

An unexpected role for serum uric acid as a biomarker for severity of asthma exacerbation

Lin Li, Chun Wan and Fuqiang Wen

Summary

Background: Although the increased uric acid (UA) levels in bronchoalveolar lavage fluid and pulmonary tissue homogenate in asthmatic patients or animal models are well established, changes in serum UA (sUA) levels during asthma exacerbation are uncertain.

Objective: This study aims to investigate the change of sUA levels during asthma exacerbation and the association between sUA and lung function.

Methods: A retrospective study was performed on 217 asthma exacerbation patients at the Department of Respiratory Medicine, West China Hospital of Sichuan University, China from 2008 till 2012. Another 142 healthy people, who participated in a health check at the same center in 2011 and 2012, served as controls.

Results: Asthmatic patients during acute exacerbation had significantly higher sUA levels, compared to the remission period and healthy controls [(301.35±92.12)μmol/L vs. (185.74±56.89) μmol/L vs. (128.06±31.56)μmol/L respectively; $p < 0.001$]. In addition, patients with severe asthma exacerbation had higher sUA levels than those with moderate exacerbation [(341.54±86.27 vs. 265.44±62.78) μmol/L; $p < 0.001$], and patients with moderate exacerbation had higher sUA levels than those with mild exacerbation [(265.44±62.78 vs. 200.10±44.71) μmol/L; $p < 0.001$]. Correlation analysis revealed that sUA was negatively associated with lung function ($r = -0.507, p < 0.001$).

Conclusion: sUA levels increased at onset of asthma exacerbation, subsided during the course of exacerbation, and had a negative association with lung function. sUA may be a valuable biomarker for the severity of asthma exacerbation. (*Asian Pac J Allergy Immunol* 2014;32:93-9)

Key words: Asthma exacerbation, serum uric acid, event severity, lung function, smoking

Introduction

Asthma is a common disorder characterized by widespread, variable, but reversible airflow limitation.¹ The airflow limitation is usually associated with an inappropriate T helper 2(Th2) cell-mediated immune response to innocuous allergens.² The cytokines produced by Th2 cell-type lymphocytes are held largely responsible for orchestrating the many features of asthma and leading to airway inflammation, mucus hypersecretion, and structural changes to the airway wall.²

Uric acid (UA), one of the end products of the purine metabolism pathway, was first identified as the aetiological agent of gout in the eighteenth century and more recently as a 'danger signal' released from dying cells.^{3,4} A recent study by Kool et al noted that increased UA levels occur in the airways of allergen-challenged asthmatic patients and mice.⁵ They also demonstrated that administration of UA crystals together with protein antigen was sufficient to promote Th2 cell immunity and clinical features of asthma by activating dendritic cells through spleen tyrosine kinase and PI3-kinase δ signaling.⁵ These results suggested that UA was an essential initiator and amplifier of Th2 cell immunity in asthma and a reflection of airway inflammation. Furthermore, strategies targeting inhibiting UA synthesis with allopurinol or the UA degrading enzyme-uricase led to a decrease in pro-Th2 cytokines production, lung inflammation, repair, and fibrosis.⁶ These results suggest that reducing endogenously released UA may be a novel

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therapeutic approach to control chronic airway inflammation by extenuating Th2 cell immunity.

However, previous studies focused on the signalling pathway and the mechanism underlying UA-induced Th2 cell immunity and airway inflammation.³⁻⁶ Although the change of UA levels in bronchoalveolar lavage fluid and pulmonary tissue homogenate in asthmatic patients or animal models are well established,⁵⁻⁹ evidence of increased levels of serum UA(sUA) during asthma exacerbation is uncertain. The aim of this study is to investigate the change of sUA levels during asthma exacerbation. Additionally, we explored the association between sUA and lung function.

Methods

Study population

Study subjects were all asthma exacerbation patients who were admitted to the Department of Respiratory Medicine, West China Hospital of Sichuan University, located in the Sichuan province in China from January 2008 to August 2012. Inclusion criteria were mild to severe asthma exacerbations of asthma (GINA criteria).¹ Exclusion criteria were having other lung diseases in addition to asthma, suspected or confirmed malignant comorbidity, advanced multiorgan disorders or infection, acute gastrointestinal bleeding, cardiac arrhythmias, ischemic or valvular heart disease, or renal failure. Patients who had known disease with elevation levels of sUA, such as gout, or took UA-increasing drugs, such as diuretics were also excluded.

