Relationship between Autonomic Nervous System Activity during Sleep and Fasting Glucose in Japanese Workers

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Received November 26, 2010 and accepted January 5, 2011

Published online in J-STAGE June 21, 2011

Abstract: Although autonomic nervous system activity is reportedly related to diurnal glucose tolerance impairment, the relationship with glucose tolerance during sleep is unclear. Since work styles have recently diversified, it is important to assess the effect of sleep on workers' health. Elucidation of the relationship between autonomic nervous system activity during sleep and glucose tolerance in workers may facilitate preventive measures against diabetes using non-pharmacological means (e.g., sleep hygiene education, relaxation techniques and stress management). We examined whether autonomic nervous system activity during sleep is related to fasting glucose or glycated hemoglobin (HbA1c) in individuals with either normal or impaired fasting glucose tolerance. The subjects were 77 apparently healthy Japanese workers with normal or impaired fasting glucose. We used high frequency (HF) and the ratio of low frequency to high frequency (LF/HF) obtained by pulse wave analysis to estimate autonomic nervous system activity. The data were analyzed using a generalized estimating equation adjusted for potential confounders (age, gender, engagement in shift work, sleep duration, and body mass index). Fasting glucose was significantly negatively related to HF, the parasympathetic component during sleep. Our results suggest that parasympathetic activity during sleep is associated with fasting glucose in apparently healthy Japanese workers.

Key words: Autonomic nervous system activity, Heart rate variability, Fasting glucose, HbA1c, Frequency domain

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Introduction

Autonomic nervous system activity can be assessed relatively easily with low invasiveness by analyzing heart rate variability. Analysis of autonomic nervous system activity based on heart rate variability uses time-domain and frequency-domain analyses. Time-domain analysis calculates the standard deviation of all normal-to-normal heart beat intervals over a 24-h period and the root mean square of successive differences of adjacent normal-to-normal intervals, while frequency-domain analysis calculates high frequency (HF) and the ratio of low frequency to high frequency (LF/HF ratio)¹⁾.

Previous studies have attempted to elucidate whether these autonomic nervous indices are involved in the development and progression of a number of diseases^{2–6)}. In diabetes, these indices are used to assess dysautonomia²⁾. It has been suggested that autonomic nervous system activity levels are involved during the daytime in both diabetes and impaired glucose tolerance. The Atherosclerosis Risk In Communities Study carried out in the United States followed 8,185 individuals for approximately 8 yr and demonstrated that the prevalence of type 2 diabetes mellitus was significantly higher in those with a higher heart rate or decreased heart rate variability observed during daytime 2-min electrocardiogram (ECG) recordings⁷⁾. The Framingham Heart Study investigated 1,919 subjects who had heart rate variability measured for 2 h during the day using a portable electrocardiograph, and it demonstrated that fasting glucose levels were significantly correlated with LF, HF, and the LF/HF ratio⁸⁾. A Taiwanese study using 1,440 subjects employing frequency-domain analysis of daytime 5-min ECG recordings revealed that HF was significantly lower and the LF/HF ratio was higher in the impaired glucose tolerance and diabetes mellitus groups than in the normal glucose group⁹⁾.

Accumulating lines of evidence indicate a relationship between glucose tolerance and sleep. A study conducted using 1,486 subjects demonstrated that sleep duration was associated with an increased prevalence of impaired glucose tolerance and diabetes¹⁰⁾. Tasali *et al.*¹¹⁾ demonstrated that suppression of slow wave sleep without any change in total sleep duration causes a decrease in glucose tolerance and insulin sensitivity, while a reduction in sleep duration might increase sympathetic nerve activity¹²⁾. Furthermore, parasympathetic nerve activity is higher during slow wave sleep than in other sleep phases¹³⁾. Therefore, it is generally believed that autonomic nervous system activity is involved in the relationship between sleep and glucose tolerance; however, this relationship has not yet been clarified.

