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A study of association between risk of airflow limitation and serum uric acid

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ABSTRACT The aims of this study were to examine the relationship between AL and s-UA and to investigate s-UA as a potential auxiliary marker for predicting AL risk in medical health check-ups. A total of 8,662 subjects aged >40 years were included. They were administered a simple questionnaire and assessed using pulmonary function tests, blood pressure (BP) measurements, and blood samplings. One hundred and fifty-six subjects (1.8%) had AL, just 29% of whom had experienced respiratory symptoms. The subjects with AL had significantly higher s-UA levels compared with never-smoking subjects without AL. Forced expiratory volume in 1 second (FEV1) %predicted showed significant correlations with age, smoking index, body mass index (BMI), mean BP, white blood cells, hemoglobin A1c, s-UA, and high-density lipoprotein cholesterol. In multiple logistic regression analysis, s-UA, in addition to age, smoking index, respiratory symptoms, and BMI, was independently associated with AL. In conclusion, elevated s-UA levels, together with respiratory symptoms, high smoking index, and weight loss, may epidemiologically predict the development of AL risk.

KEYWORDS : uric acid, airflow limitation

Introduction:

There is a high prevalence of Asthma and COPD which are major chronic airway diseases (CADs) that lead to airflow limitation (AL).1,2 Based on the International Asthma Guidelines, 300 million people worldwide are estimated to have asthma, and the rates vary among countries with prevalence between 1% and 18%.1 COPD is currently the fourth leading global cause of death and is likely to become the third cause by 2020.3 A meta-analysis of studies published between 1990 and 2004 revealed that the prevalence of COPD was estimated to be 9%–10% around the world.4 The patients with early-stage CADs may be either unaware of their condition or reluctant to consult their physician for respiratory symptoms.7 One of the best ways to detect CADs early on could be to screen for AL either in general practice or at medical health check-ups. However, only subjects suffering from respiratory symptoms are candidates for spirometry. Furthermore, spirometry is not yet sufficiently widespread within primary care settings or medical health check-ups.8,9 It would be useful if there were a simple predictive marker used in combination with spirometry for AL in epidemiological settings.

Serum uric acid is frequently measured when screening for gout and when assessing renal dysfunction. Recently, s-UA has also been suggested to have an association with respiratory disorders such as stable COPD,11 asthma with acute exacerbation, COPD with acute exacerbation,12,13 obstructive sleep apnea,14 pulmonary hypertension,15 and chronic respiratory failure.16,17. The aims of this study were to examine the relationship between AL and s-UA and to investigate s-UA as a potential auxiliary marker for predicting AL risk in a medical health check-up.

Materials and methods:

A total of 8,783 subjects aged >40 years were registered from January 2014 to december 2016 in a tertiary hospital in Maharashtra, of whom 121 subjects were excluded because of incomplete data of pulmonary function and blood testing. After exclusion, 8,662 subjects (5,191 men and 3,471 women) were entered into the data analysis. All subjects answered a simple self-reported questionnaire that included questions on respiratory symptoms (coughing, sputum, and dyspnea), smoking status, and medical histories. In addition, pulmonary function tests, blood pressure (BP) measurements,18 and blood samplings, including peripheral blood count, blood glucose levels, hemoglobin A1c (HbA1c), serum levels of total protein (TP), creatinine (Crea), UA, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C), were conducted as routine screening tests for lifestyle-related disorders. All data were assessed retrospectively. AL was defined as forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) <0.7.19.

Results:

Table 1 shows the characteristics of the subjects divided into two groups according to AL. There were 156 subjects (1.8%) with AL, only 29% (45 of 156) of whom exhibited respiratory symptoms (coughing, sputum, or dyspnea). Table 2 shows the correlations between FEV1 %predicted and parameters measured during medical check-ups. FEV1 %predicted was positively associated with age (r=0.13, P<0.001) and HDL-C (r=0.11, P<0.001) and was negatively correlated with smoking index (r=−0.14, P<0.001). Multiple logistic regression analysis to determine the relevant parameters for predicting AL risk showed that increased s-UA (odds ratio [OR], 1.158; 95% confidence interval [95% CI], 1.003–1.337; P=0.04) (Table 3).

Discussion:

In this study, there were 156 subjects (1.8%) with AL. However, only 29% (45 of 156 subjects) of those experienced respiratory symptoms. In addition, the subjects with AL had significantly higher s-UA levels compared to never-smoking subjects without AL.

In this study, 71% of subjects with AL were asymptomatic at examination, which is slightly higher compared to other epidemiological studies, where 40%–60% of the subjects with AL were free of respiratory symptoms.6,20,21 A possible reason for this could be that the number of subjects with severe AL in this study was relatively small compared to the other studies. In any case, from an early diagnostic point of view, respiratory symptoms do not always predict AL,22 and spirometry is essential for early detection of AL.6,20,21,23.

