Positive association of plasma leptin with sleep quality in obese type 2 diabetes patients

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ABSTRACT

Aims/Introduction: Poor sleep quality is associated with obesity and diabetes. The adipocyte-derived hormone, leptin, was recently shown to underlie the link between abnormal sleep and obesity. We aimed to investigate the association between leptin and sleep quality in type 2 diabetes patients.

Materials and Methods: In the present cross-sectional study, we studied 182 type 2 diabetes patients, among whom 113 were diagnosed with obesity (body mass index ≥25 kg/m²). Fasting plasma leptin levels were measured, and sleep architecture was assessed using single-channel electroencephalography.

Results: Using unadjusted analyses, the obese type 2 diabetes patients, but not their non-obese counterparts, showed a positive correlation between plasma leptin levels and a parameter for deep sleep assessed by delta power during the first sleep cycle. Multivariate analysis showed that plasma leptin levels were positively associated with delta power, but not with the total sleep time, after adjusting for potential confounders including age, body mass index and the apnea–hypopnea index, in the obesity group. However, neither delta power nor total sleep time was associated with leptin in the non-obesity group.

Conclusions: Plasma leptin levels are independently associated with sleep quality in obese, but not in non-obese, type 2 diabetes patients. The present study indicates a favorable relationship between leptin and sleep quality in obese type 2 diabetes patients.

INTRODUCTION

Insufficient sleep has been increasingly recognized to underlie the epidemic of obesity, type 2 diabetes, hypertension and cardiovascular diseases¹. Previous studies have shown that reduced sleep duration is associated with impaired glucose and energy metabolism, obesity, and type 2 diabetes²-⁴. Recent evidence has shown that poor sleep quality was associated with obesity and metabolic syndrome⁵-⁹. Several lines of evidence also show poorer sleep quality as a predictor of the risk and severity of type 2 diabetes¹⁰-¹³. Furthermore, we recently reported that better sleep quality was independently associated with better glycemic control in type 2 diabetes patients¹⁴. However, to date, factors linking poor sleep quality and obesity in type 2 diabetes patients, independent of the relationship of obesity with obstructive sleep apnea syndrome, remain largely unknown.

Leptin, an adipocyte-derived hormone, is known to play a key role in the regulation of appetite and bodyweight¹⁵. Recently, leptin has been proposed as a possible link between the risk of obesity and abnormal sleep duration and/or quality in healthy individuals¹⁶,¹⁷. Several observational studies have inconsistently shown a relationship between plasma leptin and sleep duration. Although studies carried out in the general population have consistently shown that lower leptin levels were associated with shorter sleep duration¹⁸-²¹, those carried out in obese individuals showed an insignificant or a U-shaped association between plasma leptin and sleep duration²²,²³. The absence of their consistent association only in obese individuals might be confounded by obesity itself or obesity-related factors, such as sleep apnea.

To our knowledge, no prior study has examined the association between leptin and sleep quality in type 2 diabetes patients, independent of body mass index (BMI) and apnea–hypopnea index (AHI), a parameter for sleep apnea²⁴. In the present study, we assessed sleep architecture using single-channel electroencephalography (EEG), which provides reliable sleep staging to objectively evaluate sleep quality²⁵, together with AHI measurement. We hypothesized that dysregulation of
ciringulating leptin might be associated with poor sleep quality in obese type 2 diabetes patients independent of sleep apnea.

METHODS

Study design and participants
This was a cross-sectional study carried out at the Diabetes Center of the Osaka City University Hospital, Osaka, Japan, between October 2011 and July 2016. We consecutively enrolled 182 type 2 diabetes patients (100 men, 82 women), who had been admitted for glycemic control, education and/or evaluation of diabetic complications. Type 2 diabetes was diagnosed based on the Japan Diabetes Society criteria. Patients with type 1 and other types of diabetes or those using sleep-promoting drugs were not included in this study. Obesity was defined as BMI ≥25.0 kg/m².

The present study was carried out in accordance with the Declaration of Helsinki (1975, revised in 2013). The study protocol was approved by the ethics committee of Osaka City University Graduate School of Medicine (approval #308). All participants provided written informed consent before enrollment in the study.

