Decreased Nocturnal Glucose Variability in Non-Diabetic Patients with Sleep Apnea: A Pilot Study

Arnon Elizur MD[1,2*], Amit Maliar MD PhD[3*], Isaac Shpirer MD[2,4], Andreas E. Buchs MD[5], Eli Shiloah MD[3] and Micha J. Rapoport MD[3]

[1]Department of Pediatrics, [2]Sleep Laboratory, [3]Department of Medicine C and Diabetes Unit, [4]Institute of Pulmonary Medicine, and [5]Department of Medicine D, Assaf Harofeh Medical Center, Zerifin, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

ABSTRACT: **Background:** Obstructive sleep apnea has been shown to be associated with impaired glucose metabolism and overt diabetes mellitus. However, the effect of hypoxic episodes on nocturnal glucose regulation in non-diabetic patients is unknown.

Objectives: To investigate the effect of hypoxemia and nocturnal glucose homeosatsis in non-diabetic patients with sleep apnea.

Methods: Seven non-diabetic patients with moderate to severe sleep apnea were connected to a continuous glucose-monitoring sensor while undergoing overnight polysomnography. Mean SpO_2 and percentage of time spent at SpO_2 < 90% were recorded. The correlation between mean glucose levels, the difference between consecutive mean glucose measurements (glucose variability) and the corresponding oxygen saturation variables were determined in each patient during REM and non-REM sleep.

Results: No consistent correlation was found for the individual patient between oxygen saturation variables and glucose levels during sleep. However, a lower mean SpO_2 correlated with decreased glucose variability during sleep ($r = 0.79$, $P = 0.034$). This effect was primarily evident during REM sleep in patients with significant, compared to those with mild, oxygen desaturations during sleep (> 30% vs. < 10% of sleeping time spent with SpO_2 < 90%) ($P = 0.03$).

Conclusions: Severe nocturnal hypoxemia in non-diabetic patients with moderate to severe sleep apnea might affect glucose regulation primarily during REM sleep.

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KEY WORDS: obstructive sleep apnea (OSA), glucose sensor, glucose variability, hypoxemia, polysomnography, REM sleep, sleep apnea

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Obstructive sleep apnea is a common disorder, characterized by frequent episodes of apnea and hypopnea associated with daytime somnolence [1]. In recent years, OSA has been considered part of the metabolic syndrome and implicated in the development of type 2 diabetes [2]. Glucose intolerance and type 2 diabetes were found by several epidemiological studies to be associated with OSA [3-5]. Both the degree of OSA and the severity of hypoxemia are associated with glucose intolerance and increased risk of diabetes [6-8].

The mechanisms whereby OSA might interfere with glucose homeostasis are not clear. One potential mechanism involves alterations in autonomic and neuroendocrine function. It has been shown that hypoxemia, hypercarbia and repeated arousals during sleep stimulate alteration in autonomic activity and influence glucose homeostasis by increasing glycogen breakdown and gluconeogenesis [9-11]. Other potential mechanisms include activation of the hypothalamic-pituitary axis, decreased hepatic production of insulin growth factor-1, and alterations in the production of adipokines and inflammatory cytokines, especially tumor necrosis factor-alpha [12]. Whether these alterations affect short-term glucose regulation and correlate with the degree of hypoxemia are not elucidated. Regardless of the exact mechanism(s), an early sign of abnormal glucose regulation is a modified insulin oscillatory secretion profile resulting in flattened concurrent glucose oscillatory profiles. These patterns of insulin secretion and glucose profiles during the so-called pre-diabetic phase are seen in subjects with impaired glucose tolerance whose type 2 diabetes mellitus develops later [13].

It is of paramount importance to identify the early changes in glucose homeostasis in patients with OSA prior to the development of frank glucose intolerance as it may enable early treatment. Continuous glucose monitoring has been used previously to demonstrate abnormal glucose responses in non-diabetic patients with mild sleep apnea [14]. However, no association was found between OSA severity and glucose control. In addition, patients with severe OSA, who are more likely to develop glucose regulation impairment, were not studied. In the present study, we used continuous glucose monitoring to investigate the correlation between oxygen saturation during sleep and glucose levels in patients with moderate to severe OSA (apnea hypopnea index > 15).