In recent years, sleep hygiene education and coun-

termeasures against metabolic syndrome have been initiated in some companies. In the field of occupational health, previous studies have also examined glucose tolerance in relation to autonomic nervous system activity. One study of the effect of night shift work on autonomic nervous system activity showed that the longer the duration of night shift work, the smaller the HF and LF components become. The results of that study might explain the positive association between the duration of night shift work and the risk of cardiovascular disease¹⁴⁾. In a study involving 223 Japanese workers, a long commute time and long overtime hours were found to reduce parasympathetic components¹⁵⁾.

Since work styles have recently diversified, it is important to assess the effect of sleep on the health of workers. Elucidation of the relationship between autonomic nervous system activity during sleep and glucose tolerance in workers may facilitate preventive measures against diabetes using non-pharmacological means (e.g., sleep hygiene education, relaxation techniques and stress management). The present study was designed to examine the relationship between autonomic nervous system activity during sleep and fasting glucose or glycated hemoglobin (HbA1c) by a wearable sensor. We obtained HF and LF/HF ratio data by pulse wave analysis recorded during the entire sleep period for 3 consecutive nights in apparently healthy workers with normal fasting glucose and those with impaired fasting glucose tolerance.

Subjects and Methods

Participants

Seventy-seven apparently healthy Japanese workers (64 men and 13 women) who received annual medical checkups sponsored by their employers in the Japanese manufacturing industry were included as subjects after obtaining written informed consent. These workers were from three work sites: steel, beverage and petrochemical manufacturers, each employing approximately 300 to 500 workers. Of 77 subjects, 8 workers (10.4%), 7 males and 1 female, worked in three 8-h shifts. The day shift was 08:00–16:00, the evening shift was 16:00–00:00 and the night shift was 00:00–08:00. They worked under a 1-wk rotating shift schedule, which usually comprised a cycle of 5 consecutive work days followed by 2 d off. Working shifts were the same in all three sites. The inclusion criteria specified that workers should be informed of the study's purpose and be given a consent form during medical checkups conducted by each company. Patients who were diagnosed as having any diseases, including those currently under medical treatment, were excluded from the study.

In addition, patients with a fasting blood glucose of 126 mg/dl or more and who were classified as diabetes type by the Japan Diabetes Association classification¹⁶⁾, were excluded, because they were most likely to have diabetic autonomic neuropathy. The present study was conducted during regular medical checkups in the spring of 2008 and 2009, with blood test and pulse wave measurements performed at the same time. A schedule was planned so that shift workers would receive blood test and pulse wave measurements during the daytime of the working week. The details of the study were approved by the ethics committee of Kitasato University.

Biochemical analysis

The subjects received blood tests in the morning after at least a 12-h fast. For fasting blood glucose and HbA1c, the results of blood tests at regular medical checkups were used. However, HbA1c was measured only in subjects for whom it was considered necessary based on fasting blood glucose values taken during regular checkups in the previous year or in those subjects requested by industrial physicians to take the test. Fasting glucose was classified based on the criteria issued by the Japan Diabetes Association in 2010 in a report by its committee on the diagnostic criteria of diabetes mellitus: normal fasting glucose is <110 mg/dl (normal type) and impaired fasting glucose is 110–125 mg/dl (borderline type)¹⁶⁾. HbA1c was expressed as recommended by the Japan Diabetes Society as follows. The value for HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula $\text{HbA1c (\%)} = \text{HbA1c (Japan Diabetes Society value) (\%)} + 0.4\%$ ¹⁶⁾.

Measurement and analysis of heart rate variability and sleep duration

A wearable physiological sensor (NEM-T1, Toshiba, Japan) with a built-in pulse wave sensor and actigraph was used to measure heart rate variability and sleep duration for 3 consecutive nights. For taking measurements, the subjects were asked to attach the sensor to themselves and to turn it on when they went to bed and to turn off the sensor and detach it from themselves when they got up. The data on pulse-peak intervals (PPIs) and the amount of activity stored in the sensor were then transferred to a PC via a USB connection for subsequent analysis using a dedicated analysis software package (NEM-SS1, Toshiba, Japan). The sensor was 50 × 60 × 13 mm in size and 35 g in weight, and came with a rechargeable battery. A 3-axis accelerometer and a 4 GB memory were built in to the sensor. It was also accompanied by an outside sensor (pulse wave sensor).

