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## Does apnea-hypopnea index alone reflect obstructive sleep apnea severity?

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## Does apnea–hypopnea index alone reflect obstructive sleep apnea severity?

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**Aim:** We aimed to assess whether there was a correlation between the apnea–hypopnea index (AHI), desaturation time under 90% (DTU-90), and mean saturation (MS) levels and the parameters associated with tissue hypoxia.

**Materials and methods:** A total of 144 subjects were included in the study. Blood C-reactive protein levels, blood uric acid levels, and urine microalbumin levels were measured and the urine uric acid/creatinine ratio and urine microalbumin/creatinine ratio were calculated.

**Results:** Our study results suggest that MS and DTU-90, as well as the AHI, are correlated with the parameters reflecting hypoxemia and the other events secondary to hypoxia.

**Conclusion:** MS and DTU-90 may reflect the severity of disease and may be used in the first evaluation of a patient with suspicion of obstructive sleep apnea before full polysomnography monitorization. Because they were not much better correlated with the parameters than the AHI, it is difficult to make a claim for their use as the only tool, or their replacement of the AHI, in the evaluation of patients with suspected obstructive sleep apnea.

**Key words:** Sleep apnea, apnea–hypopnea index, desaturation time under 90%, mean saturation, hypoxia, ambulatory monitorization

### 1. Introduction

Obstructive sleep apnea (OSA) syndrome is characterized by recurrent episodes of partial or complete pharyngeal collapse (hypopneas or apneas) occurring during sleep. It is a growing health concern affecting up to 5% of middle-aged males and females in the general population (1). People with OSA have a night-time peak in occurrence of sudden death and an increased rate of cardiovascular morbidity and mortality (2–4).

The apnea–hypopnea index (AHI) or respiratory disturbance index (RDI) are the common parameters used to assess the severity of OSA (5). However, it is unclear whether cases that have a longer duration of apnea and/or hypopnea, or longer and/or more severe oxygen desaturation levels, have the same disease severity as the cases with shorter duration of apnea and/or hypopnea, or shorter and/or less severe oxygen desaturation levels, although they have similar AHI/RDI scores. Nevertheless, it is reasonable to expect that the hypoxic damage caused by an apnea or hypopnea event lasting for 10 s will not be the same as an event lasting for more than 10 s. Similarly, the hypoxic damage of a 4% desaturation and shorter event

may not be same as that of an event that has more than 4% desaturation and is longer. There is a continuing debate as to whether ambulatory monitorization tools, measuring desaturation levels during the night, can be used instead of polysomnographs (6).

In the current management of patients with OSA, that AHI has been used, but desaturation level and duration has not. However, the main problem for these patients is hypoxia and the other events secondary to hypoxia, such as sympathetic discharge, ischemia–reperfusion injury, and production of reactive oxygen species during reoxygenation (7,8). The effect of these events may be evaluated by measuring serum C-reactive protein (CRP) (9,10), blood uric acid levels and urine uric acid/creatinine (UA/cr) ratio (11), microalbuminuria level, and microalbuminuria/creatinine ratio (12–14).

With this study we aimed to assess whether there was a correlation between AHI, desaturation time under 90% (DTU-90), and mean saturation (MS) levels and the above parameters associated with tissue hypoxia; to determine whether DTU-90 and MS levels were better correlated with those parameters than the AHI; and to discover whether or

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not they would be able to be used in determining disease severity in the ambulatory monitorization of cases with OSA suspicion instead of the AHI.

## 2. Materials and method

### 2.1. Study population

A total of 144 consecutive subjects (115 men and 29 women) with OSA were included in this study. Exclusion criteria were regular medication, hypertension, chronic heart failure, diabetes mellitus, chronic renal disease, and pulmonary disease. Subjects who had smoking history of 1-pack-year or more and who had any infections at the time of the study, or within the 2 weeks before the study, were also excluded.

### 2.2. Measurements

After initial clinical evaluation a questionnaire was used to obtain information about the subject's history of snoring, witnessed apnea, and excessive daytime sleepiness. The Turkish version of the Epworth Sleepiness Scale was used (15,16). A detailed physical examination was done and anthropometric measurements, including neck and waist circumference (cm), height (cm), weight (kg), and body mass index (BMI, kg/m<sup>2</sup>), were obtained. Chest X-rays, pulmonary function tests, electrocardiograms, and echocardiograms were also obtained.

