Glucose and arterial blood pressure variability in obstructive sleep apnea syndrome

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Abstract. – INTRODUCTION: Current evidence supports an association between Obstructive Sleep Apnea Syndrome (OSAS), insulin resistance, type 2 diabetes mellitus (DM) and cardiovascular disorders. The relationship is complex and still remains poorly understood.

AIM: The aim of this study was to examine the potential correlation of sleep characteristics with glucose and arterial pressure values variability in non – diabetic, non-hypertensive patients with OSAS.

SUBJECTS AND METHODS: We examined 22 subjects, 11 men and 11 women (mean age 54 ± 14,5 years), recently diagnosed with OSAS (Apnea – Hypopnea Index (AHI) ≥ 5 apneas/hypopneas per hour of sleep) by full night polysomnography (PSG). Fasting and postprandial after a 2 hour oral glucose tolerance test (OGTT) glucose and insulin levels were measured, and homeostatic model assessment of insulin resistance (HOMA(IR)) index profile as well as Matsuda insulin sensitivity index (ISI) were calculated. A 24 hour glucose monitoring with subcutaneous measurements every 5 minutes and a 24-hour arterial blood pressure (ABP) monitoring (Holter monitoring) were evaluated.

RESULTS: AHI, a widely accepted marker of the severity of OSAS, was correlated with HOMA and Matsuda index ($p = 0.016$ and $p = 0.022$, respectively), Standard Deviation (SD) of glucose measurements ($p = 0.05$) and mean diastolic blood pressure ($p = 0.007$). Percentage of sleep time with saturation of hemoglobin with oxygen, as measured by pulse oximetry, (SpO_2) < 90% was also correlated with HOMA and Matsuda index ($p = 0.014$ and $p = 0.012$, respectively), coefficient of variation (CV) of glucose measurements ($p = 0.009$) and SD of 24-hour systolic blood pressure. Moreover, minimum SpO_2 was correlated with glucose levels ($p = 0.018$), Matsuda index ($p = 0.30$) and SD of 24-hour diastolic and systolic blood pressure ($p = 0.005$ and $p = 0.022$, respectively).

CONCLUSIONS: Glucose and arterial pressure variability were associated with markers of OSAS severity (AHI, % sleep time with SpO_2 < 90%, min SpO_2), among nondiabetic patients. Thus, glucose and arterial pressure variability in OSAS may be an additional marker of cardiovascular risk as well as of future diabetes in these subjects. Nevertheless, the clinical significance of our observations remains to be confirmed by prospective studies.

Key Words:
  Obstructive sleep apnea syndrome (OSAS), Glucose variability, Insulin resistance, Diabetes mellitus (DM), Arterial blood pressure, Cardiovascular disease.

Introduction

OSAS is characterized by repeated episodes of complete or partial obstruction of the upper airway during sleep, associated with increased respiratory efforts, intermittent arterial oxygen desaturation, systemic and pulmonary arterial blood pressure alterations and sleep fragmentation. This clinical condition is a common disorder, affecting approximately 3%-7% of adult men and 2%-5% of adult women in the general population[1]. Recent evidence suggests that one out of five adults suffers from at least a mild degree of OSAS and the prevalence in adults 30-69

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years of age is estimated to 17% (AHI ≥ 5) and is rising to 41-58% in obese patients. This makes the disease almost an epidemic[2,3].

OSAS is associated with considerable morbidity and mortality. The chronic intermittent hypoxia and the sleep loss and fragmentation associated with OSAS increase the levels of various markers of inflammation, oxidative stress, and procoagulant and thrombotic activity[4]. These alterations may contribute to the development of endothelial and metabolic dysfunction, atherosclerosis and cardiovascular disorders associated with OSAS[4].

OSAS and type 2 diabetes mellitus (DM) are common comorbid conditions. Indeed, the prevalence of OSAS is estimated to be between 18% and 36% in patients with type 2 DM[5,6]. Vice versa, the prevalence of type 2 DM is approximately 30% in OSAS patients[7]. Several lines of evidence suggest an independent association of OSAS with insulin resistance and DM[8-13]. However, the exact pathophysiological mechanism of this association remains unclear.

According to the literature, glucose variability seems related to oxidative stress in *in vitro* and animal studies and, although not consistently, in an experimental setting in type 2 diabetes patients[14]. As OSAS is also associated with oxidative stress, glucose variability may be an intermediate link leading to coexistence of the two phenomena.

It is also known that OSAS is associated with increased risk of developing hypertension and its complications, independently of concomitant risk factors such as obesity[15]. The underlying mechanisms still not clear. Normotensive individuals are characterized by a normal diurnal variation of blood pressure, with higher daytime than nighttime levels, primarily caused by the combined effects of physical activity, postural changes, and the sleep-wake transitions[16]. In contrast, hypertensive patients can be divided into two groups, based on circadian blood pressure patterns 17: dippers manifest a reduction of blood pressure during the night, whereas nondippers exhibit persistently elevated blood pressure through the 24-h time period.