The sensor was attached to the wrist with an accompanying wristband like a watch and the pulse wave sensor was attached to a finger. The sampling rate of the pulse wave and 3-axis accelerations was 64 Hz. However, the resolution of the PPIs was 0.1 ms using linear interpolation to detect the pulse peak. This sensor detects body motion by an acceleration of 0.01 G or higher, which is the same as an actigraph^{17, 18)}.

Autonomic nervous system activity indices were computed using a software package (NEM-SS1, Toshiba, Japan) accompanying the sensor, from the frequency analysis of PPI variations. First, the PPI dataset sampled in 1 min was interpolated at even intervals by cubic spline interpolation by the min. Fast Fourier transform was then executed for the even-interval PPIs to obtain the frequency spectrum. In the frequency domain, the integral value of the power from 0.04 Hz to 0.15 Hz is called LF, which shows both sympathetic and parasympathetic nervous activities. The integral value of the power from 0.15 Hz to 0.4 Hz is called HF, which shows parasympathetic nervous activity¹⁷⁾. The ratio of these elements is employed to express sympathetic nerve activity with the LF/HF ratio¹⁾. The analysis software automatically calculates the sleep duration based on the algorithm of the Cole equation from the body motion detected by the actigraph¹⁸⁾.

The validity of the sensor is explained as follows. First, the correlation coefficient between the amount of activity counted by the sensor worn on the left forearm and that measured by an actigraph (Micromini-Motionlogger Actigraph, Ambulatory Monitoring Inc.) worn on the right forearm during sleep was 0.95. The correlation coefficients between the PPIs computed by the pulse wave measured by the sensor and the R-R intervals computed by a simultaneously measured ECG during sleep were also evaluated. Single-channel ECG was measured by the CM5 lead using polysomnography (Polymate AP1124, TEAC Corporation, sampling rate: 1 kHz) simultaneously with the PPIs measured by this sensor. R-R intervals were computed using commercially available R-R interval analysis software for polysomnography (NoruPro Light Systems, Japan). The correlation coefficient was 0.96¹⁷⁾.

Statistical analysis

We first determined Pearson's correlations of fasting glucose and HbA1c with the HF and LF/HF ratios. In univariate analysis, the mean values of data obtained in 3 nights were used for the HF and LF/HF ratios. The autonomic nervous system components, which were not normally distributed, were subjected to logarithmic transformation to calculate the log HF and log LF/HF ratio. To perform analysis after adjusting for potential

Table 1. Attributes of the participants

	Total (n=77)	Males (n=64)	Females (n=13)	<i>p</i> value ¹⁾
Age (yr)	41.0 (10.7)	41.8 (10.4)	36.9 (11.6)	0.19
BMI (kg/m ²)	23.8 (4.0)	23.8 (3.5)	24.0 (5.8)	0.36
Fasting blood sugar level (mg/dl)	91.0 (10.0)	92.2 (9.4)	84.8 (11.0)	<0.01
HF (ms)	31.86 (20.62)	28.90 (19.2)	35.12 (12.77)	0.35
LF/HF ratio	1.35 (0.55)	1.41 (0.46)	0.98 (0.36)	<0.01
Sleep duration (min)	346.5 (91.8)	347.8 (95.7)	340.2 (72.5)	0.17
Engagement in shift work, n (%)	8 (100)	7 (87.5)	1 (12.5)	<0.01
HbA1c (%) [n]	5.6 (0.3) [n=19]	5.6 (0.3) [n=18]	5.1 (–) [n=1]	<0.01

Metric variables are shown as the mean (SD). Categorical variables are shown as n (%). Sleep duration was detected by a sensor.

Abbreviations: BMI: body mass index; HF: high frequency component; LF: low frequency component; HbA1c: glycated hemoglobin.

