

Uric acid as a marker of severity of obstructive sleep apnoea syndrome in older patients

Ácido úrico como marcador de gravidade da síndrome da apneia obstrutiva do sono em pacientes idosos

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ABSTRACT

Objective: Uric acid has been shown to be related to the severity of obstructive sleep apnoea syndrome (OSAS) in adults. We assessed the role of uric acid in OSAS in a cohort of older patients. **Methods:** A total of 164 patients aged >65 years, admitted to our sleep laboratory between January 1st, 2016 and July 1st, 2018 with a complaint of snoring, underwent overnight polysomnography and were retrospectively evaluated. **Results:** A total of 126 patients who fulfilled the inclusion criteria (mean age 69.16±3.68 years, 56% men) were included. The control group was comprised of 14 patients, while the OSAS group consisted of 112 patients (31 mild, 44 moderate and 37 severe cases). No differences were observed in age, sex, hip circumference, waist/hip ratio or comorbidities between the groups. The Epworth Sleepiness Scale score, body mass index (BMI), and waist circumference were significantly higher in OSAS patients than in controls ($p=0.001$, $p=0.02$, and $p=0.36$, respectively). Uric acid was not correlated with any of the sleep parameters, and no significant differences were detected between the groups. Hyperuricemic patients were similar in terms of sleep parameters and comorbidities in comparison with the other patients. **Conclusions:** No relationship was observed between uric acid level and OSAS severity, as defined by the apnoea-hypopnea index. Further studies are needed to determine the value of uric acid as a marker of OSAS, after controlling for cardiovascular comorbidities, in older patients with this syndrome.

Keywords: Aged; Sleep Apnea, Obstructive; Uric Acid.

RESUMO

Objetivo: o ácido úrico mostrou estar relacionado à gravidade da síndrome da apneia obstrutiva do sono (SAOS) em adultos. Avaliamos o papel do ácido úrico na SAOS em uma coorte de pacientes idosos. **Métodos:** Um total de 164 pacientes com idade >65 anos, admitidos em nosso laboratório do sono entre 1º de janeiro de 2016 e 1º de julho de 2018 com queixa de ronco, foram submetidos à polissonografia durante a noite e avaliados retrospectivamente. **Resultados:** Foram incluídos 126 pacientes que preencheram os critérios de inclusão (média de idade 69,16±3,68 anos, 56% homens). O grupo controle foi composto por 14 pacientes, enquanto o grupo SAOS foi composto por 112 pacientes (31 leves, 44 moderados e 37 graves). Não foram observadas diferenças na idade, sexo, circunferência do quadril, relação cintura/quadril ou comorbidades entre os grupos. O escore da Escala de Sonolência de Epworth, o índice de massa corporal (IMC) e a circunferência da cintura foram significativamente maiores nos pacientes com SAOS do que nos controles ($p=0,001$, $p=0,02$ e $p=0,36$, respectivamente). O ácido úrico não se correlacionou com nenhum dos parâmetros do sono e não foram detectadas diferenças significativas entre os grupos. Os pacientes hiperuricêmicos não apresentaram diferença em termos de parâmetros de sono ou comorbidades dos demais pacientes. **Conclusões:** Não foi observada relação entre o nível de ácido úrico e a gravidade da SAOS, definida pelo índice de apneia-hipopneia. Mais estudos são necessários para determinar o valor do ácido úrico como marcador de SAOS, após controle de comorbidades cardiovasculares, em pacientes idosos com SAOS.

Palavras-chave: Idoso; Apneia Obstrutiva do Sono; Ácido Úrico.

INTRODUCTION






Obstructive sleep apnoea syndrome (OSAS) is defined as recurrent partial or complete pharyngeal closure during sleep resulting in apnoea or hypopnea. These recurrent episodes result in a cycle of intermittent hypoxia and subsequent

reoxygenation¹. Patients exhibit oxidative stress, endothelial dysfunction, and inflammation².

Uric acid is a significant and powerful marker of morbidity and mortality in cardiovascular disease, chronic renal disease, and metabolic syndrome. In particular, studies including older populations have shown that high uric acid levels

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are related to mortality³. The recurrent hypoxia observed in OSAS increases xanthine degradation of adenosine triphosphate, which causes increased serum uric acid levels. Uric acid is an end-product of purine metabolism, and an increase in its concentration may reflect heightened activity of the xanthine oxidase pathway, which is in turn related to increased free radical and cytokine production, cell apoptosis and endothelial dysfunction^{4,5,6}. Previous studies in patients with OSAS have shown that their serum uric acid levels are elevated compared to controls^{7,8}.