Hypertension was defined by a casual blood pressure of  $\geq 140/90$  mmHg as according to the National Heart, Lung, and Blood Institute criteria (17) or by current use of antihypertensive agents. Diabetes mellitus was defined by a fasting blood glucose level of  $\geq 126$  mg/dL. Obesity was defined by a BMI of  $\geq 25$  kg/m<sup>2</sup>.

A venous blood sample and single void urine sample were obtained in the morning after the completion of polysomnography. Blood CRP levels, blood uric acid levels, and urine microalbumin levels were measured. Urine UA/cr ratios and urine microalbumin/creatinine ratios were calculated. Blood uric acid, urinary uric acid, and urinary creatinine measurements were determined with the Cobas® 8000 Modular Analyzer Series (USA). Blood CRP and urinary microalbumin analyses were obtained by nephelometry (Siemens, Germany).

### 2.3. Sleep study

Full polysomnographic monitoring was performed with the Compumedics E-series Sleep System (Compumedics Sleep, Profusion 2, Australia). Electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), and electrocardiography were performed simultaneously. Surface electrodes were used to record EEG channels (C3/A2, C4/A1, O1/A2, O2/A1), right and left EOGs, and submental EMG. Ventilatory flow, either at the nose or the nose and mouth, was measured with airflow. Respiratory movements of the chest and abdomen, and the body position, were monitored by inductive

plethysmography bands. The arterial oxygen saturation was measured transcutaneously with a finger oximeter. Apnea was defined as continuous cessation of airflow for  $\geq 10$  s, and hypopnea was defined as at least a 50% reduction of airflow for  $\geq 10$  s with an oxygen desaturation of  $\geq 3\%$  or an EEG arousal from sleep. Apneas were classified as obstructive, central, or mixed according to the standard criteria of the American Academy of Sleep Medicine (4).

The study was planned according to the ethics guidelines of the Helsinki Declaration and the study protocol was approved by the local ethics committee.

### 2.4. Statistical analysis

The statistical analyses were performed with a statistical software package (SPSS 17.0). All data are presented as mean  $\pm$  standard deviation for normally distributed data and as median (quartile) for nonnormally distributed data. The Kolmogorov–Smirnov test was used to test normality. Correlations were determined using Pearson's correlation or Spearman's correlation analysis when data were not normally distributed. Because of skewed distribution of the AHI, urine microalbumin, urine UA/cr, and urine microalbumin/creatinine, they were log-normalized before correlation analysis. To examine whether blood uric acid, CRP, urine microalbumin, urine UA/cr, and urine microalbumin/creatinine were correlated with AHI, MS, or DTU-90, we calculated Pearson's or Spearman's correlation coefficients. In the case of a significant correlation, we performed a multiple regression analysis to determine whether the correlation persisted after controlling for BMI, sex, and age. Values of  $P < 0.05$  were considered statistically significant.

## 3. Results

A total of 144 subjects, 115 (79.8%) men and 29 (20.2%) women with mean age of  $47.2 \pm 11.6$  years, were included in the study. Demographic characteristics and laboratory findings of the subjects were shown in Table 1.

All of the studied parameters, blood uric acid, CRP, urine microalbumin, urine microalbumin/creatinine ratio, and UA/cr ratio were positively correlated with AHI, MS, and DTU-90 (Table 2). The correlations between them, except that between blood uric acid and AHI, were statistically significant (Figures 1A–1C). However, the correlations between urine microalbumin and AHI, MS, and DTU-90, and between microalbumin/creatinine and DTU-90, remained after controlling for confounding factors such as age, sex, and BMI (Table 3). The most important factor affecting the results was BMI.

## 4. Discussion

Our study results suggest that MS and DTU-90 were correlated with the parameters, reflecting hypoxemia and the other events secondary to hypoxia as well as the AHI.