PATIENTS AND METHODS

Seven consecutive patients between the ages of 40 and 80 years with moderate to severe OSA and without diabetes mel-

*The first two authors contributed equally to this study

REM = rapid eye movement

OSA = obstructive sleep apnea

litus participated in the study. All patients signed an informed consent and the study was approved by our institutional ethics committee. Patients filled a questionnaire on baseline demographics (age, gender, and weight and height for calculating body mass index) and underlying diagnoses (diabetes mellitus, hypertension, ischemic heart disease). Patients underwent initial screening polysomnography to determine the severity of obstructive sleep apnea. Subsequently, patients with moderate to severe OSA underwent a second PSG concomitantly with continuous glucose measurements. At the beginning of that night, a subcutaneous electrode connected to a continuous glucose monitoring sensor was inserted into each patient. The CGMS was calibrated with the capillary glucose level before and after PSG. Patients underwent a fasting blood glucose test on the morning following the PSG.

POLYSOMNOGRAPHY

A standard in-laboratory overnight PSG using a computerized PSG system (Embla, Flaga Medical; Reykjavik, Iceland) with the following channels was performed: electroencephalography (C3-A2 and O2-A1), electrooculogram (right and left), chin electromyogram, arterial oxygen saturation, nasal pressure, electrocardiogram, chest and abdominal wall motion, bilateral tibialis electromyogram, and body position. The PSG recordings were scored manually for REM sleep stages, non-REM (NREM) stages (STAGE 1, STAGE 2, and STAGE 3 and 4), and for respiratory events (apnea/hypopnea), according to the American Academy of Sleep Medicine criteria (1999) [15-17]. Hypopnea was defined as a 10 second airflow reduction > 50% of baseline or a reduction > 30% with ≥ 4% oxygen desaturation. Scoring was performed by a single-blinded experienced scorer. The exact hour of the PSG system and the CGMS monitor were calibrated.

CONTINUOUS GLUCOSE MONITORING

The CGMS is a belt-worn device connected to a subcutaneous electrode that continuously measures the subcutaneous interstitial glucose. The monitor measures the glucose level in 10 sec intervals and stores the average value every 5 minutes. The correlation coefficient between glucose levels measured by blood glucose meters and those measured by CGMS are reported to be between 0.84 and 1.0 with a mean absolute error of 7% to 17% [18]. The measured interstitial blood glucose levels may lag after blood glucose acute change by 4 to 10 minutes [19]. Data were downloaded to a personal computer using the CGMS software (Minimed Medtronic Northridge, CA, USA) and were processed. Glucose levels were measured by the CGMS in 5 minute intervals. Mean 5 min glucose was defined as the average of all 5 min glucose measurements. Differences in interstitial glucose levels between all consecutive measurement points were also calculated. Mean 5 min glucose variability was defined as the average value of all these measurements. The PSG data, which are measured in 1 second intervals, were combined to create averages of all the recordings in the 5 min corresponding to the same 5 min of the glucose levels reading. Mean 5 min SpO_2 was defined as the average of all 5 min SpO_2 recordings. The percent time spent at $SpO_2 < 90\%$ during each 5 min epoch was also calculated. Mean 5 min $SpO_2 < 90\%$ was defined as the average value of all these recordings. Mean 5 min heart rate was defined as the average of all 5 min heart rate recordings. Continuous parameters analyzed for each patient for every 5 min interval included mean SpO_2, mean heart rate, time spent at $SpO_2 < 90\%$, mean glucose level, and glucose variability.

