

# Low-grade urinary albumin excretion in normotensive/non-diabetic obstructive sleep apnea patients

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**Abstract** Previous studies have indicated that high levels of urinary albumin excretion (UAE) are associated with an increased incidence of cardiovascular morbidity and mortality. This study examined the association between UAE and obstructive sleep apnea syndrome (OSAS). The study included 35 newly diagnosed OSAS patients and 11 nonapneic controls. Subjects with diabetes mellitus, hypertension, a history of renal failure, cardiac failure, coronary heart disease, collagen tissue disease, high serum creatinine, and urinary infection, and who use angiotensin-converting enzyme inhibitors and were women were excluded from the study. A single void morning urine sample at the baseline examination was used to measure UAE. There were no significant differences in the age, body mass index (BMI), and smoking habits of the OSAS patients and controls.

UAE of the OSAS group was significantly higher than that of the control group ( $23.3 \pm 6.1$   $\mu\text{g}/\text{min}$  vs.  $6.5 \pm 2.1$   $\mu\text{g}/\text{min}$ , respectively;  $P=0.002$ ). UAE was positively correlated to length of time spent at an oxygen saturation of  $<90\%$  ( $r=0.503$ ,  $P=0.002$ ) and BMI ( $r=0.361$ ,  $P=0.033$ ). Regression analyses ( $r^2=0.504$ ,  $P<0.0001$ ) showed that the length of time spent at an oxygen saturation of  $<90\%$  ( $P<0.0001$ ) was risk factor for UAE, independent of age and BMI. Our study supports the notion that low-grade UAE is associated with non-hypertensive/non-diabetic OSAS, independent of age and BMI. Low-grade UAE may be a marker for subclinical vascular damage that predisposes OSAS patients to future cardiovascular disease.

**Keywords** Urine albumin · Sleep apnea · Cardiovascular disease

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder associated with excessive daytime sleepiness, disruptive snoring, witnessed apnea and nocturnal hypoxemia, and significant morbidity and mortality due to cardiovascular events [1–3]. The prevalence of OSAS in adults aged 20–100 years has been reported in a community-based study to be 3.9% among males and 1.2% among females [4]. Several studies have demonstrated that OSAS may be one of the important factors for cardiovascular disease (CVD), including hypertension, and ischemic heart disease [5–8].

Microalbuminuria is defined as a urinary albumin/creatinine ratio (UACR) of  $30 < 300$  mg/g [9]. The threshold levels defining the pathological spectrum of urinary

albumin excretion (UAE) have been questioned [10]. Low-grade UAE (0–30 mg/g) may also be a consequence of hypertension and a marker of target organ damage [10]. Epidemiological and experimental studies have indicated that high levels of UAE are associated with an increased incidence of cardiovascular morbidity and mortality [11, 12]. Microalbuminuria, a marker of vascular dysfunction, in both the kidneys and systemic vasculature, and glomerular hyperfiltration, have been described in individuals with hypertension [13]. In addition, UAE was significantly associated with intima–media thickness of the common carotid artery in clinically healthy men [14]. Some studies suggest that patients with OSAS rarely demonstrate nephrotic-range proteinuria [15, 16]; however, other studies have not found a relationship between severity of sleep apnea and severe proteinuria [17].

This study examined the association between UAE and OSAS. UAE is a marker of vascular dysfunction and systemic vascular dysfunction is common in OSAS. We hypothesized that increased UAE would be associated with OSAS. In order to investigate this hypothesis, we compared the degree of UAE of non-diabetic/normotensive OSAS patients to nonapneic controls.

## Materials and methods

### Subjects

A cross-sectional study was performed, which included subjects referred to the same sleep center for the evaluation of suspected OSAS. The study was planned according to the ethics guidelines of the Helsinki Declaration and was approved by the Institutional Research Ethics Board of Uludağ University Medical Hospital, Bursa, Turkey. All patients gave written informed consent regarding participation in this study. Plasma glucose was measured after an overnight fast. Blood pressure was measured twice between the hours of 10 and 12 A.M. with the subject in the supine position after a 5-min rest. Subjects with diabetes mellitus (fasting plasma glucose >126 mg/dl), hypertension (systolic blood pressure  $\geq$ 140 mmHg or diastolic blood pressure  $\geq$ 90 mmHg) and/or history of hypertension, a history of renal failure, cardiac failure, coronary heart disease, collagen tissue disease, high serum creatinine concentration (>1.4 mg/dl), and urinary tract infection, and who use angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and were women were excluded from the study.

