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**Significance of serum uric acid in pulmonary arterial hypertension  
due to systemic sclerosis: a pilot study**

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## **Abstract**

Systemic sclerosis (SSc) is a connective tissue disease, which may lead to elevated pulmonary arterial pressure due to pulmonary arterial hypertension and/or left ventricular diastolic dysfunction. Uric acid (UA) has been shown to be elevated in patients with pulmonary hypertension (PH) and heart failure. We aimed to investigate the potent relationship between serum UA and pulmonary pressure as well as functional capacity in patients with SSc. We studied 66 patients (mean age  $57.7 \pm 12.1$  years, 63 women), presenting with SSc. Systolic pulmonary artery pressure assessed by echocardiography, lung function tests, six-minute walk test (6MWT) and serum UA levels were recorded in all patients. In 24 (36%) patients the diagnosis of PH was established by echocardiography (systolic pulmonary artery pressure  $\geq 40$  mmHg). PH patients had higher UA serum levels compared to patients without PH ( $5.1 \pm 2.1$  mg/dl vs  $4.2 \pm 0.9$  mg/dl,  $p = 0.04$ ). Amongst PH patients, UA values were inversely correlated with the SMWT distance ( $r = -0.51$ ,  $p = 0.01$ ). Serum UA values increased in proportion to the functional capacity PH in patients with scleroderma. Further investigations in prospective studies will unfold in detail the pathophysiological significance of UA in SSc patients with PH, and determine its role as a prognostic marker in the assessment and monitoring of the disease.

**Key words:** uric acid, systemic sclerosis, pulmonary arterial hypertension, six minute walking test

## Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by excessive collagen deposition in the skin and the internal organs and vascular involvement with generalized disturbance of the microcirculation [1-3]. Systemic sclerosis related pulmonary arterial hypertension (SScPAH) is a serious and devastating complication of the disease affecting 8-15% of SSc patients [4,5]. Pulmonary hypertension (PH) in these patients may also be caused by left ventricular diastolic dysfunction due to myocardial involvement [6]. The presence of elevated pressure in the pulmonary circulation conveys bad prognosis in this population irrespective of the etiology of PH [7].

Uric acid (UA) is the final oxidation product of purine metabolism. Serum UA levels have been shown to be elevated in conditions of impaired oxidative metabolism such as chronic heart failure [8], and obstructive pulmonary disease [9]. Elevated UA values have been described in various rheumatic diseases [10] including lupus nephritis [11] and gout [12]. Several studies have demonstrated that increased UA serum concentrations in patients with PH of various etiologies correlate with the severity and the prognosis of the disease [13-15].

There is very little information available on the clinical significance of UA in SSc patients with PH. Therefore, we hypothesised that 1) uric acid levels are elevated in patients with SSc and PH and 2) elevated pulmonary pressure are associated to functional capacity in this population.

## **Patients and Methods**

### **Study population**

This study enrolled 66 patients with SSc as defined by the revised ACR [16] criteria who visited our center for follow-up care between February 2007 and February 2008. Patients were selected after exclusion of hypertrophic, dilated or restrictive cardiomyopathy, left ventricular ejection fraction (LVEF) < 55%, any left and right sided valvular disease more than moderate degree severity, symptomatic lower limb vascular disease, severe interstitial lung fibrosis defined as functional volume capacity (FVC) < 60% of predicted, medical history of hypertension and renal failure determined by serum creatinine levels > 1.2 mg/dl. Smoker patients were also excluded, since smoking has been shown to affect pulmonary function in SSc patients [17]. None of the patients received treatment with diuretics which may affect UA serum levels. All patients were evaluated for cardiac and pulmonary involvement. Exercise capacity was assessed by six minute walking test (6MWT). The study received ethical approval from the scientific committee of the Aristotle University of Thessaloniki and patients provided written informed consent.