The age and sex-matched healthy controls were selected from a cohort of subjects in a health check at the same center in 2011 and 2012. They were healthy outpatients who did not have asthma or other respiratory diseases.

Study design

The primary objective of the study was to investigate the change of sUA levels during asthma exacerbation. So we compared sUA levels in asthmatic patients at two time points (the acute exacerbation and remission period) and compared sUA levels in asthmatic patients in varying degrees of acute exacerbation (mild, moderate and severe) with those in healthy controls. We also explored the effect of cigarette smoking on sUA levels. The secondary objective of the study was to investigate the association between sUA and lung function. The study was approved by the Ethics Committee of the West China Hospital of Sichuan University.

Event definitions and severity grading of exacerbations

The diagnosis of asthma exacerbations and assessment of severity were based on GINA consensus guidelines,¹ including a complex set of typical clinical findings: relevant medical history, progressive increase in shortness of breath, cough, wheezing, chest tightness, pulse rate, respiratory rate, blood oxygen saturation, and peak flow measurement. Remission of asthma exacerbations was defined as: 1) completion of treatment with bronchodilators and glucocorticosteroids or; 2) control of manifestations of disease and discharge.

Since objective measurements still provide the best information about the patient's asthma severity¹⁰ and that measuring the PEF can be a reliable, useful tool for evaluating respiratory flow of asthma,¹¹ the severity of asthma exacerbation was defined by peak flow measurement (PEF% predicted after initial bronchodilator) according to GINA criteria,¹ 1) mild exacerbation (PEF% predicted > 80%); 2) moderate exacerbation (PEF % predicted 60%-80%); and 3) severe asthma exacerbation (PEF% predicted <60% or PEF <100L/min).

Data collection

Two investigators (L.L. and C.W.) reviewed hospital charts to collect data independently. A pre-specified extraction form based on GINA consensus guidelines¹ was used and included the following information: age, sex, smoking index (measured by pack-years), presenting symptoms (i.e. shortness of breath, cough, wheezing, chest tightness), physical examination (i.e. pulse rate, respiratory rate). Pulse oximetry (blood oxygen saturation) and peak flow measurement (percent predicted peak expiratory flow [PEF% predicted] after initial bronchodilator) within the first 24 hours of admission were also obtained. Differences of opinions were resolved by consensus. If there was still disagreement, consensus would be reached with the help of the third person. We recorded the measured sUA values for healthy controls during a health check, and for each asthma patient at two time points: on admission before bronchodilators or glucocorticosteroid administration as exacerbation values and before discharge as remission values.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 software. Continuous values were shown as means \pm standard deviations. Categorical values were expressed as counts and percentages. To

compare continuous values we used analysis of variance and for categorical values we used χ^2 tests. The link between sUA and lung function was investigated with Pearson’s correlation analysis. For all statistical analyses, a two-sided *P* value of < 0.05 was considered significant.

Results

Change of sUA levels during asthma exacerbation

After applying inclusion and exclusion criteria, 273 patients were identified. An additional 56 of them in whom data collection was incomplete were excluded. Therefore, the study included 217 adult male and female asthma exacerbation patients and 142 healthy controls. The characteristics of the asthma patients and controls are shown in Table 1.

Asthma patients during acute exacerbation had significantly higher sUA levels, compared to the remission period and the healthy controls (301.35±92.12 vs. 185.74±56.89 vs. 128.06±31.56 $\mu\text{mol/L}$, respectively; *p* <0.001). Although sUA levels decreased during the asthma remission period, they were still significantly higher than those in healthy controls (185.74±56.89 vs. 128.06±31.56 $\mu\text{mol/L}$; *p* <0.001). (Figure 1A)

Table 1. Characteristics of asthma patients and controls

	No.(%) of subjects			<i>p</i>
	All (n=359)	Patients (n=217)	Controls (n=142)	
Age, mean±SD (years)	49.24±13.30	49.08±13.42	49.48±13.16	0.781
Sex:				
male	185(51.5)	111(51.2)	74(52.1)	0.914
female	174(48.5)	106(48.8)	68(47.9)	
Smoking:				
smokers	170(47.4)	100(46.1)	70(49.3)	0.402
nonsmokers	189(52.6)	117(53.9)	72(50.7)	
Smoking index, mean±SD (pack-years)	28.49±5.54	29.01±5.17	27.73±5.99	0.139
PEF %predicted	70.95±21.18	58.43±18.07	90.08±5.41	<0.001