The questionnaire inquired about the presence of any history of snoring, witnessed apnea, excessive day time sleepiness, and Epworth Sleepiness Scale (ESS). Demographic information (age, gender, and smoking habits) and

anthropometric measurements (height, weight, and body mass index (BMI): weight/height kg/m<sup>2</sup>) were obtained upon presentation to the sleep center.

### Sleep analysis

Full polysomnography (PSG) monitoring was performed on all participants using the Compumedics P-series Sleep System (Compumedics Sleep: Melbourne, Australia). All participants reported to the sleep laboratory at approximately 20:30 and PSG was initiated at approximately 2,030. Polysomnographic recordings included two electroencephalography channels (C3/A2 and O2/A1), two electrooculogram channels, one submental electromyogram (EMG) channel, and one electrocardiography (ECG) channel. Ventilatory monitoring included recording of oronasal airflow (with an oronasal thermistor), hemoglobin oxygen saturation by pulse oximetry (SaO<sub>2</sub> was measured via a finger oximeter), respiratory movement (with an inductive plethysmography), including chest and abdomen, and body position.

Sleep staging was performed according to the standard criteria of Rechtschaffen and Kales [18]. To assess ventilation during sleep, nasal airflow was analyzed carefully. Apnea was defined as episodes of airflow cessation lasting  $\geq$ 10 s. Hypopnea was defined as episodes lasting  $\geq$ 10 s, with reductions of thermistor signal amplitude  $\geq$ 50% and an associated fall of  $\geq$ 3% in oxygen saturation, or an arousal that lasted  $\geq$ 10 s. Arousals were defined in accordance with the definition of standard criteria [19]. The sum of time spent in apnea and hypopnea was divided by the total sleep time to determine the apnea–hypopnea index (AHI). Subjects with AHI  $\geq$ 5 were considered to have OSAS. Subjects with AHI <5 were included in the control group.

### Urinary albumin measurement

A single void morning urine sample at the baseline examination was used to measure UAE. Urinary albumin was determined by immunoturbidimetry (Immulite 2000 Albumin, EURO/DPC, UK).

### Statistical analysis

Statistical analysis was performed using the SPSS package for Windows, version 13.0 (SPSS, Inc., Chicago, USA). Comparisons between data of the OSAS and control groups were carried out with Student's *t* test, chi-square test, and the Mann–Whitney *U* test. The concordance of normal distribution of all variables was calculated with the Shapiro–Wilk test before comparison between OSAS and control groups. If the data were not normally distributed,

we used non-parametric tests for dependant variables. The relationship between UAE and ESS, number of total apnea events, number of total respiratory events, time spent in apnea and hypopnea, average oxygen desaturation, oxygen desaturation index, REM sleep, slow wave sleep, and respiratory arousal index were calculated using Pearson's correlation analysis. We performed regression analyses to identify any significant relationships between parameters of sleep disorders and UAE. A *P* value <0.05 was considered statistically significant.

## Results

### Baseline characteristics

One hundred fifteen subjects satisfied our inclusion criteria and were screened in our study. Sixty-nine subjects were excluded because 33 were women, eight had diabetes mellitus, 12 had hypertension, one had renal failure, three had cardiac failure, seven had coronary heart disease, two had collagen tissue disease, and three had high serum creatinine concentration (>1.4 mg/dl). The study included 35 consecutive newly diagnosed OSAS patients and 11 nonapneic controls. Baseline clinical and PSG characteristics of the study sample are shown in Table 1. There were no significant differences in age, BMI, smoking habits, total sleeping time, sleep efficiency, and baseline oxygen saturation between the two groups. ESS, sleep stages 3 and 4, REM stage, arousals per hour, AHI, duration of