Although many studies have investigated the association between uric acid levels and sleep parameters, most included only middle-aged individuals. Cardiovascular comorbidities increase with ageing. Some studies have evaluated the association between uric acid levels and cardiovascular mortality in older subjects^{6,9,10}. These studies show that such patients have a higher prevalence of hyperuricemia and a higher risk of experiencing cardiovascular events.

OSAS is now considered an independent risk factor for cardiovascular disease^{11,12}. The older population is growing worldwide so a better understanding of this association is needed. As life span increases, more and more patients of this age-group are presenting to sleep laboratories. In this study, we determined the relationship between sleep parameters and serum uric acid concentrations in older patients with OSAS.

METHODS

A total of 164 patients (age >65 years) admitted to our sleep laboratory with the complaint of snoring, and who underwent full-night polysomnography between January 1st, 2016 and July 1st, 2018, were evaluated retrospectively.

Patients previously diagnosed with OSAS, renal dysfunction, liver disease, acute infection, hypoxemia, malignant neoplasms, or connective tissue diseases were excluded from the study. Inclusion criteria for patients are being older than 65 years old and diagnosed with OSAS. A total of 126 patients who fulfilled the inclusion criteria and whose uric acid values were available from blood analysis were included. Their demographic and clinical characteristics, including age, gender, comorbidity status, drug history, smoking history and Epworth Sleepiness Scale (ESS) score were recorded. Waist and hip circumference measurements, as well as weight and height, were obtained from the patients' files. Ethical committee approval was obtained from the Istanbul Research and Training Hospital (protocol number: 26.04.2019-1809).

Polysomnography

All patients underwent overnight polysomnography under the supervision of a sleep technician in the sleep laboratory. The standard procedure was performed in all patients

using an Embla N7000 data acquisition and analysis system (Medcare Flaga, Reykjavik, Iceland), from 10 p.m. to 6 a.m. The physiological signals monitored included electroencephalography (EEG) (C4-M1, C3-M2, O2-M1 and O1-M2), electrooculography, and submental electromyography (EMG). The following were also obtained: ribcage and abdominal effort, measured by respiratory inductive plethysmography (RIP) (XactTrace, Medcare Flaga); body position, measured with a calibrated sensor; snoring, measured with a piezoelectric sensor; and oronasal flow, measured with an SpO₂ nasal pressure cannula over an average of 3 s. The ECG (lead II) was sampled at 512 Hz. Sleep stage and arousal were scored by two experienced scorers, with 80–95% concordance, using the Somnologica Studio software package according to standard criteria. Respiratory events were scored as follows. Apnoea was defined as a cessation of airflow for ≥ 10 s. Apnoea was classified as obstructive in the presence of continued movement on RIP, and as central in the absence of movement on RIP. Hypopnea was defined as a $\geq 50\%$ reduction in oronasal flow amplitude for ≥ 10 s, accompanied by a $\geq 3\%$ desaturation or arousal. Hypopnea was classified as obstructive, central, or mixed by calibrated respiratory inductance plethysmography. Hypopnea was classified as obstructive in the presence of continued movement on RIP. The oxygen desaturation index (ODI) measured the number of times that the blood oxygen level dropped by $\geq 3\%$ from baseline per hour of sleep.

Laboratory analyses

The full blood count and biochemical analyses were performed on venous blood samples taken in the morning after eight hours of fasting and polysomnography evaluation, using an Olympus AU2700 Plus Analyser (Beckman Coulter, Tokyo, Japan). The patients were divided into two groups according to established uric acid concentration cut-off values for hyperuricemia (>7 mg/dL in men and >6 mg/dL in women).

Statistical analyses

Statistical Package for the Social Sciences (SPSS) for Windows software was used for the statistical analyses (version 16.0; SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as percentages. All variables were tested for normality with the Kolmogorov-Smirnov test. Mean values and standard deviations were calculated for normally distributed continuous variables, and median values and interquartile range for non-normally distributed variables. Spearman and Pearson correlation analyses were used to evaluate the relationships among variables. The relationships between categorical variables were evaluated with the chi-square test. Comparisons between independent groups were performed using the Mann-Whitney U test and t-tests, or by Kruskal-Wallis one-way analysis of variance with the Bonferroni correction applied. A $p < 0.05$ was considered significant.

