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Original Research Article

Study Of Serum Uric Acid Level In patients With Systemic Lupus Erythematosus

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Abstract

Background: Pulmonary Hypertension (PH) is a serious and often fatal complication of systemic lupus erythematosus (SLE). Because the diagnosis of PH often is made years after symptom onset, early diagnostic strategies are essential. Serum uric acid (U A) currently is considered a marker for screening of PH in patients with SLE .

Aim : To study the association between PH and serum uric acid in SLE patients and the possibility of using serum uric acid as a surrogate marker for screening of PH in patients with SLE.

Patients and Methods : A Case control study was conducted on 80 subjects 60 of them were SLE patients.The included subjects were divided into 4 groups as follows : Group I: 30 SLE patients with PH , Group II : 30 SLE without PH , Group III : 10 subjects as a positive controls (with PH) and Group IV : 10 subjects as a negative controls (without PH) . All patients and controls were subjected to the following : Full history taking, complete physical examination, Serum uric acid , CBC , ESR , C-reactive protein , serum creatinine , blood urea , anti-nuclear (ANA)   and anti-double-stranded DNA antibodies , anti-scleroderma 70 (SCL-70) and anti ribonucleoprotein (RNP) antibodies , lupus anticoagulant , anti cardiolipin , b2- glycoprotein I antibodies   and Doppler echocardiography .

Results : serum UA levels were significantly higher in SLE patients with PH (p-value<0.001) than in SLE patients without PH (p-value=0.403) and than control positive group (p-value=0.771) and than control negative group (p-value= 0.343) . Also there is a Positive correlation and significance between systolic pulmonary arterial pressure (sPAP) with uric acid in SLE patients with PH.

Keywords: Serum uric acid level may be useful as a surrogate marker for screening of PH in patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin characterized by inflammation of multiple organs (kidneys, brain, heart, liver, lungs, joints, muscles, skin, etc.) (**1**).

Pulmonary involvement is relatively frequent in adult patients rather than children. Pulmonary hypertension is the most severe forms of lupus associated pulmonary involvement, although they occur infrequently in children with SLE (**2**).

Right heart catheterization is the only method that definitively establishes a hemodynamic diagnosis of PH because it directly measures pulmonary artery (PA) pressure. However, serious complications related to catheterization are found in 1% of all procedures performed in experienced centers, with occasional fatal events (*3*).

Moreover, right heart catheterization is an expensive procedure that it is not easily accessible in most health care centers. In contrast, echocardiography is a non-invasive, reproducible, inexpensive and widely available imaging technique useful for estimating PA systolic pressure and other haemodynamic parameters (*4*).

The reasons for the underestimation of PH are that the awareness of physicians of the early asymptomatic phase is low and that symptoms associated with PH, such as dyspnea, non-productive cough, impaired exercise tolerance and fatigue, are frequently considered to be attributable to the underlying connective tissue disease and its comorbidities (*5*).

Accumulating evidences demonstrated that currently available therapeutic agents when administered timely in the early phase of PH significantly improved pulmonary vascular resistance, functional capacity and survival. Thus, early disease detection in the preclinical asymptomatic or mildly symptomatic phase is a critical step in the therapeutic strategy to improve the outcome (*6*).

Previous reports documented that several factors were associated with the presence of PH in SLE but yielded conflicting results. Positive rates of anti-cardiolipin antibody were significantly higher in SLE patients with PH than those without in retrospective studies (**7**). In a recent prospective study, lupus anticoagulant was the only significant risk factor for PH in SLE (**5**). However, these associations were not confirmed by other reports (**8**). Raynaud's phenomenon was suggested to be associated with the presence of PH in SLE patients in some studies but not in the others (**7**).

These inconsistent results give us a lesson that these factors are not the determining factors and they are insufficient to predict the development of PH in SLE patients. Both the plasma brain natriuretic peptide (BNP) and the N-terminal pro-BNP (NT-proBNP), have been shown to detect PH with reasonable sensitivity and specificity in high-risk populations (**9**). However, elevation in BNPs is a relatively late event related to right ventricle dysfunction and lacks sensitivity to be used as a standalone test to detect early PH (**10**).

Therefore, a further in-depth study to establish the clinical or serologic factors for predicting PH in SLE patients is required.