Measurement and analysis of sleep architecture
An overnight sleep recording was carried out using a portable single-channel EEG (SLEEP SCOPE; SleepWell Co., Osaka, Japan), as we previously reported. Participants were placed in a single room in the hospital and were instructed to place one electrode on the forehead and another behind the ears before going to bed. The raw EEG recording was sent to SleepWell Co., and the sleep architecture data were obtained for each participant, including the total sleep time (min), rapid eye movement (REM) sleep (min), non-REM sleep (min) and delta power during the first sleep cycle. Based on sleep scoring criteria established by the American Academy of Sleep Medicine, sleep recordings were divided into 30-s sequential periods, and manually classified into REM and non-REM sleep. Total sleep time was calculated as the total sleep period minus the time spent awake. Sleep efficiency was calculated as total sleep time divided by total sleep period. Power spectral analysis for the delta frequency band (0.5–2.0 Hz; μV²), or delta power, was calculated as a marker of deep sleep. Because sleep time and number of sleep cycles differ among individuals, delta power during the first sleep cycle was utilized for analysis in the present study.

At the time of EEG measurement, respiratory flow pressure, oxygen saturation and the heart rate was monitored simultaneously (SAS-2100; Nihon Koden Co., Tokyo, Japan). The AHl was defined as the ratio of the number of episodes of apnea and hypopnea per hour of sleep, as described previously.

Ambulatory blood pressure monitoring
Non-invasive ambulatory blood pressure monitoring was carried out in a hospital setting using an automated system (TM-2431; A&D, Tokyo, Japan), as described previously.

Nocturnal blood pressure was defined as mean blood pressure readings during the sleep period, which was determined on the basis of written diaries recorded by participants during the ambulatory blood pressure monitoring.

Physical and laboratory analyses
Blood pressure was determined using an automatic sphygmomanometer with a conventional cuff after the participant had rested for at least 5 min. Blood was drawn after an overnight fast and biochemical parameters were analyzed using a standard laboratory method at the Central Laboratory of the Osaka City University Hospital. Fresh frozen plasma samples were stored at −30°C for measurement of leptin levels, which were measured using a commercial enzyme-linked immunosorbent assay kit (R&D Systems Inc., Minneapolis, MN, USA), as described previously. The minimum detectable levels of leptin was 0.16 ng/mL. The intra- and interassay coefficients of variation of leptin were 3.2 and 3.5%, respectively. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese eGFR equation. Glycated hemoglobin (HbA1c) levels were estimated in terms of National Glycohemoglobin Standardization Program equivalent values (%) using the conversion formula established by the Japan Diabetes Society.

Statistical analysis
Data are expressed as the number (%) or median (interquartile range). Participants were divided into the non-obesity (BMI <25.0 kg/m²) and obesity groups. Correlations were examined using the non-parametric Spearman’s rank correlation test. Using multiple regression analyses for determination of each sleep-related parameter, plasma leptin level was considered an independent variable in addition to age, sex, BMI, nocturnal systolic blood pressure, eGFR, HbA1c and AHl. Plasma leptin levels were logarithmically transformed before carrying out regression analyses due to its skewed distribution. P-values < 0.05 were considered statistically significant. Statistical analyses were carried out using JMP 10 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics of all, obese and non-obese type 2 diabetes patients
Clinical characteristics of the entire study population of type 2 diabetes patients, as well as of subgroups with and without obesity are shown in Table 1. The median age and duration of type 2 diabetes for the entire population were 61 and 10 years, respectively. We observed that 152 (84.1%), 60 (33.0%) and 81 (44.5%) out of 182 type 2 diabetes patients had been receiving antidiabetic drugs including insulin, statins for dyslipidemia and antihypertensive drugs, respectively. The median BMI was 26.7, 30.0 and 22.3 kg/m² for the entire population, obesity and non-obesity group, respectively. In the participants, obese patients were significantly younger and showed significantly
higher diastolic blood pressure than non-obese patients. No significant difference existed between two groups of patients in terms of duration of type 2 diabetes, nocturnal systolic blood pressure, renal function, glycemic control or lipid profile.

Plasma leptin and objective sleep-related parameters in all, obese and non-obese type 2 diabetes patients

As shown in Table 1, the median plasma leptin in all type 2 diabetes patients was 6.6 ng/mL. Among the type 2 diabetes patients, the median plasma leptin was 9.9 ng/mL in the obesity group, which was significantly higher than that of 3.6 ng/mL in the non-obesity group. Objective sleep-related parameters, such as total sleep period, total sleep time, sleep efficiency, and delta power, did not differ significantly between two groups of patients. The median AHI in all type 2 diabetes patients was 10.8/h. Obese patients showed significantly higher median AHI (13.9/h) than non-obese patients (5.8/h).