¹⁾ To test for differences between sexes for each variable, continuous variables were tested by *t*-test and categorical variables were tested by Fisher's exact test.

confounders, i.e., age, gender, body mass index (BMI), engagement in shift work, and sleep duration, a generalized estimating equation (GEE) model was used, with fasting glucose levels and HbA1c as dependent variables. In the GEE, records containing missing values can be used in analysis. If measurements are performed multiple times in the same individual, it is possible to perform analysis without reducing statistical power by fixing an appropriate working correlation matrix and introducing individuals as a random effect^{19, 20)}. In the analyses, HF, LF/HF ratio, age, gender, BMI, engagement in shift work, and sleep duration, were introduced into the model as a fixed effect, as well as individuals as a random effect. HF and LF/HF ratios did not show a normal distribution. These were divided into tertiles and introduced into the model as continuous variables. We constructed a linear regression model using an exchangeable working correlation matrix. The data were analyzed using the PASW version 17.0 software program (SPSS Japan Inc, Japan). A value of *p*<0.05 was used to denote a statistically significant difference.

Results

Attributes of the participants are shown in Table 1. Seventy-three subjects (94.8%) were found to have normal fasting glucose (<110 mg/dl) and 4 subjects (5.2%) had impaired fasting glucose (110–125 mg/dl). Only 19 subjects underwent HbA1c measurement.

Correlation coefficients of autonomic nervous system components with fasting glucose and HbA1c are shown in Table 2. Pearson's correlation coefficients were significant between fasting glucose and log HF (*p*<0.01) and the log LF/HF ratio (*p*=0.03). Pearson's correlation coefficient between HbA1c and log HF was significant (*p*=0.02). Pearson's correlation coefficient between

Table 2. Correlation coefficients of autonomic nervous system components with fasting glucose (n=77) and HbA1c (n=19)

	Correlation coefficient	<i>p</i> value
Fasting glucose - log HF	−0.308	<0.01
Fasting glucose - log LF/HF ratio	0.254	0.03
HbA1c - log HF	−0.546	0.02
HbA1c - log LF/HF ratio	0.299	0.21

logHF: HF after logarithmic transformation; log LF/HF: LF/HF ratio after logarithmic transformation.

Table 3. The relationship between fasting glucose and autonomic nervous system activity during sleep

HRV indices	B ¹⁾	(95%CI)	<i>p</i> value
HF ²⁾	−1.579	(−2.461~−0.697)	<0.001
LF/HF ratio ²⁾	−0.380	(−1.462~0.701)	0.49

¹⁾ Partial regression coefficient adjusted for age, gender, BMI, shift work, and sleep duration.

²⁾ HF and LF/HF ratios were divided into tertiles and introduced into the model as continuous variables.

Abbreviations: HRV: heart rate variability; B: partial regression coefficient; CI: confidence interval; BMI: body mass index; HF: high frequency component; LF: low frequency component.

HbA1c and the log LF/HF ratio was not significant (*p*=0.21).

Table 3 shows the results of analysis using a GEE of the relationships of fasting glucose adjusted for potential confounders. Fasting glucose was significantly negatively related to HF (*p*<0.001). There was no significant relationship between fasting glucose and the LF/HF ratio.

Table 4 shows the relationship between HbA1c and autonomic nervous system activity during sleep, analyzed by the same method as mentioned above. There was no significant relationship between HbA1c and both autonomic nervous system components.

Table 4. The relationship between HbA1c and autonomic nervous system activity during sleep

HRV indices	B ¹⁾	(95%CI)	p value
HF ²⁾	-0.047	(-0.105-0.011)	0.113
LF/HF ratio ²⁾	-0.013	(-0.073-0.046)	0.66

¹⁾ Partial regression coefficient adjusted for age, gender, BMI, shift work, and sleep duration.

²⁾ HF and LF/HF ratios were divided into tertiles and introduced into the model as continuous variables.

Abbreviations: HRV: heart rate variability; B: partial regression coefficient; CI: confidence interval; BMI: body mass index; HF: high frequency component; LF: low frequency component.

Discussion

The results of our study identified that a significant negative correlation was present between HF and fasting glucose during sleep. Since there were only 4 subjects in the impaired fasting glucose group, we did not divide the population into a normal fasting glucose group and impaired fasting glucose group for statistical analysis. With regard to the difference in HbA1c results between univariate analysis and multivariate analysis, the consistency of results appeared to be reduced because HbA1c was determined in only a limited amount of subjects with a resulting decrease in statistical power.