**Table 1.** Demographic characteristics and laboratory findings of the subjects.

Age	47.2 ± 11.6
BMI (kg/m <sup>2</sup> )	30.5 ± 5.8
Neck circumference (cm)	40.7 ± 3.2
Waist circumference (cm)	105.8 ± 13.3
AHI	30 (14–50)
Mean saturation	5 (4–7)
DTU-90 (min)	72 (15–217)
Blood uric acid	5.18 ± 1.63
CRP	0.317 (0.302–0.404)
Urine microalbumin	13.0 (8.3–19.0)
Microalbumin/creatinine	0.09 (0.06–0.15)
UA/cr	0.45 (0.37–0.54)

Data are presented as mean ± standard deviation or median (quartile). BMI: Body mass index, AHI: apnea–hypopnea index, DTU-90 (min): desaturation time under 90%, CRP: C-reactive protein, UA/cr: uric acid/creatinine ratio.

**Table 2.** The correlation between the studied parameters and the AHI, MS, and DTU-90.

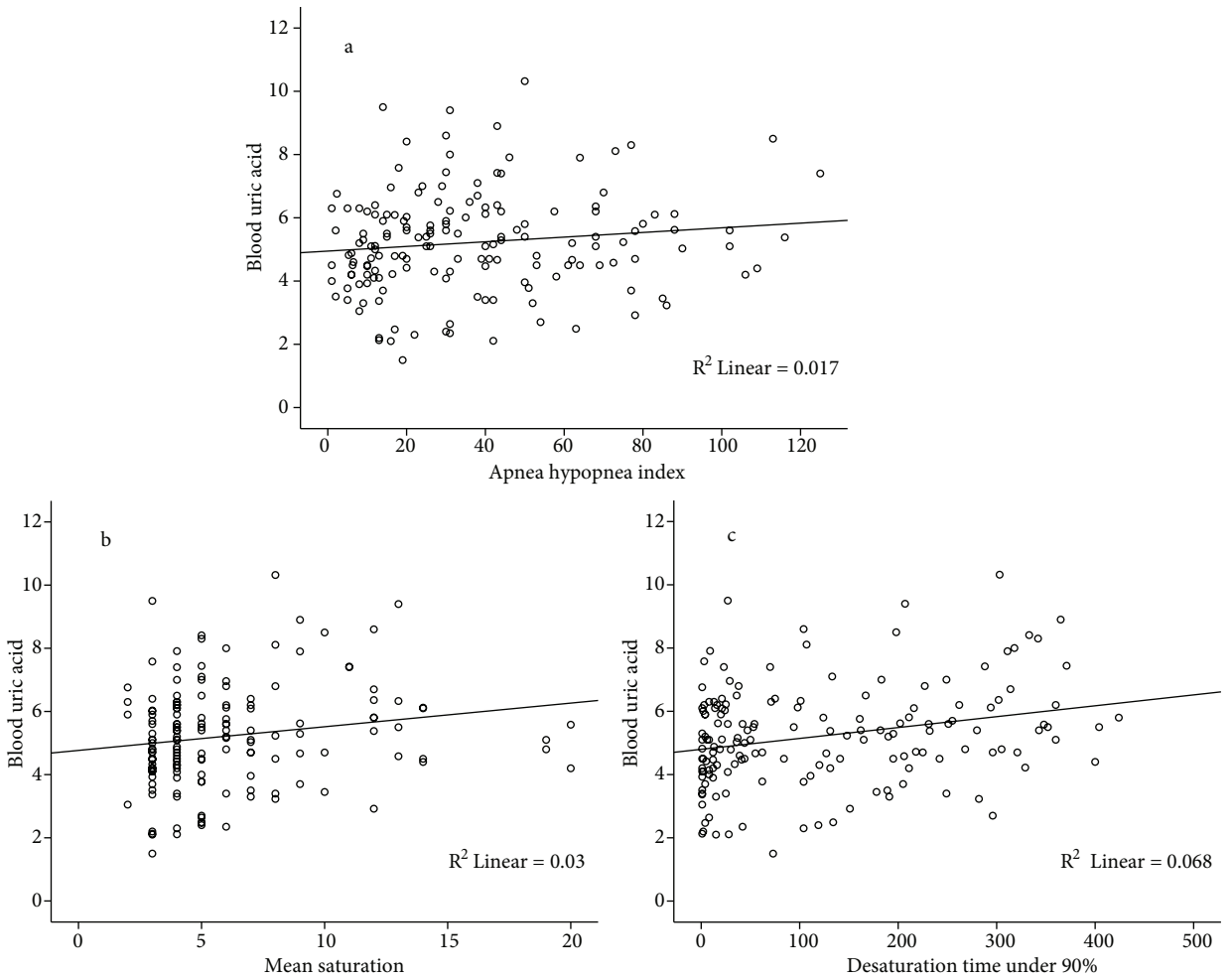
	AHI		MS		DTU-90	
	R	P	R	P	R	P
Blood uric acid	0.118	0.079	0.196*	0.009	0.259*	0.001
CRP	0.192*	0.011	0.232*	0.005	0.155*	0.032
Urine microalbumin	0.230*	0.003	0.241*	0.002	0.269*	0.001
Microalbumin/creatinine	0.226*	0.03	0.225*	0.003	0.332*	<0.0001
UA/cr	0.156*	0.031	0.164*	0.025	0.148*	0.038