Unadjusted correlations between plasma leptin and objective sleep-related parameters in all, obese and non-obese type 2 diabetes patients

Next, we examined the correlation of plasma leptin with sleep-related parameters using univariate analyses in all type 2 diabetes patients and also after separating those into two groups of patients based on the presence or absence of obesity (Table 2). Plasma leptin was significantly and positively correlated with delta power ($p = 0.193$, $P = 0.009$), and AHI ($p = 0.277$, $P < 0.001$) in the entire population. Notably, the positive correlations of plasma leptin with delta power were preserved only in obese type 2 diabetes patients ($p = 0.248$, $P = 0.008$), but not in non-obese patients. Plasma leptin failed to correlate with AHI either in obese or non-obese patients.

Multivariate analyses of the determinants of delta power in all, obese and non-obese type 2 diabetes patients

Next, multiple regression analysis was carried out to determine whether plasma leptin might associate independently with delta power in type 2 diabetes patients (Table 3). Furthermore, to examine the influence of obesity on the association between the two parameters, multiple regression analysis was carried out separately in obese and non-obese patients. In all patients, model 1, which included age, sex, BMI, nocturnal systolic blood pressure, eGFR, HbA1c and AHI, showed age ($\beta = -0.478$, $P < 0.001$) and male sex ($\beta = -0.254$, $P = 0.001$) as independent factors that negatively associated with delta power, whereas AHI failed to associate with delta power. In model 2, which included log leptin in place of AHI, log leptin showed a significant and positive association with delta power ($\beta = 0.268$, $P = 0.034$). When AHI and log leptin was simultaneously included, log leptin, but not AHI, tended to associate positively

### Table 1 | Clinical characteristics, plasma leptin levels and sleep-related parameters in all type 2 diabetes patients, as well as in subgroups with and without obesity

| Clinical variables | All participants | Subgroups | $P$ |
|--------------------|------------------|-----------|-----|
|                    |                  | Obesity   | Non-obesity |
| $n$ (men %)        | 182 (55.0)       | 113 (55.8) | 69 (53.6)  | 0.779 |
| Age (years)        | 61 (46–71)       | 56 (45–68) | 65 (54–71) | 0.006 |
| Duration of diabetes (years) | 10 (2–19) | 8 (2–18)   | 10 (6–21)  | 0.063 |
| BMI (kg/m$^2$)     | 26.7 (23.5–31.6) | 30.0 (27.1–34.3) | 223 (207–238) | $<0.001$ |
| Systolic BP (mmHg) | 130 (120–145)    | 131 (120–145) | 128 (118–144) | 0.299 |
| Mean arterial BP   | 83 (71–96)       | 81 (70–95)  | 86 (71–98)  | 0.155 |
| Triglycerides (mg/dL) | 120 (94–165)      | 125 (95–179) | 113 (92–149) | 0.125 |
| HDL cholesterol (mg/dL) | 41 (35–49)   | 40 (35–48)  | 43 (34–50)  | 0.454 |
| LDL cholesterol (mg/dL) | 113 (87–138)   | 114 (88–143) | 106 (83–137) | 0.507 |
| Leptin (ng/mL)     | 6.6 (3.3–13.9)   | 9.6 (5.6–17.5) | 3.6 (2.2–6.6) | $<0.001$ |
| Total sleep period (min) | 487 (446–516)    | 487 (438–519) | 487 (446–513) | 0.670 |
| Total sleep time (min) | 348 (290–404)     | 343 (281–404) | 358 (310–403) | 0.447 |
| Sleep efficiency (%) | 74.9 (64.7–83.1) | 73.9 (64.2–83.2) | 76.1 (66.5–83.1) | 0.554 |
| Delta power ($\mu V^2$) | 113,761 (61,596–186,326) | 117,332 (61,577–193,357) | 113,511 (61,939–177,416) | 0.442 |
| AHI (n/h)          | 10.8 (4.0–20.1)  | 13.9 (5.2–27.1) | 5.8 (3.0–14.4) | $<0.001$ |

Values are expressed as $n$ (median (interquartile range)). $P$-values were determined using the $\chi^2$-test or Wilcoxon rank-sum test for comparison between the obesity and non-obesity group. AHI, apnea-hypopnea index; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
with delta power in all type 2 diabetes patients ($\beta = 0.226, P = 0.075$). When type 2 diabetes patients were restricted to obese patients, log leptin emerged as a significant factor positively associated with delta power (model 2: $\beta = 0.428, P = 0.003$; model 3: $\beta = 0.399, P = 0.006$). However, log leptin failed to associate with delta power in non-obese patients.