Previous studies on the relationship between sleep and glucose tolerance used the subjective component of sleep quality along with sleeping time to assess sleep^{21, 22)}. The only previous study in which objective physiological indices were used employed an electroencephalograph to examine slow wave sleep, glucose tolerance and insulin resistance¹¹⁾. In addition, only one study, by Perciaccante *et al.*²³⁾, has examined the relationship between glucose tolerance or insulin resistance and autonomic nervous system activity during nighttime. They examined autonomic nervous system activity over a 1-d period, the relationship between LF, the sympathetic component at night (from 00:00 h to 06:00 h), and the homeostasis model assessment-index, which is an index of insulin resistance, and reported that the higher the LF at night, the greater the insulin resistance. Thus, they focused on the circadian rhythm of the autonomic nervous system and demonstrated a relationship between sympathetic nerve activity at night and insulin resistance²³⁾.

Although a number of previous studies have examined heart rate variability in diabetic patients²⁴⁻²⁹⁾, only a few studies have examined the relationship of normal fasting glucose and impaired fasting glucose with heart rate variability^{8, 23, 30, 31)}. We have shown, for the first time, that there is a relationship between autonomic nervous system activity during sleep and fasting glucose

in apparently healthy workers with either normal fasting glucose or with impaired fasting glucose.

The measurement of cardiovascular autonomic nervous system activity can be performed simply and with low-invasiveness¹⁾; generally, an electrocardiograph is used to take measurements and brief recordings in the resting position are made in the examination room. However, to obtain long recordings, it is necessary to have a portable electrocardiograph attached and to also take into account constraints in terms of measurement locations and attachment to relatively large equipment. However, the advantage of our study is that it was possible to assess actual autonomic nervous system activity during sleep at home by using a small sensor that hardly disrupts sleep. Although autonomic nervous system activity during the day is affected by various daily activities^{32, 33)}, since measurements were taken during sleep in this study, we believed that these effects were minimal and that measurements were taken in a relatively stable manner.

The results of our study suggest that parasympathetic stimulation during sleep at night may improve glucose tolerance. For parasympathetic nervous system during sleep at night to be predominant, relaxation techniques (e.g., breathing techniques, progressive muscle relaxation, appropriate music, and aromatherapy) can be applied, as well as techniques to reduce stimulation to the sympathetic nervous system (e.g., coping with stress, limiting the intake of caffeine and other stimulants, and adjusting the lighting)³⁴⁾. Studies need to be conducted to verify whether sleep guidance may be effective for causing parasympathetic nervous system during sleep to be predominant, thereby improving impaired glucose tolerance and insulin resistance.

A limitation of this study is that no adjustments were made for any confounders that may have affected autonomic nervous system activity, e.g., smoking, caffeine intake, exercise habits, and diet. In this study, an oral glucose tolerance test was not performed. Therefore, it was impossible to completely exclude patients with diabetes mellitus. In addition, diabetes is one of the most common causes of autonomic neuropathy^{9, 35, 36)}, and cardiac autonomic dysfunction is a complication that can be easily overlooked³⁷⁾. In our study, we measured normal fasting glucose and impaired fasting glucose based on the supposition that diabetic autonomic neuropathy would not affect the results of this study; however, this was not possible to verify. In our study, there was a limit to the compatibility of units for the data on the autonomic nervous system. In general, LF and HF are expressed as the area (ms²) obtained by fast Fourier transform analysis, but this equipment measures the peak height (ms) of every component in

the areas obtained to approximately express LF and HF. Autonomic nervous system activity is affected by body position³³), but in our study, measurements were taken without controlling for any shift in body position during sleep or for any differences in posture between individuals.

Suppression of slow wave sleep by sleep fragmentation has been reported to significantly reduce glucose effectiveness and insulin sensitivity³⁸). In the present study, because sleep evaluation by an electroencephalograph was not performed, it was not possible to assess the effect of sleep stages on glucose tolerance. Although there are limitations to our study, our results suggest that parasympathetic activity during sleep is associated with fasting glucose in apparently healthy Japanese workers.

Acknowledgements

The present study was supported by a Grant-in-Aid (No. 20590613) from the Japan Society for the Promotion of Science.

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