

Serum uric acid and lactate levels among patients with obstructive sleep apnea syndrome: Which is a better marker of hypoxemia?

Harmanjit Singh Hira,^{ab} Anuj Shukla,^a Amandeep Kaur,^a Seema Kapoor^b

From the ^aDepartments of Pulmonary, Internal, ^bPaediatrics Medicine, Maulana Azad Medical College and Lok Nayak Hospital, University of Delhi, New Delhi, India

Correspondence: Dr. H. S. Hira, · House 74, Block 21, Lodi Colony, New Delhi - 110 003, India · T: 009111 24631653, F: 009111 24652828 · drhshira@hotmail.com · Accepted: January 2011

Ann Saudi Med 2011; 32(1): 37-42

PMID: 22156638 DOI: 10.5144/0256-4947.2012.37

BACKGROUND AND OBJECTIVES: Tissue hypoxia due to repeated sleep apneas leads to increased serum levels of uric acid (UA) and lactate in patients with obstructive sleep apnea syndrome (OSAS). Studies on assessment of serum level of UA in patients of OSAS are available. However, research on simultaneous evaluation of levels of serum lactate and UA is lacking.

DESIGN AND SETTING: Prospective, case-control study.

PATIENTS AND METHODS: Forty patients suffering from OSAS, diagnosed by night polysomnography (PSG), were included in this study. Forty age- and sex-matched subjects in whom the presence of OSAS was ruled out by night PSG were included as healthy controls. Participants underwent a procedure for the measurement of serum UA and lactate before and after sleep.

RESULTS: Both before and after sleep UA levels of patients with OSAS were found to be significantly higher ($P=.001$ and $.002$, respectively) as compared to UA levels of controls. A statistically significant ($P=.02$) overnight (after sleep) rise was observed in the serum lactate level of OSAS patients. The correlation between serum UA values and %TSTs (percentage of total sleep time spent) below 95% SaO₂ (arterial oxygen saturation) ($P=.02$) was statistically significant. The correlation was positive with %TSTs below 90% SaO₂, whereas it was found negative with normal basal oxygen. No significant correlation was observed between serum UA and the AHI (apnea-hypopnea index). Polysomnographic variables failed to show significant correlation with serum UA on respective multiple regression models controlling for age, body mass index, and waist-hip ratio. However, plasma lactate levels after sleep correlated with %TSTs below 95% of SaO₂ and AHI with P values of $.02$ and $.01$, respectively.

CONCLUSIONS: Both serum UA and lactate were positively correlated with the degree of hypoxia in OSAS. The measurement of serum lactate level was a better marker of oxidative stress among patients with OSAS.

Sleep apneas are present in patients with obstructive sleep apnea syndrome (OSAS). These apneas cause a decrease in arterial oxygen saturation (SaO₂) and tissue hypoxia. Reoxygenation follows the termination of apneas. This cycle causes the evolution of hypoxic oxidative stress (HOS). Because of HOS, the production of ATP (adenosine triphosphate) from ADP (adenosine diphosphate) is impaired, leading to a net degradation of ATP to ADP and adenosine monophosphate. This cascade leads to the release of inter-

mediates of purine nucleotide (adenosine, inosine, hypoxanthine, and xanthine).¹ Uric acid (UA) is biosynthesized from these purine catabolic products. HOS triggers exaggerated degradation of glucose through the glycolytic pathway, resulting in an accumulation of pyruvate.² Lactate dehydrogenase converts accumulated pyruvate to lactate. The lack of ATP in a state of hypoxemia markedly impairs the utilization of lactate by a process of gluconeogenesis in the liver (Cori cycle) and renal cortex. Thus tissue hypoxia results in hyper-

lactemia and lactic acidosis.^{3,4} Therefore, hyperuricemia and hyperlactemia are markers of tissue HOS in OSAS patients.