Serum uric acid (UA), the final product of purine degradation, has been shown to be increased in hypoxic states such as chronic heart failure, cyanotic congenital heart disease, and obstructive pulmonary disease. Because tissue ischemia and hypoxia deplete adenosine triphosphate (ATP) and promote degradation of adenine nucleotides to inosine, hypoxanthine, xanthine, and UA, increased serum UA levels may reflect impaired oxidative metabolism in such diseases (**11**).

Pulmonary hypertension is characterized by progressive increase in pulmonary artery pressure, ultimately producing severe right ventricular (RV) failure associated with markedly reduced cardiac output and mild hypoxia. These findings raise the possibility that serum UA levels may also increase in patients with pulmonary hypertension (**12**).

Materials and Methods

Patients

This case control study was conducted at Internal medicine department and outpatient clinic, Al hussein Hospital, Al Azhar University, Cairo, Egypt during the period from October 2016 to June 2017. 60 patients with SLE gave informed consent to participate in this study. All these patients fulfilled at least four of the 1982 revised criteria of the American College of Rheumatology for SLE (13). As disease controls, 3 patients with interstitial lung disease (ILD), 4 patients with chronic obstructive pulmonary disease (COPD) and 3 patients with idiopathic pulmonary arterial hypertension(IPAH) who were diagnosed as having PH were compared as control positive, also 10 complete healthy subjects were compared as control negative.

Clinical and laboratory profiles

The clinical and laboratory data of SLE patients were obtained at the time of transthoracic Doppler echocardiography. A clinical evaluation, including the review of their medical records, physical examination, blood tests and assessment of SLE disease activity was undertaken.

Laboratory parameters included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, blood urea, serum uric acid and antibodies against double-stranded DNA (dsDNA), ANA, ribonucleoprotein (RNP), Lupus Anticoagulant, Scleroderma 70, cardiolipin and b2-glycoprotein I were measured.

Doppler echocardiography

Transthoracic echocardiography (TTE) was performed in all patients as a screening test for PH, by experienced cardiologists. Two-dimensional, M-mode and color Doppler echocardiography were used to evaluate the cardiac morphology, flow abnormalities and cardiac functional status. Continuous wave Doppler sampling of the peak regurgitant jet velocity was used to estimate the right ventricular

to the right atrial systolic pressure gradient using the modified Bernoulli equation (49 [tricuspid regurgitant jet velocity]2). sPAP was calculated by adding the Bernoulli-derived pressure gradient to the estimated mean right atrial pressure. The current hemodynamic definition of PH is a mean pulmonary artery pressure > 25 mmHg; a pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure of 15 mmHg. In this study, PH was defined as sPAP above 40 mmHg at rest, estimated by TTE, as described previously **(14).**

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Correlation analysis between the two variables was performed using Pearson's correlation coefficient. The independence of the association with PH was assessed using a multivariate logistic regression procedure in which all variables that had a significant bivariate relation with the outcome in the previous reports were evaluated. Chi-square (X^2) test of significance was used in order to compare proportions between two qualitative parameters. P-value ≤ 0.05 was considered significant, P-value ≤ 0.001 was considered as highly significant and P-value >0.05 was considered non significant.

Results

Clinical and laboratory characteristics of SLE patients with PH

There were no statistically significant differences in age, disease duration, previous history of cardiovascular disease (coronary artery disease, stroke), and risk factors for cardiovascular disease (diabetes, hypertension), between the two groups. Frequency of Raynaud's phenomenon, ILD, and lupus nephritis did not differ between patients with and without PH (as shown in table 1). Also, the positivity of lupus anticoagulant, anti-cardiolipin, and anti-b2 glycoprotein I antibody did not differ between the two groups .

Interestingly serum UA levels were significantly higher in SLE patients with PH (p-value<0.001) than in SLE patients without PH (p-value=0.403) and control positive group (p-value=0.771) and control negative group (p-value= 0.343) as shown in tables (2 and 4) . None of the patients with PH had a history of gout or were being treated with diuretics.

Table (1) Comparison of demographic and clinical features in SLE patients with pulmonary arterial hypertension versus those without.