Glucose concentration and hemodynamic parameters seem to be tightly linked, both in health and in disease. We investigated continuously measured glucose concentrations and arterial pressure during a 24-hours cycle in patients with OSAS, in order to establish a possible functional coupling in the pathophysiology of impaired glucose tolerant states or hypertension.

Subject and Methods

Study Group

Twenty two consecutive male and female patients, with recently diagnosed OSAS (AHI ≥ 5/hour) by full polysomnography between January and June 2011, comprised the study group. Each participant was evaluated by full clinical examination and completed a validated questionnaire about sleep habits (Pittsburgh Sleep Quality Questionnaire).

Exclusion criteria were: known diabetes mellitus or fasting glycemia (fasting glucose < 126 mg/dl or glycosylated hemoglobin [HbA1c] < 6.5%), current smoking, cardiovascular or cerebrovascular disease, hypertension or other chronic disease, systemic medication use, as well as previous diagnosis/treatment for OSAS.

The study was approved by the Institutional Ethics Committee and all subjects gave written informed consent.

Polysomnography

Each subject underwent standard full night polysomnography (PSG). Sleep records were manually scored, according to standardized criteria[18].

Apnea was defined as the breathing cessation that exceeded 10 sec. In addition, hypopnea was defined as the reduction in airflow of approximately 30% which was associated with a reduction of 3% or more of oxyhemoglobin saturation. Arousal was defined as continuous alpha activity in electroencephalogram (EEG) and increased electromyographic (EMG) activity of > 3 sec. AHI was defined as the total number of apneas and hypopneas per hour of electroencephalographic sleep. Arousal Index (AI) was the total number of arousals per hour of recorded sleep.

OSAS was defined as an AHI of ≥ 5/hour. Continuous Positive Airway Pressure (CPAP) was adjusted during attended laboratory polysomnography if indicated for the treatment.

Blood Assays

Fasting venous blood samples were collected the day after PSG, between 8 and 9 AM, after an overnight fast. Biochemical analyses were performed in an ILAB 600 analyzer (Biochem, Tokyo, Japan) with enzymatic method for glucose (mg/dL), while HbA1c was measured by high-performance liquid chromatography (Adams A1c HA-8160; Arkray, Kyoto, Japan). Insulin was measured using commercially avail-

able enzyme-linked immunosorbent assay (Yanaihara Institute Inc., Shizuoka, Japan). The homeostasis model assessment (HOMA) insulin resistance index, as a measure of insulin sensitivity, was calculated using the following calculation: fasting insulin concentration ($\square$U/ml) × fasting glucose concentration (mmol/l)/22.5. The Matsuda index of insulin sensitivity was calculated as follows, with glucose and insulin values in mmol/L and pmol/L, respectively: 10.000/(G0 × I0 × Gm × Im) 0.5, where G0 and I0 are pre-meal values for insulin and glucose and Gm and Im are mean post-meal values during the first 120 min of the liquid meal tolerance test.

Continuous Glucose Determinations

Continuous glucose measurements were performed when every 5 min by means of a MiniMed continuous glucose monitoring system (Medtronic, Inc., Northridge, CA, USA)[16], designed to measure a range of glucose concentrations from 2.2 to 22.2 mmol/l by an amperometric method, using the MiniMed Continuous Glucose Monitor (MMT-7102), a special CGMS electrochemical sensor with glucose oxidase immobilized to an electrode, fitted on a tiny catheter inserted endodermally through a sterile 22-gauge needle and secured into the abdominal subcutaneous tissue for sampling at 5-min intervals and the MiniMed communication station (Com-Station; MMT-7301), where from data collected were processed through a serial port to an external personal computer by using the proprietary MiniMed Solutions CGMS Sensor Software program (MMT-7310), designed to eliminate outlier noise during each 5 min interval and to produce a weighted average that reflects glucose during the interval.

After electrode insertion, at least 5 minutes was allowed before the MiniLink™ REAL-Time transmitter was connected to the sensor, allowing time for the electrode to be wetted properly by interstitial fluid. After a 2 hour initialization period, the patient was instructed to conduct a FSBG measurement and to enter it into the CGMS for the first calibration. The FSBG reading needed to be within the 40- to 400-mg/dl range for calibration to be successful. After the initial calibration, the device was calibrated before breakfast, lunch, and dinner throughout the duration the patient wore the sensor.

A total of 288 average measurements were recorded throughout a routine 24-h monitoring period. Patients were advised to have breakfast between 08: 00 and 09: 00 h, lunch between 13: 00 and 14: 00 h and dinner between 18: 30 and 19: 30 h that day.