Conditions such as infant respiratory syndrome, strenuous exercise, hypotension, acute respiratory distress syndrome, and critical illness cause a raised level of UA in the human body.⁵⁻⁹ Both ischemia and hypoxia are responsible for the higher level of UA in these entities. However, no study exists to show the measurement of both serum UA and plasma lactate levels simultaneously in OSAS patients, prompting us to undertake this study.¹⁰ Various studies have experimentally and clinically shown that inadequate oxygen delivery to maintain tissue oxygenation elevates the serum lactate level.¹¹⁻¹⁷ Studies related to the measurement of the serum lactate level in OSAS patients are very few. In 2009, Ucar et al¹⁸ demonstrated a relationship between nocturnal hypoxia and arterial lactate levels in sleep-related breathing disorders.

PATIENTS AND METHODS

This was a case-control study that included 40 OSAS patients and 40 control (healthy) subjects. The institutional academic board and ethical committee approved the protocol of the study. All participants gave informed written consent. All subjects underwent overnight polysomnography (PSG), using VIASYS Healthcare Sleep Screen Apnea Screen Cardio Polysomnography (VIASYS Healthcare, Germany) equipment for the duration of 6-8 hours. The parameters recorded by PSG included central electroen-

cephalography (C3/A2 and C4/A1), electrooculography, submental electromyography, anterior tibialis electromyography, electrocardiography, continuous-pulse oximetry, thoracic and abdominal movements, and oro-nasal airflow. The period for which patients underwent PSG was recorded as TST (total sleep time) spent. The percentage of total sleep time spent (%TST) below 95%, 90%, and 85% of SaO₂ was recorded.

A decrease in inspiratory flow to less than 20% of waking level for at least 10 seconds was considered apnea. The presence of more than 5 apneas per hour of sleep established the diagnosis of OSAS. A decrease in inspiratory airflow to <50% of waking level was considered hypopnea. The apnea-hypopnea index (AHI) was the average of the total number of apneas and hypopneas per hour of TST. The grading of severity of OSAS was based on AHI. OSAS was considered mild (AHI, 5-10), moderate (AHI, 10-30), or severe (AHI, >30). Forty subjects with no apnea or less than 20 apneas during 6-8 hours (TST) of sleep were taken as healthy controls.

Over a period of 1 year, physicians referred 64 patients with suspected OSAS to the Sleep Laboratory of the Department of Pulmonary Medicine. Based on criteria, a history of loud snoring and excessive daytime sleepiness, 40 patients suffering from OSAS were selected. Forty persons in whom overnight PSG ruled out OSAS were included as healthy subjects (controls). To eliminate confounding effects, inclusion of patients and controls was based on matching of age and sex, and presence of obesity (**Table 1**). All participants of the study underwent anthropometry and biochemical tests. Anthropometry included measurement of height, weight, waist, and neck circumference and waist-hip ratio (WHR), using standardized techniques. The body mass index (BMI) was calculated. On the basis of BMI, OSAS patients were categorized as normal, overweight, obese, or morbid obese (**Table 1**).

Two samples of peripheral arterial blood of all participants were drawn; the first one drawn before beginning the PSG and second one at the end of PSG. Immediately, blood was transported to the biochemical-genetic laboratory for estimation of lactate in a fluorized tube and UA in a plain glass bottle.

The serum lactate was measured using a lactate pap fluid mono-reagent kit (Centronic GmbH, Wattenberg, Germany), and was analyzed on double-beam UV-VIS spectrophotometer UV5704SS (Electronic Co. of India Ltd., India) analyzer. The serum UA was measured using an auto-analyzer.

Table 1. Matching between obstructive sleep apnea syndrome patients and controls.

Independent variables	Value	Number of subjects	
		OSAS group (n=40)	Control group (n=40)
Age (years)	<40	10	12
	40 to 50	20	16
	>50	10	12
Sex	Male	36	36
	Female	4	4
Body mass index (kg/m ²)	<25 (normal)	0	0
	25 to 29.99 (overweight)	6	8
	30 to 39.99 (obese)	30	32
	>40 (morbidly obese)	4	0

Table 2. Analysis of serum uric acid and lactate variables in obstructive sleep apnea syndrome patients and controls.