	SLE patients with PH	SLE patients without PH	P value
Age (yr) Range Mean ± SD	12-30 23.50 ± 5.95	11-45 25.93 ± 8.14	0.4
Age of onset of disease Range Mean ± SD	11.7–29 21.53 ± 5.97	10-37.5 21.54 ± 6.76	0.9
Duration of disease Range Mean ± SD	0.3-6 1.98 ± 1.86	0.1-16 4.39 ± 3.42	0.05
Fever	25%	37.9%	0.7
Malar Rash	87.5%	81.8%	1
Photosensitivity	75%	77.3%	1
Alopecia	75%	63.6%	0.7
Oral Ulcers	62.5%	72.7%	0.7
Raynaud's phenomenon	62.5%	27.3%	0.1
Arthralgia	87.5%	95.5%	0.4
Arthritis	62.5%	77.3%	0.4
Myalgia	62.5%	69.7%	0.7
Pleurisy	0	16.7%	0.6
Renal Affection Proteinuria casts	25% 12.5%	51.5% 36.4%	0.1 0.1
Eye Affection	0	1	1
SLEDAI Range Mean ±SD	6-24 12.5± 5.55	0-39 17.18± 8.93	0.2

Abbreviations: PH, pulmonary hypertension; SLEDAI, SLE disease activity index.

Table (2): Comparison between groups according to serum uric acid

	Group I: SLE patients with PH	Group II: SLE patients without PH	Group III: Control group with PH	Group IV: Control group without PH	ANOVA	p-value
Mean±SD	8.55±0.86	4.87±0.52	5.05±0.41	4.88±0.54		
Range	6.9-10.2	3.9-5.8	4.5-5.8	4-5.8		
P1		<0.001	<0.001	<0.001	190.165	<0.001
P2			0.450	0.956		
P3				0.567		

P1: Comparison between group I vs. Group II, III and IV
P2: Comparison between group II vs. Group III and IV
P3: Comparison between group III vs. Group IV

Serum UA levels in patients with pulmonary hypertension according to underlying causes

Despite a similar hemodynamic profile, the pathobiology and clinical course of PH differs considerably according to the underlying or associated diseases **(15).**

To determine whether association of serum UA levels with PH observed in SLE patients is also applied to different forms of PH, we compared serum UA levels in patients with different underlying diseases at the time of diagnosis of PH. 3 patients with ILD, 4 patients with COPD and 3 IPAH who were diagnosed with PH were compared. All of them were symptomatic in cardiopulmonary systems. Serum UA levels in patients with underlying ILD or COPD or IPAH were as low as those of SLE patients without PH . Taken together, SLE patients with PH had significantly higher serum UA levels than those in the ILD and COPD patients with PH .

Clinical usefulness of serum UA measurement for screening of PH in SLE patients

In the present study serum UA levels were significantly higher in SLE patients with PH (p-value<0.001) than in SLE patients without PH (p-value=0.403) and than control positive group (p-value=0.771) and than control negative group (p-value= 0.343) as shown in tables (2 and 4)

Table (3) : Comparison between groups according to sPAP.

sPAP	Group I: SLE patients with PH	Group II: SLE patients without PH	Group III: Control group with PH	Group IV: Control group without PH	ANOVA	p-value
Mean±SD	63.77±10.76	15.10±3.23	45.90±6.06	19.30±1.95		
Range	36-80	10-21	38-56	16-22		
P1		<0.001	<0.001	<0.001	250.276	<0.001
P2			<0.001	0.118		
P3				<0.001		

P1: Comparison between group I vs. Group II, III and IV
P2: Comparison between group II vs. Group III and IV
P3: Comparison between group III vs. Group IV

This table shows highly statistically significant difference between groups according to sPAP.

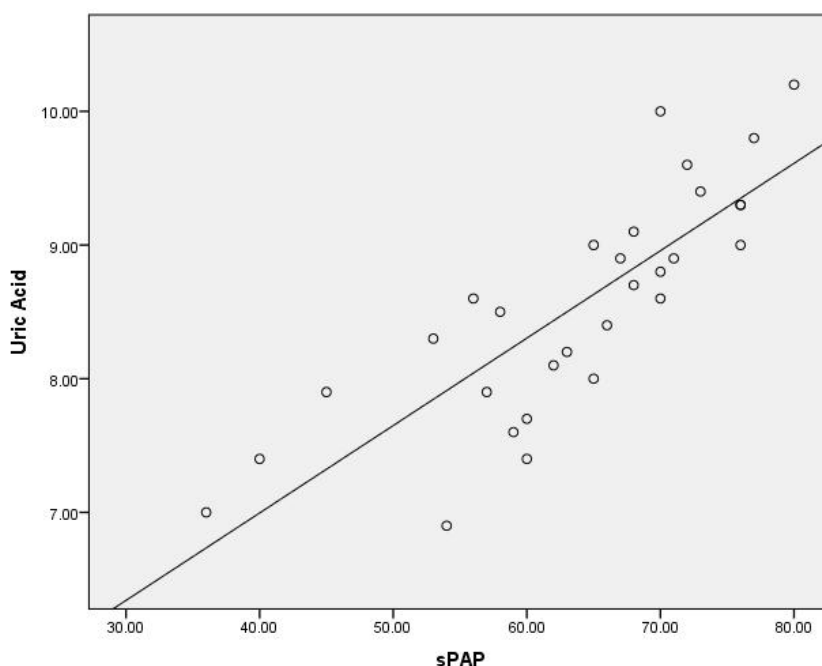**Table 4:** Correlation between sPAP with uric acid, using Pearson Correlation Coefficient in each group.