STATISTICAL ANALYSIS

Analyses were performed using SPSS 16.0 for Windows. Fisher's exact test was used to analyze the relationship between categorical variables. Continuous variables were not normally distributed and the Mann-Whitney non-parametric test was used to analyze the relationship between these variables. Pearson's correlation coefficient was used to analyze the correlation between continuous variables. Values are expressed as means ± standard deviation unless otherwise stated. A P value < 0.05 was considered significant.

RESULTS

A total sleeping time of 2710 minutes was recorded. The mean recording time for a patient was 385.7 minutes (range 330–450 min). The demographic characteristics, sleep parameters and glucose recordings (mean levels and variability) of each patient are shown in Table 1. None of the patients had known diabetes, and fasting blood glucose was normal in six patients and borderline in one. Three patients were overweight (BMI > 25) and four were obese (BMI > 30). Of the seven patients studied, four had spent > 30% of the sleep time at $SpO_2 < 90\%$ compared to < 10% in the other three [Table 1].

EFFECTS OF HYPOXEMIA ON GLUCOSE VARIABILITY

Analysis of single patients did not provide significant correlations between oxygen saturation variables during sleep and glucose measurements. Large variations were found among single patients. Therefore, we analyzed the correlation between demographic variables, sleep-related parameters, and glucose measurements (mean 5 min glucose levels and mean 5 min glucose variability) in the whole group. No correlation was found between age or BMI and sleep-related parameters (AHI, oxygen desaturations, heart rate, arousals). BMI was inversely correlated with mean nocturnal glucose levels, i.e., the higher the BMI the lower the glucose levels during sleep (r = -0.83, P = 0.02), but

PSG = polysomnography
CGMS = continuous glucose monitoring sensor
BMI = body mass index
AHI = apnea hypopnea index

Table 1. Demographic and sleep characteristics of the study patients

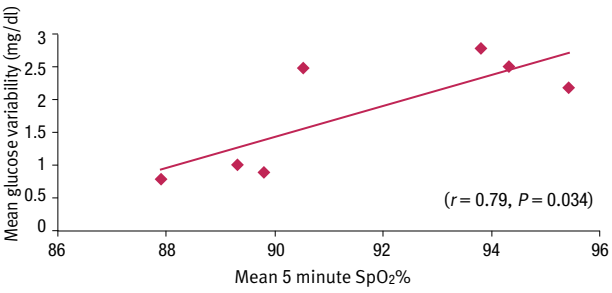
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (yr)	77	51	44	45	47	58	55
Gender	F	M	M	M	M	M	F
BMI	34.1	26.8	34.3	32.7	26.6	37.6	26.7
Apnea hypopnea index	47.8	80.4	70.4	43	42.5	22.5	37.2
Mean SpO_2%	93.9 ± 1.1	90.5 ± 1.1	89.5 ± 2.6	89.3 ± 3.6	95.4 ± 2.8	94.2 ± 1.7	87.3 ± 7.4
Mean pulse (1/min)	60.8 ± 2.5	91.9 ± 8.2	69.1 ± 6.4	67.6 ± 5.0	59.8 ± 3.9	74.1 ± 2.7	79.0 ± 5.1
Time with SpO_2 < 90%	8.3%	41.1%	37.3%	34.6%	7.1%	4.1%	33.8%
Desaturation index (1/hr)	42.3	79	74.6	42.3	28.2	23	37.2
Mean glucose (mg/dl)	77.2 ± 14.2	101.0 ±11.7	98.1 ± 6.2	101.1 ± 5.8	107.2 ± 11.8	77.4 ± 10.7	106.5 ± 8.4
Mean glucose variability (mg/dl)	2.8 ± 3.5	2.5 ± 3.5	0.9 ± 1.4	1.0 ± 1.3	2.2 ± 3.0	2.5 ± 3.2	0.8 ± 0.6
REM sleep	10%	5.9%	7.7%	18.8%	6.8%	13.1%	16.1%
Mean REM SpO_2%	94.3 ± 1.0	90.6 ± 0.4	87.2 ± 1.0	83.8 ± 3.1	93 ± 3.1	92.5 ± 3.3	88.7 ± 6.4
Mean NREM SpO_2%	93.8 ± 1.1	90.4 ± 1.1	89.7 ± 2.6	90.2 ± 2.3	95.6 ± 2.7	94.4 ± 1.1	87 ± 7.6
REM time with SpO_2 < 90%	7.5 ± 8.4	43.1 ± 7.9	78.3 ± 13.9	68 ± 14.9	19.6 ± 23.7	22.4 ± 30.3	25 ± 27.6
NREM time with SpO_2 < 90%	8.7 ± 9.0	40.1 ± 12.5	33.8 ± 19.3	27.5 ± 24.3	6.0 ± 15.6	1.7 ± 5.8	37.4 ± 34.7
Mean REMglucose (mg/dl)	89.3 ± 23	107.3 ± 0.5	89.5 ± 0.8	98.1 ± 5.1	128.8 ± 2.8	77.6 ± 2.9	107.1 ± 8.4
Mean NREM glucose (mg/dl)	75.8 ± 12.4	100.6 ± 11.9	98.8 ± 5.9	101.8 ± 5.8	105.6 ± 10.6	77.3 ± 11.5	106.3 ± 8.5
Mean REM glucose variability (mg/dl)	5.4 ± 4.8	0.5 ± 0.6	0.5 ± 0.8	1.1 ± 1.2	2.4 ± 2.0	2.0 ± 3.2	0.6 ± 0.7
Mean NREM glucose variability (mg/dl)	1.9 ± 3.2	2.6 ± 3.6	0.9 ± 1.5	1.0 ± 1.3	2.1 ± 3.1	2.6 ± 3.3	0.8 ± 0.6