Variable parameters	Group	Mean value	Standard deviation	P value (Mann-Whitney U test)
Serum uric acid before sleep (b)	Control	5.38	1.12	.001
	OSAS	7.54	1.63	
Serum uric acid after sleep (a)	Control	5.30	1.43	.002
	OSAS	7.66	2.10	
Serum uric acid change (a-b)	Control	-0.07	0.70	.27
	OSAS	0.18	1.07	
Plasma lactate before sleep (b')	Control	1.46	0.62	.2
	OSAS	1.74	0.60	
Plasma lactate after sleep (a')	Control	1.53	0.89	.03
	OSAS	2.28	0.98	
Plasma lactate change (a'-b')	Control	-0.19	0.64	.02
	OSAS	0.56	0.94	

a: after sleep, b: before sleep

Table 3. Correlation between polysomnographic variables and serum levels of uric acid and lactate among patients with OSAS.

Variable (n=40)		Desaturation index	Basal oxygen	95% ^a	90% ^a	AHI
Serum uric acid after sleep (a)	r	0.212	-0.425	0.494*	0.418	0.264
	P value	.370	.062	.027	.067	.260
Plasma lactate after sleep (a')	R	0.487 ^b	-0.492 ^b	-0.654 ^b	0.553 ^b	0.670 ^b
	P value	.030	.028	.002	.011	.001

r: correlation coefficient for serum uric acid, R: correlation coefficient for plasma lactate, AHI: apnea-hypopnea index.

^a%TST below X oxygen saturation; ^bsignificant correlation after sleep

SPSS (version 14) software (SPSS, Inc, Chicago, IL) was used to analyze the data. The nonparametric Mann-Whitney U test was performed to analyze both serum UA and lactate variables in OSAS patients and controls (Table 2). The unpaired *t* test and *P* values helped to compare variables between the OSAS patients and controls. Because the common variance assumption required by the *t* test was not appropriate for some of the measurements, the nonparametric analysis using the Mann-Whitney U test assessed the significance of differences. The Wilcoxon nonparametric analysis for paired parameters tested the significance of overnight changes in the serum UA and plasma lactate levels in both patients and controls; the difference between parameters was considered statistically significant with *P* value of <.05. PSG variables, as well as serum levels of UA and lactate, among patients with OSAS were correlated (Table 3). To observe the independent effects of age, BMI, and WHR on such correlations, multiple linear regression models were used and variables were examined (Tables 4-6).

RESULTS

Statistically significant differences were not observed in age, sex, and BMI between OSAS patients and controls (Table 1). However, OSAS patients had greater waist circumference (*P*=.03) and neck circumference (*P*=.001) as compared to controls. No statistically significant differences were recorded between the weights and WHPs of both groups. Comparing BMI between OSAS patients and controls revealed that obesity had a greater central fat distribution among patients as compared to controls. On the basis of AHI, OSAS was mild in 6 patients, moderate in 6, and severe in 28.

The mean serum level of UA in OSAS patients was 7.54 (1.63) mg/dL and 7.66 (2.1) mg/dL before and after sleep, respectively (Table 2); both these values were higher than the laboratory standard reference value of 7 mg/dL. In the control group, the mean serum UA level was 5.38 (1.12) mg/dL and 5.30 (1.43) mg/dL before and after sleep, respectively (Table 2), and this was less than the standard laboratory reference value. A statistically significant difference was observed

Table 4. Multiple linear regression analysis of serum UA as an outcome variable (adjusted $R^2=0.38$) and %TSTs below 95% SaO₂ as a predictor variable (controlling for age, BMI, and WHR).

Independent variables	Coefficient	Standard error	t	P
Constant	-3.74			
Age (year)	0.01	0.04	0.24	.82
BMI	-0.04	0.06	-0.67	.51
WHR	10.92	3.97	2.75	.01
%TSTs below 95% SaO ₂	0.02	0.02	1.17	.26

UA: uric acid, %TSTs:percentage of total sleep time spent, SaO₂: arterial oxygen saturation, BMI: body mass index, WHR: waist-hip ratio.

Table 5. Multiple linear regression analysis with serum lactate as an outcome variable (adjusted $R^2=0.49$) and AHI as a predictor variable (controlling for age, BMI, and WHR).