RESULTS

The mean age of the 126 patients was 69.16 ± 3.68 (65–83) years, and 71 (56%) were men. The control group included 14 patients (50% men), while the OSAS group consisted of 112 patients (57.1% men). No significant difference between total sleep time and sleep efficiency in patients and controls was detected (358.65 ± 65.05 and 77.08 ± 13.54 vs. 328.2 ± 70.06 and 87.60 ± 13.98 ; $p > 0.05$), while minimum O_2 saturation and ODI were significantly different between groups (80.43 ± 11.15 and 25.37 ± 21.06 vs. 86.64 ± 3.3 and 3.7 ± 2.90 ; $p = 0.016$ and $p = 0.001$).

The OSAS group included 31 mild, 44 moderate and 37 severe cases of OSAS, grouped according to the apnoea-hypopnea index (AHI) value. No differences were observed in age, sex, hip circumference, waist/hip ratio, comorbidities (diabetes, hypertension, coronary artery disease, congestive heart failure, hyperlipidaemia and chronic obstructive pulmonary disease — COPD) between the control and OSAS subgroups. ESS score ($p = 0.001$), body mass index (BMI) ($p = 0.02$) and waist circumference ($p = 0.036$) were significantly higher in the OSAS group than in the controls (Table 1). When the patients with OSAS were grouped by their AHI value, no significant difference in uric acid level was detected among groups (Figure 1).

No differences in demographic parameters or comorbidities were observed when all patients with OSAS were compared to controls, except in AHI value (Table 2).

Uric acid level was not correlated with the AHI value, ODI, mean overnight saturation, minimum saturation, time spent below with $SpO_2 < 90\%$, BMI or waist or hip circumference (Table 3).

When patients were divided into two groups according to the established cut-off values for hyperuricemia,

no differences in sleep parameters or comorbidities were observed between the hyperuricemic and non-hyperuricemic patients, although there were differences in BMI and waist circumference ($p = 0.011$ and $p = 0.014$, respectively) (Table 4).

DISCUSSION

We found no relationship between uric acid levels and OSAS severity, as defined by the AHI, in older patients. Furthermore, we detected no correlation between uric acid level and polysomnography parameters. Hyperuricemia was only correlated with BMI and waist circumference in our geriatric population.

Previous studies conducted on children and adults with OSAS have shown that serum uric acid levels are elevated

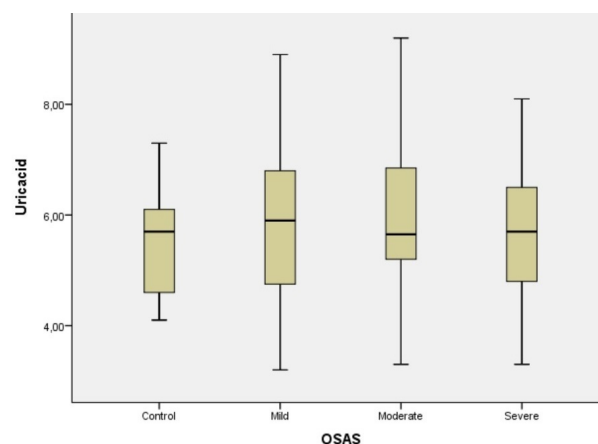


Figure 1. Box plot graph of uric acid levels of patients grouped by obstructive sleep apnoea syndrome (OSAS) severity using the apnoea hypopnea index (AHI)

Table 1. Demographical properties and comorbidities of patients grouped by obstructive sleep apnoea syndrome severity by the apnoea-hypopnea index.