The glucose variability was calculated by both, the standard deviation (SD) of glucose measurements and the coefficient of variation (CV).

Ambulatory Blood Pressure Measurements

Blood pressure values were measured when every 15 min with a validated portable device (model 90207; SpaceLabs, Inc., Redmond, WA, USA) based on an oscillometric technique and fitted to the nondominant arm, which was programmed to automatically record BP readings every 15 min for 24 hours[19].

For each patient we computed mean 24 h, daytime and night-time SBP and DBP as well as standard deviation (SD) of SBP and DBP. Daytime was defined as the interval between 09:00h and 21:00 h and night-time was the interval between 01:00 h and 06:00 h. According to the BP nocturnal fall, patients were divided into 2 groups: dippers (BP nocturnal fall > 10 mmHg) and non dippers (BP nocturnal fall < 10 mmHg). All subjects were instructed to rest and sleep during the night-time and to maintain their usual activities during the day. None of the study participants were bedridden or hospitalized during ambulatory BP monitoring. The accuracy of the ambulatory BP monitoring devices was checked monthly by obtaining 10 automatic and 10 auscultatory BP readings simultaneously from the same arm via a Y-tube. In all instances the values did not differ by more than 5 mmHg.

Statistical Analysis

Analysis was performed with SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Normality was examined by the Kolmogorov-Smirnoff test. Descriptive results for continuous variables are expressed as mean ± SD. Regression analysis was applied to explore relationships between glucose, HbA1c values, glucose and arterial blood pressure variability and apnea-related characteristics, independently of body mass index (BMI). Statistical significance was defined at a level of 5% ($p < 0.05$).

Results

Mean age was 54 ± 14.5 years (ranging between 27-77 years) and mean BMI was 35 ± 8 kg/m² (ranging between 22.6 and 51.4 kg/m²).

Waist circumference was 106.32 ± 18.45 cm, while waist to hip ratio was 0.55 ± 0.11. Sleep and metabolic characteristics of patients are presented in Table I.

AHI was correlated with HOMA and Matsuda index ($p = 0.016$ and $p = 0.022$, respectively) and SD of glucose measurements ($p = 0.05$). Percentage of sleep time with saturation of hemoglobin with oxygen, as measured by pulse oximetry, (SpO_2) < 90% was also correlated with HOMA and Matsuda index ($p = 0.014$ and $p = 0.012$, respectively) and CV (coefficient of variation) of glucose measurements ($p = 0.009$). Moreover, minimum SpO_2 was correlated with Matsuda index ($p = 0.30$) and glucose levels.

Matsuda index was also correlated with SE (sleep efficiency) ($p = 0.011$), whereas SD of glucose measurements was correlated with Total Sleep Time (TST, $p = 0.049$). Additionally, glucose levels and CV of glucose measurements were correlated with arousal index ($p = 0.019$ and $p = 0.079$, respectively).

AHI was correlated with mean Diastolic Blood Pressure (DBP), ($p = 0.007$). Percentage of sleep time with SpO_2 < 90% was correlated with SD of Systolic Blood Pressure (SBP), ($p = 0.013$). Moreover, minimum SpO_2 was correlated with mean DBP ($p = 0.047$) and SD of 24-hour mean DBP and SBP ($p = 0.022$ and $p = 0.005$, respectively).

Finally, SD of glucose measurements was correlated with 24-hour mean DBP ($p = 0.017$) and SBP ($p = 0.033$). Correlations between different parameters are summarized in Table II.

Table I. Sleep and metabolic characteristics of OSAS patients.

Parameters	Mean ± SD
AHI (events/hour)	29.27 ± 25.13
Minimum SpO_2 (%)	83.55 ± 6.68
t < 90 (%)	22 ± 18.74
AI (events/hour)	32.27 ± 23.45
SE	68.64 ± 14.07
TST (min)	240.68 ± 63.4
Fasting glucose (mg/dl)	101.81 ± 18.39
HbA1c (%)	5.39 ± 0.65
HOMA index	5.47 ± 3
Matsuda index	1.98 ± 1.41
SD of glucose	18.1 ± 6,41
CV of glucose	0.18 ± 0.07
24-hour mean DBP (mmHg)	76.874 ± 6.8
24-hour mean SBP (mmHg)	125.93 ± 10.16
SD of 24-hour DBP	10.788 ± 1.99
SD of 24-hour SBP	13.223 ± 3.27
Non-Dippers (%)	83

Abbreviations: AHI: Apnea Hypopnea Index, AI: Arousal Index, DBP: Diastolic Blood Pressure, HbA1c: glycosylated hemoglobin, SD: standard deviation, CV: coefficient of variation, SBP: Systolic Blood Pressure, SpO_2: saturation of hemoglobin with oxygen as measured by pulse oximetry, SE: Sleep Efficiency, TST: Total Sleep Time.