Independent variables	Coefficient	Standard error	t	P
Constant	-2.48			
Age (year)	0.03	0.02	1.40	.18
BMI	-0.01	0.02	-0.12	.90
WHR	2.83	1.51	1.86	.08
AHI	0.02	0.01	3.27	.005

AHI: Apnea-hypopnea index, BMI: body mass index, WHR: waist-hip ratio.

Table 6. Multiple linear regression analysis with serum lactate as an outcome variable (adjusted $R^2=0.37$) and %TST below 95% SaO₂ as a predictor variable (controlling for age, BMI, and WHR).

Independent variables	Coefficient	Standard error	t	P
Constant	-2.36			
Age (year)	0.02	0.02	0.99	.33
BMI	0.01	0.03	0.28	.78
WHR	1.93	1.86	1.04	.31
%TSTs below 95% SaO ₂	0.02	0.01	2.40	.02

%TST: percentage of total sleep time, SaO₂: arterial oxygen saturation, BMI: body mass index, WHR: waist-hip ratio.

in the mean level of serum UA between OSAS and controls before ($P=.001$) and after ($P=.002$) sleep, as computed by the nonparametric Mann-Whitney U test. Thus OSAS patients had consistently higher UA levels as compared to those of the controls, and this was independent of age, sex, and obesity. However, the Wilcoxon nonparametric analysis demonstrated no

statistically significant ($P=.8$) difference between the paired UA levels before and after sleep in OSAS patients. The increase in levels of serum UA after sleep in both OSAS patients and controls (Mann-Whitney U test, $P=.27$) was not significantly different (Table 2). Thus there was no significant overnight rise in the level of UA in OSAS patients.

Serum UA values correlated significantly with %TST below 95% SaO₂, with a P value of .02, using the Pearson correlation. Although correlation was positive with %TSTs below 90% SaO₂ and with negative with basal oxygen, these observations were not found to be statistically significant ($P=.06$), as shown in Table 3. Moreover, the polysomnographic variables failed to show significant correlation with serum UA on respective multiple regression models controlling for age and BMI. WHR had a significant independent effect on the serum UA of OSAS patients (Table 4). No significant correlation was found between serum UA and AHI. Thus, the OSAS group had consistently high levels of serum UA that correlated with the degree of hypoxia below 95% and 90%, and with basal SaO₂, but WHR influenced this correlation.

The mean level of plasma lactate of OSAS patients measured before sleep was 1.74 (0.6) mmol/L and after sleep was 2.28 (0.98) mmol/L; both these values were higher than the standard laboratory reference value. In the control group, the mean serum level of plasma lactate was 1.46 (0.62) mmol/L and 1.53 (0.89) mmol/L before and after sleep, respectively; both these values were lower than the standard laboratory reference value. There was no statistically significant difference in serum levels of lactate ($P=.2$) between patients and controls before sleep. However, after sleep, the overnight rise in the lactate level was observed in OSAS patients, with statistical significance (Mann-Whitney U test, $P=.02$); while a similar overnight rise was not observed among controls (Wilcoxon analysis, $P=.7$). Thus the OSAS group had a higher basal lactate level before sleep, and the level of lactate showed a further significant overnight rise after sleep. Plasma lactate levels after sleep were correlated best with SaO₂ below 95% ($P=.02$) and high AHI ($P=.01$). The correlation was also observed with the desaturation index of basal SaO₂ especially when less than 90% (Table 3). Moreover, PSG variables like AHI and less-than 95% SaO₂ showed a significant correlation with plasma lactate on regression models controlling for age and obesity, BMI, and WHR (Tables 5, 6). The degree of hypoxia correlated significantly with serum lactate levels and severity of OSAS; and both age and obesity did not influence the correlation.

DISCUSSION

In our study, the mean level of serum UA both before and after sleep was found higher in the OSAS group as compared to that in the control group and the standard laboratory reference value; and this observation was independent of age, sex, and obesity. However, an overnight rise in serum UA levels was not observed. The raised serum UA correlated with the degree of hypoxia, but regression analysis models revealed that WHR did influence this correlation.