### **Pulmonary function testing**

Pulmonary involvement was assessed by high sensitivity computed tomography. Lung function tests measured FVC, forced expiratory volume in 1 second (FEV<sub>1</sub>), and diffusing capacity for carbon monoxide (DLCO).

### **Echocardiography**

Complete two-dimensional and Doppler echocardiographic examinations were performed in all patients at the same day of the UA evaluation. We used a

commercially available system (Vivid 7, Vingmed, GE, Norway). From the apical 4-chamber view, RV inflow view, and parasternal short axis or subcostal view, continuous-wave Doppler echocardiography was used to assess the peak tricuspid regurgitant velocity [18]. Systolic pulmonary artery pressure was estimated by calculating the maximal velocity of the tricuspid regurgitant jet and then, further using the Bernoulli equation, adding to this value an estimated right atrial pressure based on both the size of the inferior vena cava and the change in diameter of this vessel during respiration [19]. PH was considered present when the systolic pulmonary artery pressure value  $\geq 40$  mmHg [20].

### **Exercise capacity**

The 6MWT was performed using a standardized protocol in accordance to guidelines in the American Thoracic Society statement 2002 [21]. Patients walked unassisted an enclosed-level corridor; length to first turn around was 30 metres. All patients were told to use their own pace, but to cover as much ground as possible in 6 min.

### **Blood sampling for UA measurement**

For the measurement of the serum UA, creatinine, triglyceride, total cholesterol, ESR and CRP levels, venous blood sample was drawn after an overnight fast, at the study entry. Serum UA levels were determined in close temporal automated chemistry analysers. This test is a colometric assay based on the oxidation of UA by the specific enzyme uricase.

## Statistical analysis

Variables are presented as mean  $\pm$  S.D, except from the duration of the disease, which is expressed as median [25th–75th percentile]. UA and 6MWT values were normally distributed (Kolmogorov-Smirnov and P-P plot). Categorical data are presented as absolute value, and comparisons were tested by Fisher's exact test. Clinical and biological characteristics between the two groups of SSc patients were compared using the Student's t-test. The relationship between UA and patient's functional state as measured by the 6MWT and other laboratory or functional pulmonary indices was assessed by the Pearson's correlation coefficient. A value of  $P < 0.05$  was considered significant. Statistical analysis was performed using SPSS 13 for Windows (SPSS Inc., Chicago, USA).

## Results

In 24 (36%) patients the diagnosis of PH was established (22 females, mean age  $60 \pm 10$  years; 19 with limited cutaneous and 6 with diffuse cutaneous SSc). The clinical and biologic characteristics of SSc patients with and without elevated pulmonary pressure are summarized in Table 1.

SSc patients with PH had higher UA values ( $5.1 \pm 2.1$  mg/dl) compared to patients with normal pulmonary pressure ( $4.2 \pm 0.9$  mg/dl,  $p = 0.04$ ) (Figure 1). Amongst PH patients, UA values were inversely correlated with the 6MWT distance ( $r = -0.51$ ,  $p = 0.01$ ) (Figure 2). No significant correlations were found between UA and serum creatinine, FVC, FEV<sub>1</sub> and DLCO values in the same population. Moreover, UA was not related with sex, subtype of the disease, autoantibodies and the clinical features of the disease. In the subgroup of patients without PH, no correlation between UA levels and exercise capacity as assessed by the 6MWT was detected.

## **Discussion**

The mechanisms responsible for the elevated serum UA concentrations in SSc patients with PH may be multifactorial. Increased UA levels have been suggested to reflect raised xanthine oxidase activity – an important source of oxygen free radicals - in patients with heart failure [22]. The latter provides a pathophysiological link of UA with a variety of detrimental processes, including increased cytokine production, inflammation and endothelial dysfunction, which are considered to be among the primary events during the progression of the scleroderma induced vasculopathy and fibrosis. Superoxide dismutase represents the major antioxidant defense system against oxygen free radicals. Elevated levels of UA are correlated with decreased superoxide dismutase activity in patients with chronic heart failure [23]. A recent study showed diminished superoxide dismutase activity in SSc patients [24], which also supports the hypothesis that oxidative stress has an important role in the progression of vascular disease, leading to an increase in UA levels in SSc patients with PH.