*Mean of all 5 minute measurements ± SD

**Mean difference between all consecutive 5 minute glucose measurements

there was no effect on glucose variability. No significant correlation was found between sleep-related parameters and mean 5 min glucose levels during sleep, although patients with lower mean oxygen saturations and larger time spent with SpO_2 < 90% had a trend for higher mean glucose levels during sleep. Glucose variability did not show a correlation with either the arousal index or desatuartion index. Interestingly, lower mean 5 min SpO_2 significantly correlated with lower glucose variability (r = 0.79. P = 0.034) [Figure 1]. The associations between glucose measurements and oxygen saturations in two 1 hour epochs from two different patients are shown in Figure 2.

Figure 1. Hypoxemia correlates with decreased glucose variability during sleep. The correlation between the average differences between all consecutive glucose measurements (glucose variability), and the average of the corresponding percent time spent at SpO_2 < 90% for all patients



HYPOXEMIA AND GLUCOSE VARIABILITY DURING REM AND NON-REM SLEEP

We next examined whether hypoxemia correlates with glucose measurements in specific sleep periods, i.e., REM vs. non-REM sleep. Of the parameters tested, increased time spent with SpO_2 < 90% during sleep correlated with lower glucose variability during REM sleep (r = -0.75, P = 0.05). REM and non-REM related hypoxemia did not correlate with REM and non-REM glucose measurements respectively. Our seven patients, although all had moderate-severe OSA, could be divided into two significantly different groups in terms of the time spent with oxygen saturation < 90% during sleep. We therefore divided the patients into those with significant and those with mild hypoxemia, i.e., > 30% vs. < 10% of the time spent at SpO_2 < 90% respectively [Table 2].

Demographic variables were not different between the two groups. Mean 5 min glucose levels and glucose variability were also not significantly different. However, when comparing these parameters based on sleep stages (REM vs. NREM) we found that patients who spent more time at SpO_2 < 90% demonstrated a significant decrease in glucose variability only during REM sleep but not during NREM periods (P = 0.03).