AHI: Apnea–hypopnea index, MS: mean saturation, DTU-90 (min): desaturation time under 90%, CRP: C-reactive protein, UA/cr: uric acid/creatinine ratio. \*Statistically significant.

They may reflect the severity of disease and may be used in the first evaluation of a patient with the suspicion of OSA before full polysomnographic monitorization. Because they were not much better correlated with the parameters than the AHI, it is difficult to claim their use as the only tool, or their replacement of the AHI, in the evaluation of the patients with suspected OSA.

To observe the effect of hypoxia, we used the parameters associated with hypoxia, including serum CRP levels, blood uric acid levels, UA/cr, urine microalbumin levels, and microalbumin/creatinine ratio. Blood CRP levels are used in the evaluation of inflammation. In OSA patients, elevated serum CRP levels, as a marker of inflammation

and the independent relationship between the severity of disease, have been reported in previous studies (9,10). Blood uric acid levels and UA/cr ratio were used as noninvasive and inexpensive markers of oxidative stress. Both are suggested to be markers of tissue hypoxia in OSA patients (11). Each episode of airway obstruction followed by hypoxemia causes episodes of ischemia–reperfusion injury. Such damage is mainly attributed to the production of reactive oxygen species during reoxygenation (7,8). This damage causes increased blood uric acid levels and the excretion of uric acid. To assess the vascular damage, urine microalbumin levels were measured and the urine microalbumin/creatinine ratio was calculated. The



**Figure 1.** The correlation between blood uric acid and apnea–hypopnea index (A), mean saturation (B), and desaturation time under 90% (C).

**Table 3.** The correlation between the studied parameters and the AHI, MS, and DTU-90 after correction for the confounding factors, age, sex, and BMI.

	AHI		MS		DTU-90	
	$\beta$	P	$\beta$	P	$\beta$	P
Blood uric acid	NA	NA	0.047	0.573	0.088	0.312
CRP	0.157	0.070	0.073	0.415	0.102	0.280
Urine microalbumin	0.172*	0.040	0.176*	0.046	0.226*	0.017
Microalbumin/creatinine	0.013	0.071	0.017	0.229	0.235*	0.012
UA/cr	0.198	0.054	0.128	0.094	0.074	0.117

AHI: Apnea–hypopnea index, MS: mean saturation, DTU-90 (min): desaturation time under 90%, CRP: C-reactive protein, UA/cr: uric acid/creatinine ratio. \*Statistically significant. To provide the importance of a predictor, the standardized beta values ( $\beta$ ) were measured after entering age, sex, and BMI variables into the model. NA: Not accounted.

vascular dysfunction caused by the endothelial damage leads to albumin loss from kidneys. Microalbuminuria has been described in hypertensive or diabetic patients as a marker of target organ damage and was evaluated in OSA patients in several studies (12–14).

The mechanism for increased risk of cardiovascular diseases in patients with OSA is unclear; it is more likely to result from increased sympathetic activation, oxidative stress, inflammation, and systemic vascular endothelial dysfunction. We found a positive correlation between blood uric acid and the AHI, MS, and DTU-90, but the correlation was not significant for the AHI. It is known that blood uric acid levels are related to OSA severity (18). In previous studies, the correlations between blood uric acid and some oxidative parameters such as AHI, desaturation index, cumulative percentage of time with SpO<sub>2</sub> less than 90%, DTU-90, and mean SpO<sub>2</sub> were determined and positive correlations for each of them were reported (19–21). In these studies the correlations were confounded by obesity, as in ours. This is thought to be due to the effect of the concomitant obesity of OSA patients. A higher BMI generally causes more severe OSA.