Discussion

To our knowledge, this is the first study identifying 24 hour patterns of altered glucose homeostasis and blood pressure levels in recently diagnosed, nondiabetic and normotensive, OSAS patients. Our study provides findings of signifi-

Table II. Correlations between different parameters.

Parameters	AHI (events/hour) p, r	Minimum SpO_2 (%) p, r	t < 90 (%) p, r
Fasting glucose (mg/dl)	0.842	0.018	0.483
	-0.045	0.496	-0.158
SD of glucose	0.050	0.456	0.80
	0.395	0.167	0.382
CV of glucose	0.081	0.362	0.009
	0.380	-0.204	0.545
24-hour mean DBP (mmHg)	0.007	0.047	0.127
	0.615	-0.474	0.345
24-hour mean SBP (mmHg)	0.136	0.022	0.116
	0.366	-0.534	0.384
SD of 24-hour DBP	0.756	0.022	0.101
	-0.079	-0.469	0.399
SD of 24-hour SBP	0.407	0.005	0.013
	-0.006	0.454	0.331

Abbreviations: AHI: Apnea Hypopnea Index, DBP: Diastolic Blood Pressure, SD: standard deviation, CV: coefficient of variation, SBP: Systolic Blood Pressure, SpO_2: saturation of hemoglobin with oxygen as measured by pulse oximetry.

cance to the physiology and pathophysiology of the integrated regulation underlying diurnal rhythmicity of critical homeostatic variables such as cardiovascular hemodynamics and prevailing tissue glucose concentrations, through a quantitative and highly reproducible approach using simultaneously and continuously monitored parameter changes, in OSAS patients.

In humans, most of the fundamental physiological processes exhibit circadian rhythmicity under homeostatic and autoregulatory mechanisms[20,21]. In normal conditions, plasma glucose homeostasis is tightly controlled so that an elegant balance exists between glucose delivery and its utilization by peripheral tissues, in order for critical metabolic fueling to be constantly optimized and matched to demand[22]. Similarly, blood pressure exhibits normal diurnal rhythmicity characterized by a biphasic curve during a 24-h cycle, with blood pressure levels rising early in the morning (around 06:00 h; the "dawn phenomenon") and remaining elevated during daytime compared with reduced blood pressure levels during nighttime[16]. The suprachiasmatic nucleus of the hypothalamus acts as a neuroendocrine clock mechanism regulating circadian rhythmicity[23].

Various studies indicate a causal relationship between OSAS and hypertension, cardiovascular disease and diabetes mellitus, independently of obesity[24]. The underlying pathophysiological mechanisms remain not clear, although there are a number of factors to consider, such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, inflammation and hypersecretion of adipocyte-derived hormones due to repetitive, short periods of asphyxia and hypoxemia and sleep deprivation. Despite the importance of both cardiovascular integrative mechanisms and glucose homeostasis in the physiological coordination of bodily functions and responses, the minute-by-minute correlation between blood pressure and prevailing glucose concentrations during a 24-hour time period, as an underlying pathophysiological mechanism, has not been previously evaluated in OSAS patients.

Our results suggest that in nondiabetic, normotensive OSAS patients, the severity of OSAS (evaluated by the number of respiratory cessation events, the indices of hypoxemia during sleep and the arousal index) is associated with glucose and blood pressure variability during a 24 hour time period, indicating a possible underlying mechanism in the pathophysiology and the complica-

tions of the disease. These findings are consistent with previous studies demonstrating that glucose concentration and hemodynamic parameters seem to be tightly linked not only under normal circumstances but also in disease states, prominently in the metabolic syndrome[25,26]. Sleep apnea is closely linked to metabolic syndrome[24].

The mechanisms responsible for this phenomenon cannot be clarified by the nature of this study. However, it is well known that autonomic dysfunction as expressed by decreased baroreceptor sensitivity has been shown to be present in OSAS[27]. Baroreceptor impairment results in activation of the sympathetic nervous system. A shift to sympathetic predominance has been reported to be associated with greater fluctuations of BP which significantly increase the risk of cardiovascular morbidity and mortality[28,29]. Furthermore, increased sympathetic outflow has been associated with developing insulin resistance, b-cell dysfunction, and impaired glucose tolerance[30].

The limitations of the present study include the small number of patients and the cross-correlation analysis. Also, we did not independently assess the pattern of synchronicity glucose levels and blood pressure. We only investigated putative associations between the 24-h cycle chronobiology of those two critical parameters of homeostatic regulation. Further research is needed to elucidate the exact association.

Conclusions

On the basis of our data, it seems plausible that in normotensive humans with normal glucose tolerance, the positive correlation between prevailing glucose and blood pressure is retained in the presence of newly diagnosed OSAS.

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