NREM = non-REM

Figure 2. The correlation between glucose levels and oxygen desaturations in two 1 hour epochs in two patients. Two 1 hour epoch recordings demonstrate continuous oxygen saturation and glucose levels (with the resulting glucose variability). **[A]** 1 hour epoch without oxygen desaturations, and **[B]** 1 hour epoch with significant oxygen desaturations

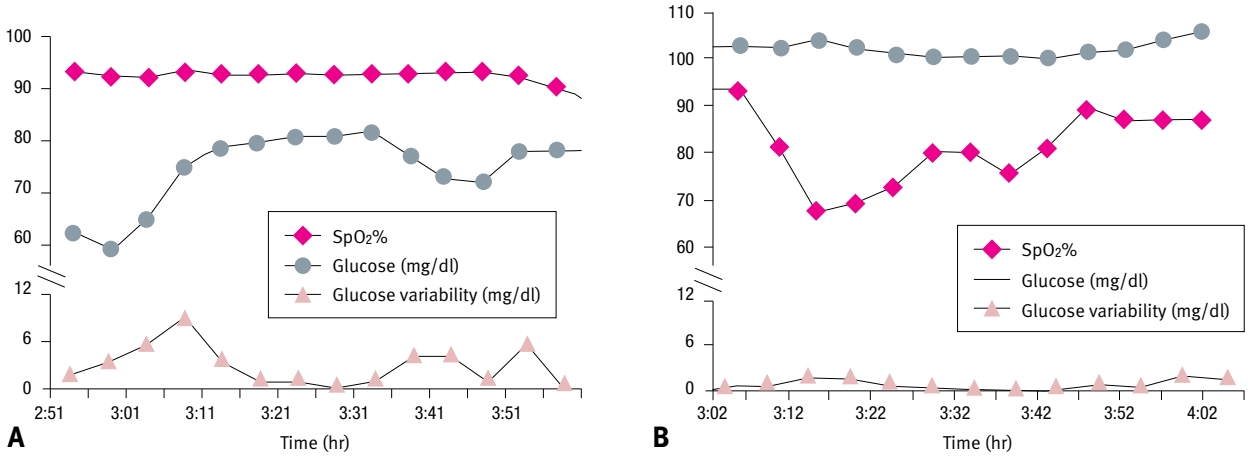


Table 2. Comparison of patients with mild and patients with severe nocturnal oxygen desaturations

	Mild group† (n=3)	Severe group†† (n=4)	*P* value
Age (yr)	60.7 ± 15.2	48.8 ± 5.2	0.16
Male gender	67%	75%	1.0
BMI	32.8 ± 5.6	30.1 ± 3.9	0.72
Apnea hypopnea index	37.6 ± 13.3	57.8 ± 20.9	0.29
Mean 5 min SpO_2 (%)	94.5 ± 0.8	87.4 ± 1.1	0.034
Mean 5 min SpO_2 < 90%	6.5 ± 2.2	36.7 ± 3.3	0.034
Mean 5 min glucose (mg)*	88.9 ± 16.5	101.8 ± 3.3	0.48
Mean 5 min glucose variability (mg)**	2.5 ± 0.3	1.3 ± 0.8	0.11
REM sleep (%)	10 ± 3.2	12.1 ± 6.3	0.62
Mean 5 min NREM glucose (mg)*	86.4 ± 16.6	101.9 ± 3.2	0.29
Mean 5 min REM glucose (mg)*	98.6 ± 26.8	100.5 ± 8.5	0.48
Mean 5 min NREM glucose variability (mg)**	2.2 ± 0.4	1.3 ± 0.9	0.21
Mean 5 min REM glucose variability (mg)**	3.3 ± 1.9	0.7 ± 2.9	0.032

†Mild group = patients who spent < 10% of their sleeping time with SpO_2 < 90%
††Severe group = patients who spent > 30% of their sleeping time with SpO_2 < 90%
*Mean of all 5 minute measurements ± SD
**Mean differences between all consecutive 5 minute glucose measurements

DISCUSSION

This study demonstrates for the first time in non-diabetic patients with moderate to severe sleep apnea that measures of hypoxemia during sleep correlate with decreased variability of interstitial glucose. The decreased glucose variability may indicate aberration of normal glucose homeostasis and loss of fine tuning in patients with nocturnal hypoxemia, which is primarily evident during REM sleep.

