabetes (years) | 15.1 ± 10.7     | 13.2 ± 8.8               | 19.1 ± 13.2| NS†      |
| Diabetic retinopathy | 17 (29%)            | 9 (23%)                  | 8 (42%)  | NS†      |
| Diabetic nephropathy  | 16 (27%)            | 12 (30%)                 | 4 (21%)  | NS†      |
| Hypertension         | 41 (69%)            | 27 (68%)                 | 14 (74%) | NS†      |
| Dyslipidemia         | 43 (73%)            | 33 (83%)                 | 10 (53%) | NS<0.05  |
| Alcohol consumption (g/week) | 460 ± 103.2    | 548 ± 118.7              | 233 ± 38.9| NS†      |
| Systolic BP (mmHg)   | 126 ± 16            | 127 ± 17                 | 124 ± 15 | NS*      |
| Diastolic BP (mmHg)  | 73 ± 13             | 75 ± 13                  | 70 ± 12  | NS*      |
| Glucose (mg/dL)      | 65.0 ± 4.4          | 153 ± 46                 | 142 ± 40 | NS†      |
| Hba1c, NGSP (%)      | 88 ± 16             | 90.5 ± 15                | 8.4 ± 1.9| NS†      |
| Serum C-peptide (ng/mL) | 2.2 ± 1.8         | 2.5 ± 2.0                | 1.4 ± 0.8| <0.05*†   |
| TG (mg/dL)           | 163 ± 249           | 192 ± 299                | 104 ± 42 | <0.01*†   |
| LDL-C (mg/dL)        | 104 ± 30            | 107 ± 32                 | 100 ± 26 | NS*      |
| HDL-C (mg/dL)        | 50 ± 16             | 45 ± 13                  | 60 ± 17  | NS*      |
| UA (mg/dL)           | 5.4 ± 1.5           | 5.6 ± 1.6                | 5.0 ± 1.2| NS*      |
| eGFR (mL/min/1.73 m²) | 7.2 ± 20.7         | 7.3 ± 23.1               | 70.0 ± 14.5| NS†      |
| uACR (mg/gCr)        | 7.1 ± 16.09         | 7.9 ± 18.45              | 54.6 ± 86.8| NS†      |
| CCA max IMT (mm)     | 1.76 ± 0.78         | 1.74 ± 0.82              | 1.79 ± 0.71| NS†      |
| CCA mean IMT (mm)    | 0.96 ± 0.26         | 0.95 ± 0.26              | 0.98 ± 0.26| NS†      |
| Serum adiponectin (µg/mL) | 7.0 ± 5.4         | 5.4 ± 3.6 (N = 47)       | 10.3 ± 7.0 (N = 15)| <0.01*†   |
| Systemic vascular score ≥2 points†‡ | 33 (61%) (N = 54) | 25 (71%) (N = 35)       | 8 (42%) (N = 19) | <0.05*†   |

**Medications**

For diabetes

- Sulfonylureas: 28 (47%)
- Glinides: 5 (8%)
- Biguanides: 18 (31%)
- Alpha-Gls: 13 (22%)
- Thiazolidinediones: 5 (8%)
- DPP-4 inhibitors: 20 (34%)
- Insulin: 12 (20%)
- GLP-1 analogs: 5 (8%)

For hypertension

- ACEI/ARBs: 24 (41%)
- Diuretics: 26 (44%)
- Statins: 13 (22%)
- Sleeping pills: 6 (15%)

Data are represented as mean ± standard deviation, or number of participants (frequency [%]). †Fisher’s exact test (men vs women). ‡Mann–Whitney U-test ([+] group vs [–] group). §Fisher’s exact test ([+] group vs [–] group). ¶Welch’s t-test ([+] group vs [–] group). ††Systemic vascular score ≥2 points means the participant had multiple arteriosclerotic lesions. For more information, see the ‘Methods’ section. ACEI, angiotensin-converting enzyme inhibitor; Alpha-Gl, alpha-glucosidase inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCA, common carotid artery; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; eVFA, estimated visceral fat area; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; LDL-C, low density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; NS, not significant; TG, triglyceride; UA, uric acid; uACR, urine albumin-to-creatinine ratio.

was also reported that late bedtime or short sleep duration was associated with eating habits in primary school children and in daytime workers. However, little has been known on the difference in sleep–wake cycle and sleep duration between type 2 diabetes mellitus with visceral fat accumulation and those without. We have shown that type 2 diabetes mellitus patients...
with visceral fat accumulation showed different eating behavior from those without. A series of recent studies showed that sleep loss resulted in metabolic and endocrine alterations, including reduction of leptin, elevation of ghrelin, dysregulation of cortisol and growth hormone, and impaired glucose tolerance. Thus, it is possible that sleep duration, sleep–wake cycle and eating behavior might be reciprocally associated with visceral fat accumulation in type 2 diabetes mellitus patients. In contrast, the present study also showed that visceral fat accumulation was associated with hypoadiponectinemia and elevated systemic vascular score (Table 1). As estimated sleep duration was significantly associated with serum adiponectin level (Figure S1), but not with systemic vascular score in the present study (data not shown), larger studies are required to elucidate the direct association between sleep duration, adiponectin and arteriosclerosis in type 2 diabetes mellitus patients. Taken together, to combat against visceral fat accumulation and arteriosclerosis, it might be helpful for physicians to inquire about the bedtime, waking time and sleep duration of type 2 diabetes mellitus patients, and to support them for modification of their sleep habits.

There were several limitations to the present. First, bedtime, waking time and sleep duration were estimated from the questionnaire. Second, sleep quality (such as sleep apnea syndrome) could not be considered. Third, the influence of factors such as sex and ethnicities cannot be excluded.

In conclusion, type 2 diabetes mellitus patients with visceral fat accumulation showed significantly later bedtime and shorter estimated sleep duration compared with those without visceral fat accumulation.

![Figure 2](http://onlinelibrary.wiley.com/journal/jdi)

**Figure 2** | Histograms of the numbers of type 2 diabetes mellitus participants with visceral fat accumulation (gray) and without (white) for each bedtime, waking time and estimated sleep duration. (a) On weekdays. (b) On holidays. *Mann–Whitney U-test (visceral fat accumulation [+] group vs [-] group). NS, not significant.
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DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION
Additional Supporting Information may be found in the online version of this article:

Figure S1 Correlation plot between estimated sleep duration on weekdays and adiponectin. Pearson’s correlation coefficient (r), its probability value (P) and 95% confidence ellipse were overlaid.