In the current study we demonstrated inverse correlation between UA levels and functional status in patients with PH. The 6MWT is commonly used for the objective assessment of functional capacity and is used in the evaluation, management, and follow-up of patients with PH [21]. As SSc patients usually present with cutaneous leg ulcers or pulmonary interstitial involvement that may invalidate the 6MWT, we excluded patients with the aforementioned clinical entities. UA concentration has emerged as a significant predictor of cardiopulmonary exercise parameters and measures of diminished functional capacity in patients with chronic heart failure [25,26].

Measurement of serum UA levels is simple, inexpensive and routinely available. Although other biochemical markers including brain natriuretic peptide [27-30], asymmetric dimethylarginine [31] and vascular endothelial growth factor [32] have been proposed as biochemical markers for the detection of PH in SSc, UA may also serve as an additional indicator for the assessment of exercise capacity in this population.

The findings have to be considered against the background of the limits of the study. This is a pilot single centre cross-sectional study and it is limited by the lack of a controlled healthy population. The small number of patients may have contributed to the borderline difference of UA and SMWT values noticed between the two groups of patients (with and without PH). Another important point is the fact that the patients did not undergo right heart catheterization and the lack of correlation between UA levels and hemodynamic indices. Additionally, UA levels are dependent on age and sex, and are affected by the renal impairment and diuretic therapy; hence their interpretation may be difficult in some patients. We took particular care to exclude patients under diuretics, but additional investigations in larger cohorts of patients are warranted to confirm the findings of the present study.

In conclusion, we established that serum UA values increase in proportion to the clinical severity of PH in patients with SSc. Further investigations in prospective studies will unfold in detail the pathophysiological significance of UA in PH in this group, and determine its role as a biochemical marker in the assessment and monitoring of the disease.

The authors have to declare no conflicts of interest.

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## TABLES

Table 1 : Clinical and biochemical data of SSc patients

	All SSc patients (n = 66)	SSc patients without PH (n = 42)	SSc patients with PH (n = 24)	p
Age (years)	57.7 ± 12.1	55.3 ± 13.1	60 ± 10	NS
Females/Males	61/3	41/1	22/2	NS
Duration of the disease (years)	10[0.2-31]	9.7[0.2-31]	11[2-25]	NS
Limited/Diffuse SSc	47/19	28/14	19/5	NS
Raynaud's	47 (71.2%)	30 (71.4%)	17 (70%)	NS
FVC (% predicted)	86.8 ± 22.6	88 ± 25.4	83 ± 18	NS
FEV <sub>1</sub> (% predicted)	89.4 ± 23.9	89.8 ± 26.8	88 ± 20	NS
DLCO (% predicted)	65.1 ± 22.1	65 ± 22	62 ± 21	NS
EF (%)	65.5 ± 4.2	65.5 ± 4.4	65.5 ± 4.8	NS
Creatinine (mg/dl)	0.73 ± 0.1	0.8 ± 0.1	0.73 ± 0.1	NS
ESR	32.3 ± 2	30.5±21	34.5 ± 20	NS
CRP (mg/ml)	0.46 ± 0.1	0.5 ± 0.3	0.4 ± 0.2	NS
ANA	58 (87.3%)	37 (88.1%)	19 (79.1%)	NS
SCL-70	21 (31.8%)	13 (30.9%)	9 (37.5%)	NS
ACA	18 (27.2%)	10 (23.8%)	8 (33.3%)	NS
Uric Acid (mg/dl)	4.68 ± 1.84	4.27 ± 0.98	5.14 ± 2.18	0.04
6MWT (metres)	405.4 ±106.4	423 ± 98	383 ± 113	0.04