Previous studies showed raised serum UA levels among OSAS patients.¹⁵⁻¹⁷ A retrospective cross-sectional study of 1135 patients had similar findings and revealed a significant correlation between UA levels and OSAS.¹⁷ Those patients with more respiratory events (AHI or respiratory event index ≥ 30) had higher UA levels than those with mild OSAS and healthy controls. However, this difference was not apparent in the univariate analysis of variance. Thus, UA levels had a positive correlation with the number of apneas and oxygen desaturation during sleep, but this correlation seems to be influenced by other factors, like obesity.¹⁷ In contrast to the above observations, in another study a relationship between the severity of sleep apnea (respiratory disturbance index and %TSTs below 89% SaO₂) and the increased level of serum UA was found independent of abdominal obesity.¹⁶

In the present study, higher levels of serum UA were independent of age, sex, and obesity of OSAS patients, but they correlated with the degree of hypoxia. There was no correlation between AHI and serum UA in the present study. This deviation from findings of earlier studies¹⁷ could be attributed to a smaller number of OSAS patients in the present study.

The overnight change in the serum UA level in OSAS patients was not investigated in previous studies.¹⁵⁻¹⁷ We could not demonstrate that hypoxia during sleep did affect the rise in the serum UA level after sleep. The basic metabolism impaired the utilization of UA. The lack of uricase enzyme in a human body metabolized UA, which is eliminated only by renal excretion, that is, in urine, with a half-life of 0.85 day.¹⁹ Thus, the slow rate of UA metabolism was attributed to the overnight change in the serum UA level in patients with OSAS.

Serum lactate is an indicator of tissue hypoxia. OSAS causes hypoxemia and tissue hypoxia during sleep, owing to apneas. In addition, conversion of pyruvate to lactate by the process of anaerobic glycolysis conversion of pyruvate to lactate occurs in the presence of sleep-associated hypoxemia in OSAS patients. Significantly, the elevated plasma lactate levels were present in OSAS patients, but these raised levels were absent in controls. A significant correlation was found between the raised lactate levels after sleep, and the severity of OSAS and the degree of hypoxemia during sleep particularly % TST below 95% of SaO₂. The correlation of age and obesity (BMI and WHR) with plasma lactate levels was also observed to be significant in the respective multiple regression models. Age and obesity variables could not influence plasma lactate levels. Although the mean basal lactate level (1.74 mmol/L) before sleep in OSAS patients did not differ significantly from that in healthy controls, it was higher than the standard laboratory reference value in OSAS patients. However, the correlation was not present with the desaturation index. This could be attributed to chronic daytime gaseous abnormalities present in OSAS patients.²⁰⁻²⁴ Rapid metabolism of lactate with a half-life of 20 minutes facilitates measuring transient nighttime hypoxemia in OSAS patients. Morning lactate was demonstrated to be significantly higher in patients with sleep-related breathing disorders in a recent study.¹⁸ However, no such study is available in which both UA and lactate levels are carried out simultaneously in patients and healthy controls.

In conclusion, an overnight rise in the lactate level seems to be a sensitive marker of the degree of HOS in OSAS patients. The serum UA level increases in OSAS patients, probably because of its increased production. The measurement of UA is not a sensitive marker of the overnight rise owing to its slower metabolism as compared to that of lactate. The effectiveness of continuous positive airway pressure therapy in patients with OSAS may be enhanced by knowing the serum lactate level before and after night PSG, as the serum lactate level is found to be a better marker of oxidative stress among patients with OSAS.