Smoking index = daily consumption of cigarettes × years of smoking

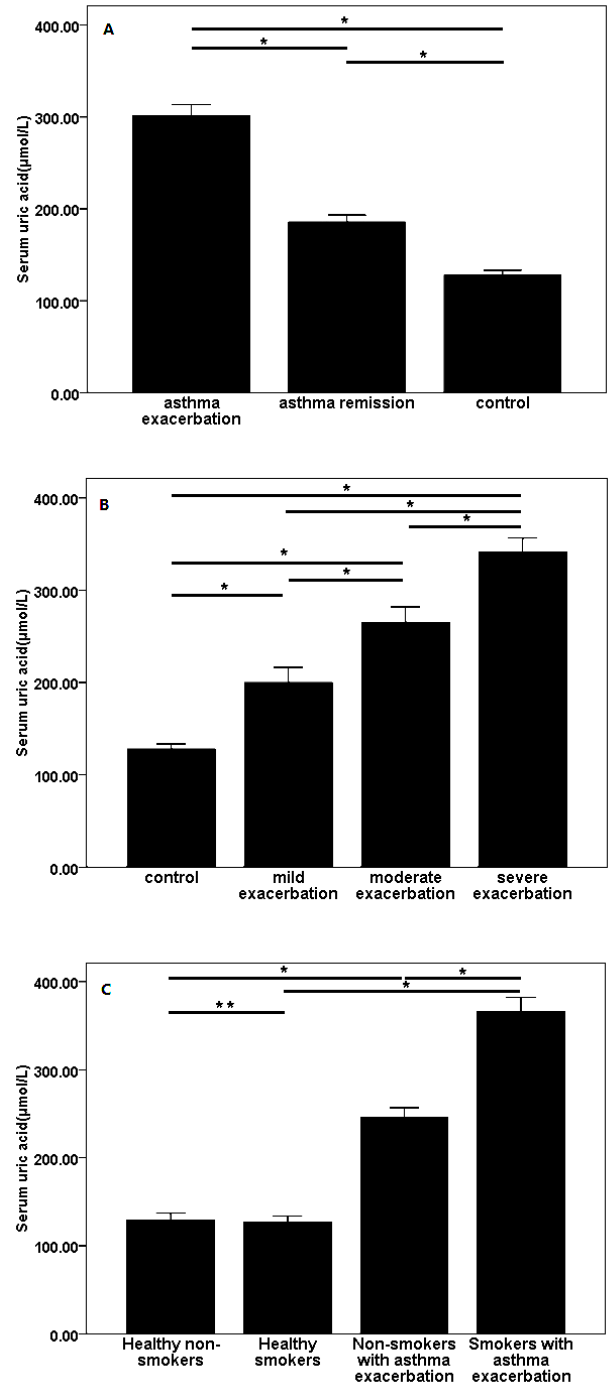


Figure 1. **1A** Serum uric acid levels in patients during asthma exacerbation, compared to remission period, and healthy controls. *, *P* <0.001. **1B** Serum uric acid levels according to the presence and degrees of asthma exacerbation. *, *P* <0.001. **1C** Serum uric acid levels according to smoking status. *, *P* <0.001; **, *P* >0.05.

Table 2. Characteristics of patients with asthma exacerbation in varying degrees and healthy controls

	n	Age, years	Sex male/female	Smoker proportion smoker/non-smoker	Smoking index, pack-years	PEF %predicted,%
Healthy control	142	49.48±13.16	74/68	70/72	27.73±5.99	90.08±5.41
Mild asthma exacerbation	31	47.39±14.05	16/15	15/16	28.16±5.96	87.65±4.69
Moderate asthma exacerbation	57	51.28±13.64	27/30	25/32	30.42±4.72	71.55±6.24 ^{#&}
Severe asthma exacerbation	129	48.51±13.16	68/61	60/69	28.64±5.12	45.60±8.91 ^{#&¶}

[#] $P < 0.05$ compared with healthy control, [&] $P < 0.05$, compared with mild exacerbation, [¶] $P < 0.05$, compared with moderate exacerbation

Pack-years = daily consumption of cigarettes × years of smoking

PEF %predicted, percent predicted peak expiratory flow

Effect of severity of asthma exacerbation on sUA levels

According to the presence and degrees of asthma exacerbation, all subjects were classified into four groups: healthy control, mild exacerbation, moderate exacerbation, and severe exacerbation. The characteristics of patients with asthma exacerbations in varying degrees and healthy controls are summarized in Table 2.