**Table 1** Baseline clinical and polysomnographic characteristics of the study sample

	OSAS	Control	<i>P</i> value
Age	45.1±10.6	45.2±11.4	NS
Body mass index, kg/m <sup>2</sup>	30.1±5.6	28.9±6.7	NS
Smoking habits, pack years	19.9±11.4	22.3±6.7	NS
Epworth sleepiness scale	10.9±5.9	5.3±4.4	<0.05
Total sleep time (TST), h	6.1±0.8	6.6±0.9	NS
Sleep efficiency, %	79.5±1.5	76.8±3.7	NS
Stages 3 and 4 (%TST)	11.9±12.9	17.7±5.3	<0.05
Rapid eye movement (%TST)	10.7±6.0	16.7±12.7	<0.05
AHI, h <sup>-1</sup>	44.8±29.2	2.5±1.4	<0.0001
Duration in apnea–hypopnea, min	130.2±97.0	3.9±2.1	<0.0001
Arousal, h <sup>-1</sup>	35.3±17.7	12.7±7.6	<0.0001
Baseline oxygen saturation, %	93.2±0.5	94.2±0.9	NS
Average oxygen saturation % in sleep	87.2±9.8	94.0±3.0	<0.0001
Average desaturation, %	9.5±5.0	4.0±1.9	<0.0001
Oxygen saturation <90%, length of time, min	90.0±115.9	19.3±58.6	<0.05

NS Statistically insignificant

apnea–hypopnea periods, average oxygen saturation during sleep, average oxygen desaturation, and length of time spent at an oxygen saturation of <90% were significantly different between the OSAS and control groups.

### Urinary albumin excretion

UAE of the OSAS group was significantly higher than that of the control group (23.3±6.1 μg/min vs. 6.5±2.1 μg/min, respectively, *P*=0.002). There were seven (14%) mild (AHI<15), eight (16%) moderate (AHI=15–30), and 20 (40%) severe (AHI>30) OSAS patients. There were no significant differences in UAE between mild, moderate, and severe OSAS patients (*P*>0.05; Table 2).

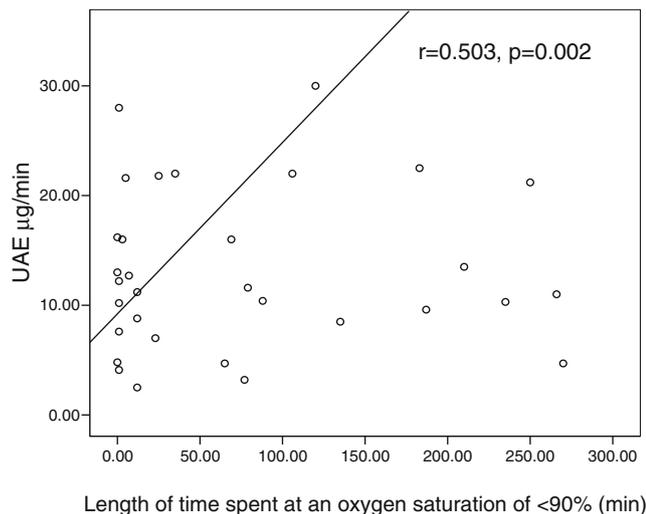
UAE was positively correlated with length of time spent at an oxygen saturation of <90% (*r*=0.503, *P*=0.002; Fig. 1) and BMI (*r*=0.361, *P*=0.033; Fig. 2). There was no significant correlation between UAE and age, smoking habits, ESS, sleep stages 3 and 4, REM sleep, arousals per hour, AHI, and duration of apnea–hypopnea periods. Regression analyses [UAE=age (0.814) – BMI (1.046) + length of time spent at an oxygen saturation of <90%, *r*<sup>2</sup>=0.504, *P*<0.0001] showed that the length of time spent at an oxygen saturation of <90% (*P*<0.0001) was a risk factor for UAE, independent of age (*P*>0.05) and BMI (*P*>0.05).

## Discussion

OSAS has clearly been demonstrated to be an independent risk factor for the development of hypertension, and it has also been implicated in the pathogenesis of atherosclerosis, congestive heart failure, pulmonary hypertension, cardiac arrhythmias, and stroke. Several studies have shown that OSAS is associated with an increased risk for cardiovascular morbidity and mortality [5–8]. The exact mechanism of development of cardiovascular disease in patients with OSAS is unknown; however, mechanisms implicated in this relationship have included increased sympathetic activation, increased oxidative stress, inflammation, increased platelet aggregability, metabolic dysregulation, and systemic vascular endothelial dysfunction [20].