**DISCUSSION**

Recent evidence has shown that sleep quality is impaired in type 2 diabetes patients\(^1,12,14\). The present study showed that plasma leptin level was positively associated with delta power during the first sleep cycle, an established marker for sleep quality\(^14\), only in obese type 2 diabetes patients, but not in their non-obese counterparts. Of importance, the association of plasma leptin with delta power in obese type 2 diabetes patients was independent of BMI and AHI (Table 3). These data indicate a favorable relationship between leptin and sleep quality, even though obesity and sleep apnea have harmful effects on sleep quality in type 2 diabetes patients. Indeed, despite markedly higher BMI and AHI, delta power was not impaired in our obese type 2 diabetes patients compared with non-obese counterparts.

Several previous studies evaluated the relationship between plasma leptin levels and sleep quality, in which sleep quality was assessed by a questionnaire\(^20\) or as sleep efficiency (percentage of time in bed spent sleeping)\(^21,22\). However, all these studies failed to find a significant relationship between them\(^20–22\). Unlike these studies, the present study evaluated sleep quality precisely by analyzing detailed sleep architecture based on EEG recordings and was able to show, for the first time, a close relationship between plasma leptin levels and delta power during the first sleep cycle, a definite parameter for sleep quality\(^14,35\).

Notably, a positive association between leptin levels and delta power was found in obese type 2 diabetes patients. Our data clearly showed that BMI was inversely associated with delta power in the obesity group, consistent with previous studies showing an association between reduced sleep quality and obesity and metabolic syndrome\(^5–9\). A positive correlation was also observed between plasma leptin levels and BMI ($\rho = 0.639, P < 0.001$), consistent with leptin resistance in obesity\(^15\). Collectively, these findings suggest that leptin is not involved in the adverse effect of obesity on sleep quality, but rather favorably affects sleep quality in obese type 2 diabetes patients. Supportive of this finding might be the accumulated recent evidence to show that sleep restriction reduced plasma leptin levels, total sleep time and the duration of slow-wave sleep in young adults\(^4,16,17\), suggesting the relationship between decreased plasma leptin levels and poor sleep quality.

One possible explanation for the favorable relationship between leptin and sleep quality in obese type 2 diabetes patients might be that leptin plays a role in maintaining deep sleep through antagonizing the action of orexin neurons in the hypothalamus. Recent evidence from animal studies showed that the orexin neurons are activated during awake periods and need be switched off to maintain non-REM sleep, and that the activity of orexin neurons is inhibited by leptin\(^36,37\). To date, no study has shown whether the development of leptin resistance

### Table 2 | Unadjusted association between plasma leptin levels and sleep-related parameters

|                      | All participants | Obesity | Non-obesity |
|----------------------|------------------|---------|-------------|
|                      | $\rho$ | $P$ | $\rho$ | $P$ | $\rho$ | $P$ |
| Total sleep time    | <0.001 | 1.000 | -0.020 | 0.838 | 0.025 | 0.841 |
| Sleep efficiency    | 0.063  | 0.397 | -0.091 | 0.340 | -0.004 | 0.974 |
| Delta power         | 0.193  | 0.009 | 0.248  | 0.008 | 0.067  | 0.585 |
| AHI                  | 0.277  | <0.001| 0.148  | 0.132 | 0.200  | 0.111 |

$p$, Spearman’s rank correlation coefficient; AHI, apnea–hypopnea index.