Compared to the healthy controls, patients with asthma exacerbations in varying degrees had significantly higher sUA levels (341.54±86.27 vs. 265.44±62.78 vs. 200.10±44.71 vs. 128.06±31.56 μmol/L respectively; $p < 0.001$). In addition, patients with severe asthma exacerbation had significantly higher sUA levels than those with moderate exacerbation (341.54±86.27 vs. 265.44±62.78 μmol/L; $p < 0.001$), and patients with moderate exacerbation had significantly higher sUA levels than those with mild exacerbation (265.44±62.78 vs. 200.10±44.71 μmol/L; $p < 0.001$). (Figure 1B)

Effect of cigarette smoking on sUA levels

According to whether or not they smoked, all subjects were classified into four groups: healthy non-smokers, healthy smokers, non-smokers with asthma exacerbation, and smokers with asthma exacerbation. Characteristics of all subjects according to smoking status are summarized in Table 3.

The results showed that sUA levels were significantly higher in smokers with asthma exacerbations, as compared to non-smokers with asthma exacerbations (366.14±80.69 vs. 245.97±59.43 μmol/L; $p < 0.001$). However, sUA levels were similar in healthy smokers and healthy non-smokers (126.81±29.74 vs. 129.26±33.39 μmol/L; $p < 0.05$). (Figure 1C)

Correlation between sUA and lung function

Pearson correlation analysis was performed to assess whether sUA levels was associated with lung function and showed that levels of sUA in asthma

Table 3. Characteristics of all subjects according to smoking status

	n	Age, years	Sex male/female	Smoking index, pack-years	PEF %predicted,%
Healthy non-smokers	72	50.49±13.16	4/68	0	90.27±5.53
Healthy smokers	70	48.44±13.17	70/0	27.74±5.99	89.89±5.31 [#]
Non-smokers with asthma exacerbation	117	49.42±13.79	11/106	0	57.51±17.71 ^{&}
Smokers with asthma exacerbation	100	48.68±13.04	100/0	29.01±5.17	59.50±18.50 ^{¶ &}

[#] $P > 0.05$ compared with healthy non-smokers, [¶] $P > 0.05$, compared with non-smokers with asthma exacerbation, [&] $P < 0.05$, compared with healthy non-smokers as well as smokers

Pack-years = daily consumption of cigarettes × years of smoking

PEF %predicted, percent predicted peak expiratory flow



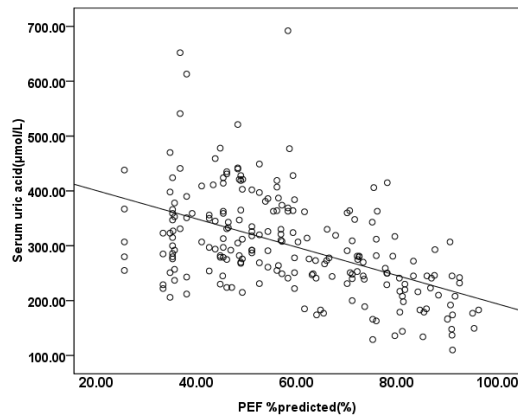


Figure 2. Correlation analysis between serum uric acid levels and lung function ($r = -0.507$, $p < 0.001$).

exacerbation patients were negatively correlated with lung function ($r = -0.507$, $p < 0.001$). (Figure 2)

Discussion

Our study is the first to report the change in circulating UA levels in asthma exacerbation patients, because previous studies have only noted changes in UA levels in BAL fluid following allergen challenge.⁵⁻⁹ This study demonstrates that sUA levels are significantly higher in patients experiencing asthma exacerbation compared with healthy controls and decrease as asthma improves. Correlation analysis in the current study also revealed a significant association of sUA levels and impaired lung function. Therefore, we concluded that sUA may be a valuable noninvasive biomarker for severity of asthma exacerbation.

Current approaches use a combination of functional criteria, clinical symptoms, and measurements, as objective surrogates of severity have proven difficult to identify. Our interesting findings of the association of raised serum uric acid with asthma exacerbations and their severity may have utility in the clinical identification, classification, and management of asthma exacerbation, and may become the asthma 'biomarker' that researchers have long hoped for. We propose that the biology of sUA may also offer new insights into pathogenic mechanisms in asthma and asthma exacerbation. Besides, the easy availability of peripheral blood samples make it attractive for daily clinical practice.