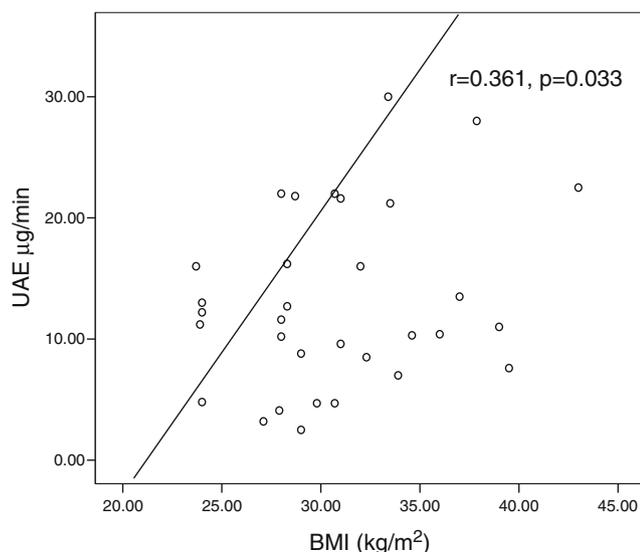
**Table 2** UAE in subjects with mild, moderate, severe OSAS, and control group

	AHI	<i>N</i>	UAE (μg/min)
Control group	<5	11	6.5±2.1
Mild OSAS	5–14	7	17.5±4.3
Moderate OSAS	15–29	8	34.6±23.9
Severe OSAS	≥30	20	27.6±14.3



**Fig. 1** Correlation coefficient between UAE and length of time spent at an oxygen saturation of <90%

Microalbuminuria, defined as an increased UAE below the detection of urinary dipstick measurement, is an established risk factor for cardiovascular morbidity and mortality, and for end-stage renal disease in individuals with an adverse cardiovascular risk profile, such as those with hypertension and diabetes mellitus [10, 11, 21]. Microalbuminuria has been viewed as a marker for vascular dysfunction in both the kidneys and systemic vasculature [12]. Studies of both diabetic and non-diabetic individuals demonstrate that increased UAE is associated with endothelial dysfunction [22, 23]. Microalbuminuria may also be associated with future cardiovascular events. Wang et al. [24] investigated the association between UAE and the risk of hypertension and blood pressure progression in 1,499



**Fig. 2** Correlation coefficient between UAE and BMI

normotensive/non-diabetic individuals. They suggest that UAE predicts blood pressure progression in normotensive/non-diabetic subjects, and UAE may be a useful biomarker for identifying individuals most likely to develop hypertension. UAE may be a predictor of CVD and all-cause mortality in the general population. Hillege et al. [25] reported a positive dose response relationship between increasing UAE and all-cause mortality in the general population. A 2-fold increase in UEA was associated with a relative risk of 1.29 for cardiovascular mortality. Data from the LIFE study showed that for each 10-fold increase in the urinary albumin/creatinine concentration ratio in hypertensive patients with left ventricular hypertrophy, the relative risks of stroke increased by 51% and all-cause mortality by 75% [26]. In the present study, in non-diabetic/normotensive and CVD-free subjects of the OSAS group, UAE was significantly higher than in those of the control group.