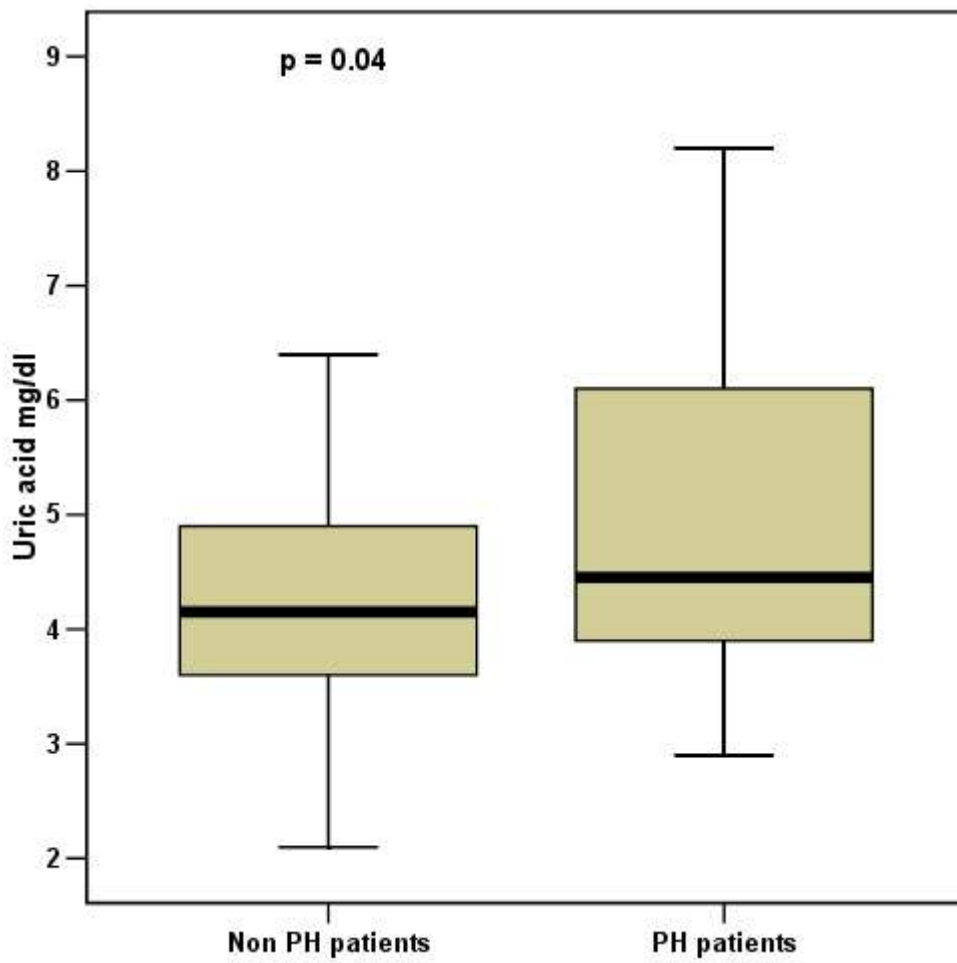
Categorical data are presented as absolute value (percentages).

FVC: forced vital capacity, FEV<sub>1</sub>: forced expiratory volume in 1 second, DLCO: diffusing capacity for carbon monoxide, EF: ejection fraction of left ventricular, sPAP: systolic pulmonary artery pressure, Cre:

serum creatinine, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: antinuclear antibodies, Scl-70 : anti-topoisomerase I antibodies, ACA: anticentromere antibodies, 6MWT: six-minute walk test

**Figure 1:**

Boxplot showing serum values of UA, with boxes indicating the mean and the 25th–75th percentile in PH patients compared with SSc patients without PH.



**Figure 2:**

Correlation between UA serum values and 6MWT in PH patients