Potential mechanism to explain our findings could be that tissue hypoxia during asthma exacerbation induces the production of UA,^{12,13} or

oxidative stress and inflammation induces lung tissue damage, resulting in the elevation of UA levels,^{12,13} or elevated levels of UA may enhance lung inflammation, which eventually impairs pulmonary function.^{12,13}

Firstly, previous studies have demonstrated that UA levels increase in hypoxic states, such as chronic heart failure, primary pulmonary hypertension, chronic pulmonary obstructive disease, as compared with either normoxia or hyperoxia.^{14,15} Similarly, hypoxia will occur during bronchospasm in asthma exacerbation. The mechanisms may be that hypoxanthine cannot be converted to xanthine and accumulates in the tissues as ATP metabolism is blocked by tissue hypoxia. At the same time, the calcium pump can't operate normally due to ATP deficiency, leading to increased levels of Ca^{2+} in the cytoplasm. Overloading with Ca^{2+} not only catalyses xanthine dehydrogenase under normal physiological condition into active xanthine oxidase irreversibly, which converts hypoxanthine into xanthine and then xanthine into UA, but also leads to pulmonary vascular and airway smooth muscle spasm, aggravating the hypoxia and creating a vicious cycle.¹⁶ Therefore, it has been suggested that pulmonary hypoxia promotes purine catabolism, leading to increased production of UA.

Secondly, oxidative stress and inflammation caused by cigarette smoking induces lung tissue damage, resulting in the elevation of UA levels. Oxidative stress is increased in the alveolar spaces of the lungs of smokers, as cigarette smoke is known to be an important source of reactive oxygen species. Vascular mRNA expression of the proinflammatory cytokines IL-1 β , IL-6, and TNF- α is significantly increased by cigarette smoking via NF- κ B activation,¹⁷ and a positive association was demonstrated between UA and inflammatory markers, such as CRP and IL-6.¹⁸ All of these changes cause chronic lung tissue damage and circulating UA levels may be elevated according to the severity of the damage.

It should be noted that in the current study sUA levels were significantly higher in the smokers with asthma exacerbation as compared to the non-smokers with asthma exacerbations, but similar between healthy smokers and healthy non-smokers. The results suggest that exposure to tobacco smoke does have an effect on sUA levels, but cigarette smoking has an amplification effect in sUA levels in the presence of asthma. In other words, airways in

asthmatic patients are more likely to be influenced by cigarette smoke-stimulated inflammatory reactions than those in controls. However, little is known about the molecular mechanisms whereby they influence the levels of sUA.

Thirdly, previous studies have described that when a 'danger signal', such as UA, is released from dying cells, human eosinophils migrate toward soluble UA in a gradient-dependent manner and rapidly released cytokines in response to the 'danger signal' via autocrine ATP into the extracellular milieu. In turn, elevated levels of cytokines and chemokines, including IL-6, IL-8, IL-1 β , IL-10, IL-17, IFN- γ , TNF- α , G-CSF, GM-CSF, fibroblast growth factor, vascular endothelial growth factor recruit more eosinophils.⁴ This response to endogenous UA may explain the self-perpetuating nature of chronic inflammation in asthma. Inflammation may result in airflow obstruction, airway hyper-responsiveness and structural changes in the airways, and these changes get worse as airway inflammation develops. Ultimately, lung function declines due to severe inflammation and structural changes in the airways. Therefore, the important role of hyperuricemia-induced impaired pulmonary function is revealed.

This is an interesting study revealing the change of circulating UA levels in asthma exacerbation patients and its association with event severity. One limitation is its retrospective design and this should be acknowledged when explaining our results. Anyway, this is the first exploratory study to date to have assessed the relationship between circulating UA and asthma exacerbation severity. In addition, our institution has started a prospective study to validate our preliminary findings. Further studies are required to clarify whether comorbid allergic rhinitis or systemic steroids prescribed to patients with asthma exacerbation may affect serum uric acid level, as well as the mechanisms underlying this association between sUA and event severity.

In conclusion, our results demonstrated that sUA levels increase at onset of asthma exacerbations, subside during the course of the exacerbation, and have a negative association with lung function. In view of these data and our results, we consider that sUA may be a useful biomarker for severity of asthma exacerbations.

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Conflict of interests

The authors declare no conflicts of interest in this work.

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