COPD, one of the major causes of CADs, is characterized by chronic AL, which is associated with chronic airway inflammation. Recently, COPD has also been recognized to be a part of systemic inflammation, leading to considerable comorbidities such as cardiovascular diseases, cerebrovascular diseases, lung cancer, diabetes, hypertension, hyperlipidemia, chronic renal failure, osteoporosis, and muscular weakness.24 In previous studies, several potential and clinically relevant blood biomarkers, such as high sensitive C-reactive protein, fibrinogen, interleukin 6, surfactant protein D, and Clara cell secretory protein-16, have been identified to discriminate COPD from healthy controls.25,26

Interestingly, s-UA levels in subjects with AL in this study were higher than those in the never-smoking subjects without AL and significantly correlated with FEV1 %predicted. Furthermore, increased s-UA was one of the independent parameters associated with AL by multiple logistic regression analysis. Recently, s-UA has

been suggested to have an association with hypertension, metabolic syndrome, and cardiovascular diseases.27 However, the relationship between s-UA and respiratory disorders remains unclear. Several studies have shown that s-UA is increased in hypoxic conditions, including in patients with stable COPD,11 asthma with exacerbation, COPD with acute exacerbation,12,13 obstructive sleep apnea,14 pulmonary hypertension,15 and chronic respiratory failure.16,17 In a large population-based epidemiological study, Aida et al28 reported that s-UA levels were negatively correlated with the presence of AL. All results from the aforementioned studies, including this study, provide evidence that s-UA could be considered as one of the candidate biomarkers for predicting future risk of AL.

Conclusions:

We have shown that s-UA is independently associated with AL. Elevated s-UA, together with respiratory symptoms, high smoking index, and weight loss, may provide better information to predict AL risk in an epidemiological setting. A further longitudinal follow-up study is needed as a next step to estimate the relationship between s-UA and the annual progression of AL.

Tables:

TABLE 1**: Comparison of individual parameters between subjects with and without AL and %FEV1**

	Total (n=8,662)	AL (+) (n=156)	AL (−) (n=8,506)	*P*-value
Gender (male/female)	5,191/3,471	117/39	5,074/3,432	<0.001
Age, years	52.5 (7.6)	58.4 (8.1)	52.4 (7.6)	<0.001
Smoking index	260 (361)	555 (501)	254 (356)	<0.001
Smoking status (C/F/N)	2,493/1,896/4,273	65/49/42	2,428/1,847/4,231	<0.001
Respiratory symptoms (±)	1,179/7,483	45/111	1,134/7,372	<0.001
Height, cm	163.0 (8.8)	163.7 (7.9)	162.9 (8.8)	0.2
Body weight, kg	62.8 (11.2)	60.9 (11.8)	62.8 (11.1)	0.02
BMI, kg/m^2	23.6 (3.1)	22.6 (3.4)	23.6 (3.1)	<0.001
%VC, %	101.6 (14.2)	92.0 (20.8)	101.7 (14.0)	<0.001
FEV_1/FVC, %	84.0 (6.2)	63.9 (6.1)	84.3 (5.5)	<0.001
Mean BP, mmHg	91.9 (11.7)	91.9 (12.0)	91.9 (11.7)	0.9
WBC,/μL	5,635 (1,631)	6,090 (1,922)	5,627 (1,624)	0.003
TP, g/dL	7.2 (0.4)	7.1 (0.4)	7.2 (0.4)	0.01
Crea, mg/dL	0.8 (0.3)	0.8 (0.2)	0.8 (0.3)	0.8
HbA1c, %	5.3 (0.8)	5.4 (0.8)	5.2 (0.8)	0.05
TC, mg/dL	202.7 (33.1)	198.0 (33.2)	202.8 (33.0)	0.06
HDL-C, mg/dL	56.6 (14.0)	55.6 (13.6)	56.6 (14.0)	0.3

Table 2: Correlation analysis between FEV1 %predicted and parameters measured at medical health check-ups.

	r	*P*-value
Age	0.13	<0.001
Smoking index	−0.14	<0.001
BMI	−0.05	<0.001
Mean BP	−0.03	0.002
WBC	−0.12	<0.001
TP	−0.01	0.3
Crea	0.003	0.7
HbA1c	−0.06	<0.001
s-UA	−0.06	<0.001
TC	0.006	0.5
HDL-C	0.11	<0.001

Table 3

: Multiple logistic regression analysis (association with AL)

	OR	95% CI	*P*-value
Gender	0.885	0.506–1.549	0.6
Age	1.093	1.071–1.116	<0.001
Smoking index	1.001	1.001–1.001	<0.001
Smoking status	0.940	0.705–1.255	0.6
Respiratory symptoms	2.017	1.392–2.921	<0.001
BMI	0.855	0.804–0.909	<0.001
WBC	1.088	0.988–1.197	0.08
TP	0.836	0.538–1.299	0.4
Crea	0.323	0.097–1.080	0.06
HbA1c	1.036	0.859–1.251	0.7
s-UA	1.158	1.003–1.337	0.04
TC	0.998	0.993–1.003	0.4