	Control n=14	Mild OSAS n=31	Moderate OSAS n=44	Severe OSAS n=37	p-value*
Age	69.14 ± 3.88	69.29 ± 3.53	68.97 ± 3.83	69.16 ± 3.71	0.987
Gender, male	7 (50%)	21 (67.7%)	26 (59.1%)	17 (45.9%)	0.956
Waist circumference	97.76 ± 17.49	100.58 ± 10.36	104.29 ± 18.35	107.41 ± 8.42	0.036
Hip circumference	104.15 ± 14.99	101.71 ± 9.90	104.95 ± 12.03	109.41 ± 8.26	0.096
Waist/hip ratio	0.94 ± 0.09	1.01 ± 0.81	0.98 ± 0.11	0.99 ± 0.07	0.142
BMI	29.99 ± 7.68	29.77 ± 4.84	32.00 ± 6.86	34.03 ± 4.77	0.020
ESS	7.79 ± 5.11	8.9 ± 4.01	8.29 ± 4.09	12.43 ± 5.74	0.001
DM	3 (21.4%)	4 (12.9%)	17 (38.6%)	11 (29.7%)	0.098
HT	7 (50%)	12 (38.7%)	30 (68.2%)	22 (59.5%)	0.080
CAD	1 (7.1%)	3 (9.7%)	12 (27.3%)	9 (24.3%)	0.146
CHF	1 (7.1%)	1 (3.1%)	8 (18.2%)	4 (10.8%)	0.224
Hyperlipidemia	2 (14.3%)	0	5 (11.4%)	3 (8.1%)	0.249
COPD	2 (14.3%)	3 (9.7%)	6 (13.6%)	2 (5.4%)	0.631
Uric acid	5.58 ± 1.01	5.83 ± 1.50	5.92 ± 1.33	5.72 ± 1.4	0.847

OSAS: obstructive sleep apnoea syndrome; BMI: body mass index; ESS: Epworth sleep scale; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease. Data are expressed as mean \pm SD or median (range). * Kruskal–Wallis one-way analysis of variance with the Bonferroni correction.

in patients with OSAS compared to controls^{7,8}. Hira et al. reported that uric acid level tended to be correlated with the amount of time spent below 90% SaO₂ in 40 adult patients with OSAS¹³. In their study, polysomnography parameters did not show significant correlations with serum uric acid level in a regression analysis that included age and BMI. They concluded that an increased uric acid level was correlated with

Table 2. Demographic characteristics and comorbidities of patients with obstructive sleep apnoea syndrome and the control group.

	Control patients n=14	All OSAS patients n=112	p-value*
Age	69.14±3.88	69.12±3.68	0.980
Gender, male	7 (50%)	64 (57.1%)	0.615
Waist	97.76±17.49	104.29±13.76	0.119
Hip	104.15±14.99	105.53±10.67	0.676
Waist/hip ratio	0.94±0.09	0.993±0.092	0.044
BMI	29.99±7.68	32.06±5.89	0.235
ESS	7.79±5.11	9.82±4.99	0.156
AHI	3.05±1.57	27.07±19.11	0.001
DM	3 (21.4%)	32 (28.6%)	0.577
HT	7 (50%)	64 (57.1%)	0.615
CAD	1 (7.1%)	24 (21.4%)	0.209
CHF	1 (7.1%)	13 (11.6%)	0.620
Hyperlipidemia	2 (14.3%)	8 (7.1%)	0.355
COPD	2 (14.3%)	11 (9.8%)	0.608
Uric acid	5.58±1.01	5.83±1.41	0.704

OSAS: obstructive sleep apnoea syndrome; BMI: body mass index; ESS: Epworth sleep scale; AHI: apnoea-hypopnea index; DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease. Data are expressed as mean±SD or median (range); * Chi-square test, Mann-Whitney U test and t-tests.

Table 3. Correlations among uric acid and the various parameters of interest.

	Uric acid	
	r	p*
Age	0.144	0.108
BMI	0.08	0.335
Waist circumference	0.097	0.280
Hip circumference	-0.045	0.617
Waist/hip ratio	0.028	0.760
ESS	-0.008	0.928
AHI	0.016	0.863
ODI	0.001	0.990
Mean SpO ₂	0.048	0.596
Minimum SpO ₂	0.143	0.111
Time spent SpO ₂ <90%	-0.101	0.262

BMI: body mass index; ESS: Epworth sleep scale; AHI: apnoea-hypopnea index; ODI: oxygen desaturation index. *Spearman and Pearson correlation analyses.

the degree of hypoxia, although the correlation was influenced by the waist-hip ratio.