The overnight change of urinary uric acid secretion was also measured many years ago, and it was suggested to be a good index of tissue hypoxia (22). In our study we found that the urine UA/cr ratio correlated with the AHI, MS, and DTU-90 and also found that these were confounded with BMI, like in blood uric acid results. There is no full compatibility in previous studies that evaluated uric acid excretion in OSA patients. In 2 of these, a significant increase in the urinary UA/cr ratio was observed in association with nocturnal hypoxemia; continuous positive airway pressure treatment led to a significant reduction in this ratio (22,23). Some other studies failed to confirm this observation (24) and no significant correlation was found between urinary UA/cr ratio and AHI (25). To validate the urinary UA/cr ratio as a marker of nocturnal hypoxemia, normal subjects, OSA patients, and chronic obstructive pulmonary disease patients were compared and the overnight change in the urinary UA/cr was confirmed to be a promising index of significant nocturnal tissue hypoxia (11).

The elevated level of CRP in OSA patients due to increased inflammation was previously known. It is one of the proinflammatory proteins and an important risk factor for atherosclerosis. In our study subjects, CRP was positively correlated with AHI, MS, and DTU-90, and the significance was confounded by BMI. In previous studies, the relation between increased CRP levels and OSA was shown, but the effect of obesity on this relation differed in various studies. Taheri et al. described a significant positive association between CRP levels and the AHI, but these relationships were not significant after adjustment

for age, sex, and BMI (26). The positive correlations with AHI, duration of O<sub>2</sub> saturation < 90%, and arousal index and negative correlation with minimal O<sub>2</sub> saturation were reported in a study independent of visceral obesity (27). Another recent study concluded high sensitive CRP levels were associated with AHI, independent of obesity in OSA patients (28).

The relationship between OSA and microalbuminuria is not certain. The present study indicates a positive correlation between microalbuminuria and AHI, MS, and DTU-90 among OSA patients. The association between OSA and albuminuria was shown with hypertensive patients, and albuminuria was found to be greater by 57% in patients with OSA compared with those without OSA (29). Ursavas et al. found urinary albumin excretion significantly higher among normotensive, nondiabetic patients in an OSA group as compared with a control group. They also found albumin excretion positively correlated to the length of time spent at an oxygen saturation of <90%, independent of age and BMI (14). There were also studies that found that microalbuminuria was not related to sleep-disordered breathing. Buchner et al. compared renal function in OSA patients with and without hypertension and concluded that microalbuminuria was not associated with OSA (30). Another study among overweight and obese children and adolescents found no difference in albumin excretion rate between subjects with and without sleep-disordered breathing, and none of the sleep-disordered breathing parameters were correlated with transformed albumin excretion (31). It was concluded that in obese adults, increasing severity of OSA was associated with higher serum creatinine but not greater degrees of albuminuria (32).

The urine microalbumin/creatinine ratio is generally used to evaluate the renal functions for target organ damage in OSA patients. In our study, the microalbumin/creatinine ratio was positively correlated with the AHI, DTU-90, and MS. The correlations of AHI and MS were insignificant after controlling for age, sex, and BMI; this was basically caused by the effect of BMI, which is to say the effect of obesity, on OSA. Both OSA and obesity have been associated with similar effects on the kidney, like glomerulomegaly and focal segmental sclerosis (33,34). As validation, Tsioufis et al. measured the albumin/creatinine ratio (ACR) from 2 nonconsecutive spot urine samples of patients with and without OSA and found the AHI to be the independent predictor of the ACR (27). In another study population, the urine albumin/creatinine ratio was not different between the subjects with OSA and those without OSA (32).

Our study aimed to show whether MS and DTU-90 reflect the tissue hypoxia and sympathetic discharge (vascular dysfunction and endothelial damage) that



occurred in OSA as did the AHI. Our study showed that MS and DTU-90 were as well correlated as the AHI within the parameters studied, as shown by previous studies. Our findings suggest that ambulatory monitorization may be

used as a screening test in OSA, because the parameters that they use are well correlated with the AHI and may decrease the work-load of sleep laboratories because of their convenience and cheapness.

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