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ORIGINAL ARTICLE

Sleep Apnea, Sleep Disturbance, and Fasting Glucose Variability: A Pilot Study

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Abstract

Background:

Disturbed sleep and nocturnal altered breathing are related to disturbances of glucose metabolism. The present uncontrolled observational study explores the role of these factors on the variability of fasting glycemia.

Methods:

The number and duration of nocturnal awakenings and the fasting glycemia of 97 patients with type 2 diabetes treated with diet, metformin, or gliptins were recorded over seven consecutive days. During the same time period, the main respiratory indexes—oxygen disturbance index, apnea/hypopnea index, and respiratory disturbance index—were recorded for one night.

Results:

The three respiratory indexes and the number of nocturnal awakenings are highly correlated with the coefficient of variation of the fasting blood glucose recorded over the 7-day period at $p < .005$ level. A multiple regression analysis showed that the variables in the model explained 86% of the variability.

Discussion:

Respiratory/sleep disturbances appear to be modulators superimposed on blood glucose levels determined by other factors.

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Abbreviations: (AHI) apnea/hypopnea index, (BMI) body mass index, (CV) coefficient of variation, (FBG) fasting blood glucose, (GV) glucose variability, (HbA1c) glycated hemoglobin, (nAW) number of awakenings, (O2 Desat) total number of episodes of oxygen desaturation, (ODI) oxygen disturbance index, (OSAS) obstructive sleep apnea syndrome, (RDI) respiratory disturbance index, (SD) standard deviation, (SLD) sleep disruption, (SMBG) self-monitoring of blood glucose, (s-time) time spent sleeping

Keywords: glucose variability, obstructive sleep apnea syndrome

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Introduction

Glucose variability (GV) is actually recognized as a major cause of diabetes complications.[1–4] A balanced analysis of the available evidence on this topic can be found in a review.[5] The role of GV is extremely complex, probably because it is one of the many factors in the pathway that leads to diabetes complications, and thus, it is exceedingly difficult to identify its role independent of others. To further complicate the context, many different metric indexes of GV have been proposed, but none have been universally accepted. At present, the extent of the influence of GV on the appearance and/or the evolution of diabetes complications is far from clear. The glucose level in the blood results from the interaction of many factors.[6] One interesting player whose role has not yet been fully elucidated is the brain, which is highly active overnight.[7,8] Among the phenomena that modulate the activity of the brain, a critical one is sleep. There is evidence of a negative effect of sleep disruption (SLD) on insulin sensitivity[9] and fasting blood glucose (FBG).[10] In turn, SLD may be caused by disturbed respiration, as experienced in obstructive sleep apnea syndrome (OSAS), and there are data pointing to a negative effect of OSAS on blood glucose control.[11] The anoxia of OSAS is a potent stimulus of catecholamine secretion[12] and can probably also increase blood glucose levels through other mechanisms. The interaction of sleep with breathing is remarkably tight; therefore, differentiating the role of one versus the other on blood glucose control is exceedingly difficult. While both can potentially increase blood glucose levels, it is not known whether they act independently of each other or synergistically or additively. We hypothesized that the irregular stimulus of the OSAS/SLD occurring overnight may be a cause of the extreme variability of the FBG commonly seen in type 2 diabetes subjects. Thus, we selected to study the variability soon after sleep to exploit the close temporal relationship and to avoid the interference of meal-related blood glucose peaks.

Materials and Methods

A total of 187 overweight obese patients with diabetes, with a history of snoring, were studied for respiratory/sleep disorders according to the internal protocol;[13] 97 subjects from this group, age range 30–68 years, 57 males and 40 females, were included in the present study. Inclusion criteria were: treatment with diet, metformin, or gliptins or a combination of them. These drugs do not cause hypoglycemia and the attendant glucose instability. Exclusion criteria were: use of insulin or sulfonylurea drugs, presence of pulmonary or other complications, use of drugs interfering with breathing (such as benzodiazepines, nonsteroidal anti-inflammatory agents, or beta blockers), or presence of more than one abnormal cardiovascular autonomic function test. Anthropometric measures were recorded, and body mass index (BMI) was calculated. The patients were prescribed a diet tailored to their metabolic needs, with 50% carbohydrate, 30% fat (mostly monounsaturated fatty acids), and the remainder as protein. During the study period, the subjects maintained their sedentary habits. All participants gave informed consent to the anonymous use of their data.