References:

1 Global Initiative for Asthma [Homepage on the Internet] Global Strategy for Asthma Management and Prevention. [Accessed July 25, 2016]. Available from: www.ginasthma.org.
2. The Global Initiative for Chronic Obstructive Lung Disease [Homepage on the Internet] Global Strategy for Diagnosis, Management, and Prevention of COPD – 2016. [Accessed July 25, 2016]. Available from: http://goldcopd.org.
3. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. Lancet. 1997;349(9061):1269–1276.
4. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523–532.
5. Matsumoto K, Seki N, Fukuyama S, et al. Prevalence of asthma with airflow limitation, COPD, and COPD with variable airflow limitation in older subjects in a general Japanese population: the Hisayama Study. Respir Investig. 2015;53(1):22–29.
6. Fukuchi Y, Nishimura M, Ichinose M, et al. COPD in Japan: the Nippon COPD Epidemiology study. Respirology. 2004;9(4):458–465.
7. van den Boom G, van Schayck CP, van Mollen MP, et al. Active detection of chronic obstructive pulmonary disease and asthma in the general population. Results and economic consequences of the DIMCA program. Am J Respir Crit Care Med. 1998;158(6):1730–1738.
8. Arne M, Lisspers K, Stallberg B, et al. How often is diagnosis of COPD confirmed with spirometry? Respir Med. 2010;104(4):550–556.
9. Han MK, Kim MG, Mardon R, et al. Spirometry utilization for COPD: how do we measure up? Chest. 2007;132(2):403–409.
10. Grassi D, Ferri L, Desideri G, et al. Chronic hyperuricemia, uric acid deposit and cardiovascular risk. Curr Pharm Des. 2013;19(13):2432–2438.
11. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. Lung. 2007;185(1):21–24.
12. Li L, Wan C, Wen F. An unexpected role for serum uric acid as a biomarker for severity of asthma exacerbation. Asian Pac J Allergy Immunol. 2014;32(1):93–99.
13. Bartziokas K, Papaioannou AI, Loukides S, et al. Serum uric acid as a predictor of mortality and future exacerbations of COPD. Eur Respir J. 2014;43(1):43–53.
14. Saito H, Nishimura M, Shibuya E, et al. Tissue hypoxia in sleep apnea syndrome assessed by uric acid and adenosine. Chest. 2002;122(5):1686–1694.
15. Voelkel MA, Wynne KM, Badesch DB, Groves BM, Voelkel NF. Hyperuricemia in severe pulmonary hypertension. Chest. 2000;117(1):19–24.
16. Sato N, Kurashima K, Ubukata M, et al. Prognostic significance of serum uric acid in patients with chronic obstructive pulmonary disease receiving home oxygen therapy. Nihon Kokyuki Gakkai Zasshi. 2003;41(2):74–80. Japanese.
17. Kadowaki T, Hamada H, Yokoyama A, et al. Significance of serum uric acid in patients with chronic respiratory failure treated with non-invasive positive pressure ventilation. Intern Med. 2007;46(11):691–697.
18. Zheng L, Sun Z, Li J, et al. Pulse pressure and mean arterial pressure in relation to ischemic stroke among patients with uncontrolled hypertension in rural areas of China. Stroke. 2008;39(7):1932–1937.
19. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338.
20. Chang JH, Lee JH, Kim MK, et al. Determinants of respiratory symptom development in patients with chronic airflow obstruction. Respir Med. 2006;100(12):2170–2176.
21. Bridevaux PO, Probst-Hensch NM, Schindler C, et al. Prevalence of airflow obstruction in smokers and never-smokers in Switzerland. Eur Respir J. 2010;36(6):1259–1269.
22. Renwick DS, Connolly MJ. Do respiratory symptoms predict chronic airflow obstruction and bronchial hyperresponsiveness in older adults? J Gerontol A Biol Sci Med Sci. 1999;54(3):M136–M139.
23. Buffels J, Degryse J, Heyrman J, Decramer M, Study D. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. Chest. 2004;125(4):1394–1399.
24. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(2):155–161.

25. Dickens JA, Miller BE, Edwards LD, et al. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res. 2011;12:146.
26. Vestbo J, Agusti A, Wouters EF, et al. Should we view chronic obstructive pulmonary disease differently after ECLIPSE? A clinical perspective from the study team. Am J Respir Crit Care Med. 2014;189(9):1022–1030.
27. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med. 2008;359(17):1811–1821.
28. Aida Y, Shibata Y, Osaka D, et al. The relationship between serum uric acid and spirometric values in participants in a health check: the Takahata study. Int J Med Sci. 2011;8(6):470–478.