REFERENCES

1. Rodwell VW. Metabolism of Purine and Pyrimidine Nucleotides. In: Murray RK, Granner DK, Rodwell VW, editors. *Harper's Illustrated Biochemistry*. 27th ed. Singapore: McGraw-Hill Education (Asia); 2006. p. 301-10.
2. Bender DA, Mayes PA. Glycolysis and the Oxidation of Pyruvate. In: Murray RK, Granner DK, Rodwell VW, editors. *Harper's Illustrated Biochemistry*. Singapore: McGraw-Hill Education (Asia); 2006. p. 145-50.
3. Kreisberg RA. Lactate homeostasis and lactic acidosis. *Ann Intern Med* 1980;92:227-37.
4. Bellomo R. Bench-to bedside review: Lactate and the kidney. *Critical Care* 2002;6:322-6.
5. Fox AC, Reed GE, Meilmam H, Silk BB. Release of nucleosides from canine and human hearts as an index of prior ischemia. *Am J Cardiol* 1979;43:52-8.
6. Ketani LH, Simon RH, Kreitz JW, Grum CM. Plasma hypoxanthine and exercise. *Am Rev Respir Dis* 1987;138:98-101.
7. Woolliscroft JD, Fox IH. Increased body fluid purine levels during hypotensive events: Evidence for ATP degradation. *Am J Med* 1986;81:472-8.
8. Christensen EF, Jacobsen J, Anker-Moller E, P Schultz, N Spangsborg. Increased urinary loss of uric acid in adults with acute respiratory failure requiring mechanical ventilation. *Chest* 1992;102:556-9.
9. Grum CM, Simon RH, Dantzker DR, Fox IH. Evidence for adenosine triphosphate degradation in critically-ill patients. *Chest* 1985;88:763-7.
10. Cain SM. Appearance of excess lactate in anesthetized dogs during anemic and hypoxic hypoxia. *Am J Physiol* 1965;209:604-10.
11. Hasday JD, Grum CM. Nocturnal increase of urinary uric acid: Creatinine ratio: A biochemical correlates of sleep-associated hypoxemia. *Am Rev Respir Dis* 1987;135:534-8.
12. Braghiroli A, Sacco C, Erbetta M, Ruga V, Donner CF. Overnight urinary uric acid: Creatinine ratio for detection of sleep hypoxemia: Validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure. *Am Rev Respir Dis* 1993;148:173-8.
13. Sahebajani H. Changes in urinary uric acid excretion in obstructive sleep apnea before and after therapy with nasal continuous positive airway pressure. *Chest* 1998;113:1604-8.
14. McKeon JL, Saunders NA, Murree-Allen K, Olson LG, Gyulay S, Dickeson J. Urinary uric acid:creatinine ratio, serum erythropoietin, and blood 2,3-diphosphoglycerate in patients with obstructive sleep apnea. *Am Rev Respir Dis* 1990;142:8-13.
15. Saito H, Nishimura M, Shibuya E, Makita H, Tsujino I, Miyamoto K, et al. Tissue Hypoxia in Sleep Apnea Syndrome Assessed by Uric Acid and Adenosine. *Chest* 2002;122:1686-94.
16. Verhulst SL, Hoeck KV, Schrauwen N, Haentjens D, Rومان R, Gaa LV, et al. Sleep-Disordered Breathing and Uric Acid in Overweight and Obese Children and Adolescents. *Chest* 2007;132:76-80.
17. Ruiz GA, Sánchez AA, Luque CE. Blood uric acid levels in patients with sleep-disordered breathing. *Arch Bronconeumol* 2006;42:492-500.
18. Ucar ZZ, Taymaz Z, Erbaycu AE, Kirakli C, Tuktavul F, Guclu SZ. Nocturnal Hypoxia and Arterial Lactate Levels in Sleep-Related Breathing Disorders. *South Med J* 2009;102:693-700.
19. Geren W, Bendich A, Bodansky O, Brown GB. The fate of uric acid in man. *J Biol Chem* 1950;183:21-31.
20. Resta, O, Foschino Barbaro MP, Bonfitto P, Talamo S, MastroSimone V, Stefano A, et al. Hypercapnia in obstructive sleep apnoea syndrome. *Neth J Med* 2000;56:215.
21. Bradley TD, Rutherford R, Lue F, Moldofsky H, Grissman RF, Zamel N, et al. Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. *Am Rev Respir Dis* 1986;134:920-4.
22. Leech JA, Onal E, Baer P, Lopata M. Determinants of hypercapnia in occlusive sleep apnea syndrome. *Chest* 1987;92:807-13.
23. Gozal DG. Determinants of chronic hypercapnia in Japanese men with obstructive sleep apnea syndrome: Is obesity the only one to blame? *Chest* 2002;121:320-21.
24. Akashiba T, Kawahara S, Kosaka N, Ito D, Saito O, Majima T, et al. Determinants of chronic hypercapnia in Japanese men with obstructive sleep apnea syndrome. *Chest* 2002;121:415-21.