In another study of 1,135 patients, uric acid levels were correlated with sleep parameters, such as the AHI; time elapsed in a state of oxygen desaturation was not correlated when confounding factors, such as BMI, cholesterol and triglyceride levels, were controlled for. As in the study of Hira et al., the conclusion reached was that the correlation between uric acid levels and sleep parameters was influenced by other factors, such as obesity¹⁴. In our older population, no correlation was observed between uric acid levels and the degree of hypoxia, but the waist-hip ratio was significantly higher in patients with OSAS than in controls. BMI and waist circumference were also significantly higher in patients with versus patients without high uric acid levels. Our findings are similar to those of a study of older Koreans showing that elevated

Table 4. Comparison between patients with high and normal uric acid values

	High uric acid level n=33	Normal uric acid level n=93	p-value*
Age	69.88±4.21	68.86±3.47	0.301
Gender, male	16 (48.5%)	55 (59.1%)	0.313
DM	10 (30.3%)	25 (26.9%)	0.821
Hypertension	23 (69.7%)	48 (51.6%)	0.102
CAD	10 (30.3%)	15 (16.1%)	0.125
CHF	7 (21.2%)	7 (7.5%)	0.049
Hyperlipidemia	3 (9.1%)	7 (7.5%)	0.721
COPD	4 (12.1%)	9 (9.7%)	0.742
OSAS	29 (87.9%)	83 (89.2%)	0.759
BMI	33.67±5.55	31.17±6.20	0.011
Waist circumference	106.85±11.7	102.45±14.95	0.014
Hip circumference	107.42±9.98	104.65±11.48	0.177
Waist/hip ratio	0.99±0.076	0.986±0.099	0.877
ESS	9.88±4.81	9.48±5.13	0.560
AHI	25.26±18.93 22.4 (iqr 26.05)	24.09±19.84 18.80 (iqr 21.55)	0.549
ODI	24.07±19.68 20 (iqr 25.95)	22.57±21.55 16.40 (iqr 21.65)	0.457
Minimum SpO ₂	80.52±11.69	81.34±10.46	0.300
Mean SpO ₂	91.16±5.32	92.31±2.46	0.885
Time spent SpO ₂ <90%	47.82±68.86 15.9 (iqr 81.95)	35.60±56.08 11.40 (iqr 41.20)	0.383
Time % spent SpO ₂ <90%	13.47±17.87 5.23 (iqr 22.68)	9.96±15.74 2.78 (iqr 10.23)	0.233

BMI: body mass index; ESS: Epworth sleep scale; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; AHI: apnoea-hypopnea index; ODI: oxygen desaturation index. Data are expressed as mean±SD or median (range); iqr: interquartile range; *Chi-square test, Mann-Whitney U test and t-tests.

uric acid levels are associated with metabolic syndrome, one of the components of which is a large waist circumference¹⁵.

A severe OSAS group had higher uric acid levels compared to controls and other OSAS groups in a study including 436 patients; moreover, hyperuricemia was associated with cardiovascular disease in the OSAS patients¹⁶. In another study including 449 individuals, uric acid level was significantly higher in an OSAS versus a control group. In addition, the proportion of hypertensive ratios was significantly higher in the OSAS population¹⁷. In our study, no significant differences in comorbidities, including hypertension and cardiovascular diseases, were detected between the OSAS group and controls. This could be a reason why the increase in uric acid was found in their studies done by Kanbay et al.¹⁶ and Parmaksız et al.¹⁷ but not in ours. The relationship between increased levels of uric acid and elevated risk of cardiovascular disease has been demonstrated in many epidemiological studies^{6,9,10}. Hyperuricemic patients with OSAS have a higher prevalence of coronary artery disease and hypertension, regardless of sex, than those without OSAS^{18,19}. However, in our series, comorbidities were not different between patients with OSAS and controls.

Healthy adult males have higher uric acid levels than women. This difference is caused by oestrogen, which affects renal tubular reabsorption of acid during the pre-menopausal period. It is also known that, among patients with cardiovascular disease, uric acid levels differ by gender²⁰. In a study including 260 male patients with OSAS, uric acid level was correlated with obesity and overnight oxygenation, but the only significant correlation in regression analysis was between uric acid and BMI¹⁸. In another study of 105 female patients performed by the same group, women with a high level of uric acid had a significantly higher BMI and showed desaturation of less than 90% for longer periods¹⁹.