The study protocol required recording the number and the characteristics of the nocturnal awakenings and the FBG for 7 days and the respiratory indexes for one night during the same period. To this aim, the subjects wore, for seven consecutive days, the armband, which is an extensively validated tool that can measure the characteristics of sleep and the number of awakenings (nAW).[14–16] This tool is applied to the forearm throughout the duration of the study. The instrument gives a report of the time spent sleeping (s-time), the nAW, the duration of the awakenings, and the number of daytime sleeping episodes. The subjects recorded their FBG within 15 min of the final awakening throughout the period of observation, with a home blood glucose monitor manufactured by Roche, using an interference-free electrochemical method [self-monitoring of blood glucose (SMBG)]. Blood glucose meters were routinely calibrated according to the internal procedure of the department. The precision of the meters was within 4% of the reference laboratory. All values were downloaded, and the standard deviation (SD) of the FBG was calculated as an index of variability. Because the SD has a strict correlation with the mean blood glucose value, the coefficient of variation (CV) was used for statistical evaluation.[17] In the study population, glycated hemoglobin (HbA1c), SD, and CV were not significantly interrelated (p = not significant). All subjects also underwent a polysomnographic analysis with the home monitor Watch Pat 200 (Itamar Medical) that calculates the main respiratory indexes: oxygen disturbance index (ODI), apnea/hypopnea index (AHI), respiratory disturbance index (RDI), the total sleep time, and the total number of episodes of oxygen desaturation (O_2 Desat). The data of seven subjects were unavailable due to technical failures.

The SPSS package (version 19) was used for statistical analysis of correlations and multiple regression. The characteristics of the population studied are reported in **Table 1**. The variables included in the correlation analysis were BMI, age, sex, s-time, AHI, RDI, ODI, nAW, and O_2 Desat.

The same variables were entered for linear regression analysis, but the model retained only s-time, RDI, AHI, and nAW.

Table 1.
Description of the Population

	BMI (kg/m^2)	Male/ female	Age (years)	Total sleep time index (h)	RDI	AHI	ODI	O_2 Desat	nAW	FBG mmol/liter	HbA1c (%)
Mean ± SD	30.76 ± 5	61%/39%	58 ± 6	6.0 ± 1.5	32.3 ± 16	29.4 ± 16	22.5 ± 14	71.8 ± 0.9	7.5 ± 2.3	8.7 ± 1.5	8.5 ± 1.8

Results

Table 1 reports the characteristics of the study population.

In the overall population, the number of awakenings and the respiratory indexes were significantly related to the CV of the FBG (**Table 2**). The HbA1c was related to the SD (p = .049) but not to the CV, the nAW, or the respiratory indexes.

Table 2.
Correlation among Some of the Variables Examined

	Total sleep time index	AHI	RDI	ODI	O_2 Desat	nAW	FBG (average)
CV, correlation coefficient	0.298[a]	0.866[a]	0.873[a]	0.781[a]	0.762[a]	0.774[a]	0.380[a]
Significant (2-T[b])	0.007	0.000	0.000	0.000	0.000	0.000	0.000

[a] Correlation significant at <0.01 level.
[b] Two-tail statistics

The linear logistic regression model, including BMI, age, respiratory indexes, O_2 Desat, and nAW, accounted for 86% of the CV. Only two respiratory indexes, AHI and RDI, as well as nAW entered the final regression with a level of significance <0.05 (**Table 3**).

Table 3.
Linear Regression of the Variables Entered in the Model ($p < .05$; r^2c of the Model = 0.864; Dependent Variable Coefficient of Variation of the Fasting Blood Glucose)

	Total sleep time index	RDI	AHI	nAW
β	0.129	0.534	0.788	0.421
Significant	0.2	0.027	0.009	0.000

The population was further divided into those with more serious OSAS (respiratory indexes ≥10; 72 subjects) and those with slight OSAS (respiratory indexes <10; 18 subjects), and the linear regression was repeated for both. The adjusted r^2 retained the same level of significance in each subgroup, and the B value of the nAW increased substantially in the slight OSAS subgroup, while the correlation between the respiratory indexes and CV lost significance. The CV of the slight OSAS subjects was 9.0% ± 3% versus 15.2% ± 5% for serious OSAS.

When the population was divided according to three levels of progressively increasing HbA1c (<7.5, 7.6–9, ≥9.1; **Table 4**), the correlation values of the three respiratory indexes and the number of awakenings remained relatively constant throughout.