The association between sleep apnea and diabetes was previously demonstrated on several levels. Insulin resistance and type 2 diabetes were shown to be more prevalent in patients with OSA and to improve after continuous positive airway pressure therapy [3-8,20,21]. However, the effect of sleep apnea on continuous glucose levels in diabetic patients has not been extensively studied. Mean glucose levels during sleep, as measured by CGMS in patients with type 2 diabetes and OSA, were found to decrease significantly following a period of CPAP therapy [22,23], underscoring the link between sleep-related breathing disorder and aberrant nocturnal glucose regulation. Even scarcer short-term data regarding the correlation between glucose and oxygen saturations are available in non-diabetic patients. Bialasiewicz and co-authors [14,19] reported that a normal REM-related downward trend in glucose concentrations is reversed in individuals with mild sleep apnea. Our study extends the evidence regarding the effect of nocturnal hypoxemia on glucose levels in non-diabetic patients with OSA. By studying patients with varying degrees of nocturnal hypoxemia we were able to demonstrate that reduced mean SpO_2 correlates with reduced variability in glucose levels throughout the night. This reduced glucose variability was most prominent during REM sleep, as observed in patients who spent > 30% of the night at SpO_2 < 90% compared to those who spent < 10% of the night at SpO_2 < 90%. The effect of hypoxemia and specifically the time spent at SpO_2 < 90% on glucose intolerance were demonstrated previously. Acute intermittent hypoxemia in healthy volunteers was previously shown to induce a decrease in insulin sensitivity, suggesting that hypoxia may interfere with glucose regulation [25]. Animal studies have suggested that increased insulin resistance may result from specific hypoxic

stresses. Hypoxic stress was found to be the best predictor of glucose intolerance and insulin resistance, and the time spent at an oxygen saturation of < 90% the strongest index associated with impaired glucose tolerance [6,8]. We previously demonstrated that HbA1C levels across the spectrum from normal to abnormal correlated with severity of hypoxemia (average SpO_2 and percent time with SpO_2 < 90%) [20]. Loss of the normal insulin oscillatory secretion rates and the resulting decrease in glucose variability is considered a predictor of future type 2 diabetes mellitus [13]. Thus, our finding of significantly decreased glucose variability in patients with severe nocturnal hypoxemia may represent initial impairment of glucose regulation.

We found that increased BMI is associated with lower mean nocturnal glucose levels, but this is in contrast to the known effect of BMI on diabetes and is thus unlikely to be of clinical significance. In addition, the known direct association between BMI and blood glucose is based on averages across time, but data on its association with continuous changes in glucose across the night are lacking and deserve further study. The lack of a consistent association between oxygen desaturations and glucose levels in individual patients suggests that the severity of hypoxemia during sleep cannot be currently used to predict future diabetes in the individual patient. However, for the group as a whole, our data may underscore the missing short-term link between the degree of hypoxemia and glucose homeostasis and suggest that these aberrations may be associated with the long-term development of type 2 diabetes. The small number of patients studied makes it difficult to draw firm conclusions but these findings raise an important link between hypoxemia and glucose regulation that deserves further study.

In summary, this is the first study, to our knowledge, to demonstrate that aberrations in nocturnal glucose homeostasis correlate with the severity of hypoxemia in non-diabetic patients with moderate-severe sleep apnea, primarily during REM sleep. Our findings support the independent effect of OSA on glucose metabolism even in patients without known diabetes. Further larger scale studies with long-term follow-up are needed to determine whether these short-term findings can be confirmed and whether they indeed correlate with the future development of diabetes.

Corresponding author:
Dr. A. Elizur
Dept. of Pediatrics, Assaf Harofeh Medical Center, Zerifin 70300, Israel
Phone: (972-8) 977-9817
Fax: (972-8) 977-9821
email: elizura@gmail.com

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