However, the same result was reported in male patients in multiple regression analysis¹⁹. Our older population was 56% male, and BMI and waist circumference were the only factors differing significantly between the hyperuricemic and non-hyperuricemic groups.

Some studies reported no significant relationship between uric acid level and OSAS severity. In a study of 600 patients aged 18–70 years, the mean serum uric acid level was significantly higher in the severe OSAS group versus the other patients, but the difference disappeared after correcting for BMI, smoking history, hypertension, diabetes and cardiovascular diseases, all of which were significantly higher in the severe OSAS group²¹.

Most inflammatory markers decrease after continuous positive airway pressure (CPAP) therapy in patients with OSAS, but the results regarding uric acid levels after CPAP therapy are controversial. In some studies, uric acid is negatively correlated with minimum SpO₂ in patients with OSAS, as in Sunnetcioğlu et al.²¹; we did not find this relationship. Uric acid decreases when OSAS is treated with CPAP²². Similarly, uric acid levels drop in overweight children and adolescents who lose weight^{8,23}. However, in another study including an adult population, no reduction in urate levels was detected after three months of CPAP treatment²⁴. Age and certain other confounding factors, such as weight loss, could have been responsible for that result.

The main limitation of this study is small sample size.

In conclusion, this study found no relationship between uric acid level and OSAS severity, as defined by the AHI, in older patients, and hyperuricemia was only correlated with BMI and waist circumference. Further studies are needed to determine the utility of uric acid as a marker in older patients with OSAS, after controlling for cardiovascular comorbidities.

References

1. Kapur VK. Obstructive sleep apnea: diagnosis, epidemiology, and economics. *Respir Care*. 2010 Sep;55(9):1155–67.
2. Atkeson A, Yeh SY, Malhotra A, Jelic S. Endothelial function in obstructive sleep apnea. *Prog Cardiovasc Dis*. 2009 Mar-Apr;51(5):351–62. <https://doi.org/10.1016/j.pcad.2008.08.002>
3. Wu CY, Hu HY, Chou YJ, Huang N, Chou YC, Lee MS, Li CP. High serum uric acid levels are associated with all-cause and cardiovascular, but not Cancer, mortality in elderly adults. *J Am Geriatr Soc*. 2015 Sep;63(9):1829–36. <https://doi.org/10.1111/jgs.13607>
4. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008 Oct;359:1811–21. <https://doi.org/10.1056/nejmra0800885>
5. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res*. 2000 Nov;87(10):840–44. <https://doi.org/10.1161/01.res.87.10.840>
6. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. *JAMA*. 2000 May;283(18):2404–10. <https://doi.org/10.1001/jama.283.18.2404>
7. Drager LF, Lopes HF, Maki-Nunes C, Trombetta IC, Toschi-Dias E, Alves MJ, et al. The impact of obstructive sleep apnea on metabolic and inflammatory markers in consecutive patients with metabolic syndrome. *PLoS One*. 2010 Aug;5(8):e12065. <https://doi.org/10.1371/journal.pone.0012065>
8. Verhulst SL, Van Hoeck K, Schrauwen N, Haentjens D, Rooman R, Van Gaal L, et al. Sleep-disordered breathing and uric acid in overweight and obese children and adolescents. *Chest*. 2007 Jul;132(1):76–80. <https://doi.org/10.1378/chest.06-2930>
9. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I epidemiologic followup study. *Am J Epidemiol*. 1995 Apr;141(7):637–44. <https://doi.org/10.1093/oxfordjournals.aje.a117479>
10. Burack RC, Keller JB, Higgins MW. Cardiovascular risk factors and obesity: are baseline levels of blood pressure, glucose, cholesterol and uric acid elevated prior to weight gain? *J Chronic Dis*. 1985;38(10):865–72. [https://doi.org/10.1016/0021-9681\(85\)90111-0](https://doi.org/10.1016/0021-9681(85)90111-0)
11. Hopps E, Caimi G. Obstructive sleep apnea syndrome: links between pathophysiology and cardiovascular complications. *Clin Invest Med*. 2015 Dec;38(6):E362–70. <https://doi.org/10.25011/cim.v38i6.26199>