Several studies observed increased cardiovascular morbidity and mortality at a UAE rate below the current conventional cutoff point for microalbuminuria. Classic microalbuminuria (UAE between 30 and <300 mg/g) is uncommon in non-diabetic subjects, but lesser degrees of UAE (0–30 mg/g) may often be found. In the 3rd Copenhagen City Heart Study, a cross-sectional analysis comprising 2,613 individuals without diabetes mellitus, or renal or urinary tract disease revealed a positive association between overnight UAE rate and a history of acute myocardial infarction. This association was independent of age, sex, conventional atherosclerotic risk factors, and glomerular filtration rate. Participants with a UAE rate exceeding the upper decile (7 µg/min) of the entire study population had a higher frequency of previous acute myocardial infarction than the others. Participants with a urinary albumin/creatinine concentration ratio exceeding the upper decile (0.65, mg/mmol) of the entire study population had a relative risk of 2.3 for developing ischemic heart disease as compared to participants with a lower urinary albumin/creatinine concentration ratio [27]. Årnlöv et al. [28] examined the association between UAE and the incidence of cardiovascular disease events and all-cause mortality in 1,568 normotensive/non-diabetic Framingham Offspring study participants who were CVD free. They indicated that the cutoff for an elevated cardiovascular event rate was the 50th percentile (3.9 mg/g UAE for men and 7.5 mg/g UAE for women). Kramer et al. [29] examined UAE and several measures of subclinical CVD, including internal carotid artery intima–media thickness, end-diastolic left ventricular mass, and coronary artery calcification scores, in 6,184 adults without clinical CVD. They demonstrated that mean left ventricular mass was significantly elevated in individuals with slightly increased UAE (13–24.9 mg/g in women, 9–16.9 mg/g in men). Current data from the MONICA/KORA Augsburg sub-

study reported that left ventricular hypertrophy was already elevated in the second tertile (4.32–8.75 mg/g in men and 4.60–9.48 mg/g in women) and third tertile ( $\geq 8.76$  mg/g in men and  $\geq 9.49$  mg/g in women) of the normal population when compared to the first tertile ( $\leq 4.31$  mg/g in men and  $\leq 4.59$  mg/g in women) [30].

Some studies suggest that patients with OSAS rarely demonstrate nephrotic-range proteinuria [15, 16]; however, other studies have not found a relationship between severity of sleep apnea and severe proteinuria. Casserly et al. [17] measured the urinary protein/creatinine ratio in OSAS patients and a control group. They did not indicate a significant association between protein/creatinine ratio and AHI. In multiple regression analysis, only age and hypertension were independent positive predictors of the urinary protein/creatinine ratio. They concluded that clinically significant proteinuria is uncommon in sleep apnea. Mello et al. [31] prospectively studied the urinary protein/creatinine ratio before and after sleep in 49 OSAS and 26 control patients. They found that there was no correlation between the urinary protein/creatinine ratio and AHI, before or after sleep. They decided that proteinuria in patients with OSAS should not be attributed to sleep apnea.

To the best of our knowledge, this is the first report about low-grade UAE in normotensive/non-diabetic OSAS patients. We determined that the UAE of the OSAS group was significantly higher than that of the control group. There are several differences between our study and previous studies which investigated about OSAS and proteinuria such as urine sample analysis method, and exclusion criteria. Significant relationship between UAE and OSAS in our study may be due to these differences. UAE was positively associated with age, female gender, cigarette pack years, blood pressure, BMI, diabetes mellitus, CVD, and length of antihypertensive medication use. The prevalence of microalbuminuria increased with age in both sexes; however, the prevalence of microalbuminuria, as defined by albumin/creatinine ratio, was higher in women than in men [32]. Mean UAE also increased significantly with increased cigarette pack years [32]. In the present study, we excluded subjects with a history of renal failure, cardiac failure, coronary heart disease, collagen tissue disease, diabetes mellitus, hypertension, high serum creatinine concentration ( $>1.4$  mg/dl), urinary tract infection, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers use, and who were women. In addition, regression analysis showed that length of time spent at an oxygen saturation of  $<90\%$  was a risk factor for UAE, independent of age and BMI. Although, UAE was positively correlated with length of time spent at an oxygen saturation of  $<90\%$ , there were no significant differences in UAE between mild, moderate, and severe OSAS patients. We think that this result may depend on our small sample size.

There are several limitations to our study. Firstly, it was a cross-sectional study and our sample size was small. Secondly, urinary albumin was assessed with only a single urine specimen. UAE may exhibit intra-individual variability [33]; however, national practice guidelines recommend the use of a spot specimen for UAE because this is easy and the results correlate well with those of 24-h collections [34]. Thirdly, we used an oronasal thermistor to measure oronasal airflow.

In conclusion, our results support the notion that low-grade UAE is associated with normotensive/non-diabetic OSAS patients, independent of age and BMI. Low-grade UAE may be a marker for subclinical vascular damage that predisposes OSAS patients to future CVD.

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