### Table 3 | Multiple regression analysis for determinants of delta power in all, obese and non-obese type 2 diabetes patients

|                      | All | Obesity | Non-obesity |
|----------------------|-----|---------|-------------|
|                      | Model 1 | Model 2 | Model 3 | Model 1 | Model 2 | Model 3 | Model 1 | Model 2 | Model 3 |
| Age (years)          | -0.478*** | -0.462*** | -0.490*** | -0.601*** | -0.633*** | -0.671*** | -0.196 | -0.194 | -0.195 |
| Sex (men = 1, women = 0) | -0.254*** | -0.145 | -0.157* | -0.353*** | -0.141 | -0.155 | -0.094 | -0.089 | -0.089 |
| BMI (kg/m\(^2\))     | -0.098 | -0.209* | -0.238** | -0.195* | -0.352*** | -0.401*** | -0.063 | -0.032 | -0.068 |
| Nocturnal systolic BP (mmHg) | -0.038 | -0.064 | -0.047 | -0.048 | -0.083 | -0.085 | -0.119 | -0.186 | -0.120 |
| eGFR (mL/min/1.73 m\(^2\)) | 0.016 | 0.017 | 0.037 | 0.040 | -0.014 | 0.035 | -0.166 | -0.114 | -0.164 |
| HbA1c (%)            | 0.018 | 0.022 | 0.020 | 0.023 | 0.042 | 0.021 | 0.121 | 0.078 | 0.121 |
| AHI                  | 0.084 | –       | 0.075 | 0.141 | –       | 0.141 | –       | –       | –       |
| Log. leptin (ng/mL)  | –     | 0.268** | 0.226* | –     | 0.428** | 0.399*** | –     | 0.011 | 0.010 |
| $R^2$                | 0.233*** | 0.252*** | 0.250*** | 0.346*** | 0.386*** | 0.401*** | 0.101 | 0.107 | 0.101 |

Values are expressed as the standard regression coefficient determined by multiple regression analysis ($\beta$, $R^2$, coefficient of determination).

* $P < 0.10$, **$P < 0.05$, ***$P < 0.01$. AHI, apnea–hypopnea index; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin.
in association with obesity might affect the interaction between leptin and orexin neurons.

In the present study, only obese patients, but not non-obese patients, showed a significant relationship between plasma leptin and delta power. Considering a potential biological effect of leptin to improve sleep quality as discussed above and high plasma leptin levels in obese patients, it is speculated that elevated plasma leptin levels were required to exert its effect on sleep quality. In addition, considering the inverse relationship between BMI and delta power, it is also speculated that leptin might play a role in promoting deep sleep to compensate for the adverse effect of obesity on sleep quality in obese patients.

The present study had several limitations. First, sleep architecture was evaluated using a portable single-channel EEG, which allowed us to evaluate a relatively large number of individuals, although its utility has been shown in a series of recent studies. Second, we obtained a single determination of plasma leptin level after an overnight fast. Recent studies carried out serial measurements of leptin throughout the sleep period, and found that circulating leptin levels reached the peak during several hours after going to bed and reached the lowest trough early in the morning. These studies also showed that sleep restriction decreased the peak leptin levels more apparently than the mean leptin level. Therefore, we could expect to find the relationship between leptin and delta power during the first sleep cycle more apparently with serial leptin measurements. Third, only leptin, but not other adipokines or obesity-related factors, was evaluated in this study. A previous study in adolescents showed that adiponectin levels were proportionally associated with sleep duration, whereas ghrelin levels were inversely associated with sleep duration. Ghrelin levels were shown to be associated not only with increased appetite, but also with limited sleep duration in healthy individuals, suggesting an antagonistic relationship between ghrelin and leptin. Thus, simultaneous measurement of those factors would help us to characterize the factors affecting sleep quality in obese type 2 diabetes patients.

In summary, the present study showed that plasma leptin levels are independently associated with EEG delta power, a marker for sleep quality, preferentially in obese type 2 diabetes patients, and that the association between the two parameters is independent of BMI and sleep apnea. These findings suggest a specific and beneficial effect of leptin on sleep quality, possibly reflecting its direct inhibitory effect on the activity of orexin neurons. The present study further suggests a role of plasma leptin level as a marker of deep sleep and as a potential therapeutic target to improve sleep quality in obese type 2 diabetes patients. Further longitudinal studies are warranted to clarify whether intervention to increase plasma leptin might cause a beneficial impact on sleep quality in obese type 2 diabetes patients.

In conclusion, it was shown that increased plasma leptin might be associated independently with better sleep quality in obese type 2 diabetes patients.

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DISCLOSURE

The authors declare no conflict of interest.

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