Table 4.
Subgroups According to the Glycated Hemoglobin Level (≤7.5%, 7.6–9%, ≥9.1%)[a]

Strata		BMI (kg/m²)	Age (years)	Total sleep time index (h)	RDI	AHI	ODI	O_2 Desat	nAW
HbA1c ≤ 7.5 (*n* = 29)	Correlation significant (2-T)	0.009 *N*	-0.282 0.139	0.534[b] 0.007	0.899[b] 0.000	0.883[b] 0.000	0.804[b] 0.000	0.765[b] 0.000	0.593[b] 0.001
HbA1c 7.6–9 (*n* = 38)	Correlation significant (2-T)	0.134 0.435	-0.266 0.106	0.254 0.135	0.879[b] 0.000	0.870[b] 0.000	0.762[b] 0.000	0.755[b] 0.000	0.681[b] 0.000
HbA1c > 9.1 (*n* = 24)	Correlation significant (2-T)	0.099 0.678	-0.097 0.650	-0.061 0.789	0.909[b] 0.000	0.941[b] 0.000	0.891[b] 0.000	0.778[b] 0.000	0.871[b] 0.000

N = number of patients; 2-T, two-tail statistics
[a] Throughout the groups, the correlation level of the respiratory indices and the nAW with the CV of the FBG remained relatively constant.
[b] Correlation significant at a <0.01 level.

Discussion

A normal breathing pattern and a normal sleep pattern are essential to survival, and the effects of their derangements on body functions are well recognized in the medical literature.[18–21] Thus it is unexpected that more papers dealing with the relationship of OSAS/sleep and glucose metabolism have appeared and, to our knowledge, none dealing with GV. This article explores a potential effect of the breathing/sleeping pattern on the day-to-day instability of the FBG (FBG variability), not with the biological entity commonly defined as GV, which has a different meaning and requires a different methodology of data collection.[22] This is one of the reasons why we did not use continuous glucose monitoring together with the greater precision of the existing blood glucose meters. All results of the present uncontrolled observational study apply only to this effect. The risk of an increased variability of the FBG on survival was demonstrated some years ago.[23] The high correlation of the CV with the number of nocturnal awakenings (0.774; $p = .000$) in the population examined is not surprising. Any form of nocturnal awakening is a stressful condition and can induce an increase in blood glucose.[24] The use of the SMBG to calculate day-to-day blood GV may be a moot point since all available glucose meters have an inherent error that may reach +15%. However, with most meters, the error is minimized, and SMBG is the most affordable way to evaluate FBG. Furthermore, the consistent number of subjects studied for a long period gives substantial statistical support to the results, and the accuracy of the meter used versus the laboratory results was 4% in our hands.

The present data indicate that both the most common respiratory indexes of OSAS/disturbed respiration and the number of nocturnal awakenings have a high degree of correlation with the CV of the FBG taken over 7 days. With multiple regression analysis, the variables in the model overall explained 86% of the variability and only RDI, AHI, and average nAW were found to contribute to it at a statistically significant rate.

Among subjects with more serious OSAS, the levels of correlation and the beta coefficients of the regression analysis were substantially the same as those found in the total population studied. Among those with mild respiratory disturbance, only the nAW retained a high level of correlation with the CV. The linear regression analysis in this latter group yielded $r^2 = 0.842$, with the only variable reaching a statistically significant level being nAW ($p = .026$; beta coefficient = 0.523). These results suggest the existence of robust effects of sleep disturbance on glucose CV. The consistency of the correlation coefficients throughout the three HbA1c levels (**Table 4**) suggests that both OSAS and sleep disturbance can be seen as modulators superimposed on a blood glucose level fixed by other factors.

There are at least two weaknesses in this study. First, this is an observational study and not a controlled intervention trial. Moreover, the question of whether increased nocturnal OSAS/nAW may cause a long-lasting effect on daytime GV has not been addressed and needs to be further investigated.

More areas need to be clarified, such as the role of other aspects of OSAS/nAW on the CV of the FBG: depth, duration, frequency of the episodes; the role of the different phases of sleep when the OSAS/awakenings occur; the role of

time when sleeping starts; and the role of the many drugs that diabetes patients take. More important, what the term "awakening" really means has yet to be explored: what is the role of awakening, which can happen in more or less stressful conditions, and what are the roles of the duration of each episode of awakening? The armband records the duration of sleep and bed rest, but no relevant correlation between these two parameters and the CV of the FBG appeared.

One consideration should be made regarding the opportunity to use three different indexes obtained from the polysomnographic analysis: AHI, RDI, and ODI. Each explores a different aspect of nocturnal breathing, thus keeping them distinct during the analysis is appropriate. On the other hand, if we combine the three indexes as an overall "respiratory burden" on glucose modulation, the role of breathing becomes overly preponderant on the variability of the FBG.

Conclusions

The respiratory disturbances and the number of nocturnal awakenings appear to act additively to determine the variability of the FBG, superimposed on a blood glucose level fixed by other factors. In the presence of severe OSAS, both the respiratory distress and the number of awakenings concur to cause the phenomenon. If the respiratory disturbance is mild, the number of nocturnal awakenings becomes the main determinant of FBG variability.

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