12. Baratta F, Pastori D, Fabiani M, Fabiani V, Ceci F, Lillo R, et al. Severity of OSAS, CPAP and cardiovascular events: A follow-up study. *Eur J Clin Invest.* 2018 May;48(5):e12908. <https://doi.org/10.1111/eci.12908>
13. Hira HS, Shukla A, Kaur A, Kapoor S. Serum uric acid and lactate levels among patients with obstructive sleep apnea syndrome: which is a better marker of hypoxemia? *Ann Saudi Med.* 2012 Jan-Feb;32(1):37-42. <https://doi.org/10.5144/0256-4947.2012.37>
14. Ruiz AG, Sanchez AA, Luque EC, Garcia DA, Romero AF, Carmona CB, Capote F. Valores de ácido úrico en sangre en pacientes con trastornos respiratorios del sueño [Blood uric acid levels in patients with sleep-disordered breathing]. *Arch Bronconeumol.* Oct;42(10):492-500. Spanish. [https://doi.org/10.1016/s1579-2129\(06\)60575-2](https://doi.org/10.1016/s1579-2129(06)60575-2)
15. Choi H, Kim HC, Song BM, Park JH, Lee JM, et al. Serum uric acid concentration and metabolic syndrome among elderly Koreans: The Korean Urban Rural Elderly (KURE) study. *Arch Gerontol Geriatr.* 2016 May-Jun;64:51-8. <https://doi.org/10.1016/j.archger.2016.01.005>
16. Kanbay A, Inonu H, Solak Y, Erden A, Uslu E, Yuksel S, et al. Uric acid as a potential mediator of cardiovascular morbidity in obstructive sleep apnea syndrome. *Eur J Intern Med.* 2014 Jun;25(5):471-6. <https://doi.org/10.1016/j.ejim.2014.04.005>
17. Parmaksız ET, Salepçi B, Güngör GA, Cömert S, Parmaksız E. Ürik Asit Obstrüktif Uyku Apne Sendromunda Bir Belirteç midir? [Is uric acid a marker in obstructive sleep apnea syndrome?] *J Turk Sleep Med.* 2016 Sep;3(3):73-8. Turkish. <https://doi.org/10.4274/jtsm.228>
18. Pływaczewski R, Bednarek M, Jonczak L, Górecka D, Sliwiński P. Hiperurykemia u mężczyzn chorych na obturacyjny bezdech senny (obs) [Hyperuricaemia in males with obstructive sleep apnoea (osa)]. *Pneumonol Alergol Pol.* 2004 Dec;73(3):254-9. Polish.
19. Pływaczewski R, Bednarek M, Jonczak L, Górecka D, Sliwiński P. Hiperurykemia u kobiet chorych na obturacyjny bezdech senny [Hyperuricaemia in females with obstructive sleep apnoea] *Pneumonol Alergol Pol.* 2005 Dec;74(2):159-65. Polish.
20. Kawabe M, Sato A, Hoshi T, Sakai S, Hiraya D, Watabe H, et al. Gender differences in the association between serum uric acid and prognosis in patients with acute coronary syndrome. *J Cardiol.* 2016 Feb;67(2):170-6. <https://doi.org/10.1016/j.jjcc.2015.05.009>
21. Sunnetcioglu A, Gunbatar H, Yildiz H. Red cell distribution width and uric acid in patients with obstructive sleep apnea. *Clin Respir J.* 2018 Mar;12(3):1046-52. <https://doi.org/10.1111/crj.12626>
22. Steiropoulos P, Kotsianidis I, Nena E, Tsara V, Gounari E, et al. Long-term effect of continuous positive airway pressure therapy on inflammation markers of patients with obstructive sleep apnea syndrome. *Sleep.* 2009 Apr; 32(4):537-43. <https://doi.org/10.1093/sleep/32.4.537>
23. Van Hoorenbeeck K, Franckx H, Debode P, Aerts P, Wouters K, Ramet J, et al. Weight loss and sleep-disordered breathing in childhood obesity: effects on inflammation and uric acid. *Obesity (Silver Spring).* 2012 Jan;20(1):172-7. <https://doi.org/10.1038/oby.2011.282>
24. Prudon B, Roddy E, Stradling JR, West SD. Serum urate levels are unchanged with continuous positive airway pressure therapy for obstructive sleep apnea: a randomized controlled trial. *Sleep Med.* 2013 Dec;14(12):1419-21. <https://doi.org/10.1016/j.sleep.2013.09.001>