Uric Acid	sPAP	
	R	p-value
Group I: SLE patients with PH	0.820	<0.001
Group II: SLE patients without PH	0.159	0.403
Group III: Control group with PH	-0.106	0.771
Group IV: Control group without PH	0.336	0.343

r- Pearson Correlation Coefficient

Positive correlation and significance between sPAP with uric acid in SLE patients with PH.

Optimal cutoff values of UA to differentiate patients with PH from those without PH were 6.5 mg/dL as deduced from receiver operating characteristics (ROC) curves (figure 1)

Figure (1): scatter plot between sPAP with uric acid in SLE with PH

Also there is Positive correlation and significance between sPAP with uric acid in SLE patients with PH as shown in table 4.

Discussion

SLE is an autoimmune disorder characterized by multisystem inflammation with the generation of autoantibodies. **(16)**.

Pulmonary Hypertension (PH) is one of the unusual cardiopulmonary manifestations in systemic lupus erythematosus (SLE), but a serious complication that carries a high mortality *(17)*.

Given that significant number of patients with systemic sclerosis (SSc) or mixed connective tissue disease in a community rheumatology practice have undiagnosed PH and the majority of them exhibit no or nonspecific symptoms, it is supposed that more SLE patients with unidentified or missed PH would also exist in rheumatology clinics **(18).**

In a previous study, the prevalence of PH, as defined by a sPAP of 40 mmHg, was 7.9% **(19)**. It is intriguing that the patients had little discernable symptoms in spite of high sPAP measured up to 90 mmHg.

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This result is consistent with the previous reports that the majority of PH cases in SLE were mild and asymptomatic (5).This was probably because most of the patients have been sedimentary, with low physical activity to manifest PH-associated symptoms and because gradually increasing pulmonary vascular resistance and pulmonary arterial pressure are met with right ventricular hypertrophy and resultant preservation of cardiac output (20). Nonetheless, pathologic change of pulmonary vessels has already initiated in this compensated phase *(21).*

Although the clinical significance and natural history of asymptomatic or mild PH in this phase is unclear, patients with identification of subclinical PH are closely monitored, thus providing at least an opportunity for early detection and treatment of future symptomatic PH since the several data available from PH trials have supported the notion that earlier intervention may improve the efficacy of current therapies as well as prognosis (10).

Of notable interest, serum UA levels were significantly higher in SLE patients with PH than in those without PH. This association is compelling since hyperuricemia is not usually observed in SLE patients except in the case of renal insufficiency and in use of drugs, such as diuretics (22). Then, what are the mechanism(s) by which an increased UA is observed in SLE patients with PH? A previous study reported that serum levels of interferon-c are correlated with disease activity in SLE patients (23). Interestingly, interferon-c was shown to potently induce the xanthine oxidase (XO) enzyme in pulmonary endothelial cells (24). Moreover, tissue hypoperfusion and ischemia from reduced pulmonary circulation could deplete adenosine triphosphate and further stimulate the expression of the XO enzyme (25).

Therefore, PH in active SLE might set up a favorable environment for generating UA. However, such a metabolic change in association with reduced pulmonary circulation would be modulated by the distinct pathobiology of the underlying diseases, giving rise to PH. For instance, high levels of oxidative stress was detected in the lungs of patients with COPD and peroxynitrite, a major and powerful oxidative product, has been known to decrease plasma UA levels by rapid oxidation of UA (26).

Moreover, XO was not detected in the lung tissue of interstitial pneumonia, while inducible nitric oxide synthase (iNOS) was intensively expressed. The former finding is explained partly by high expression of transforming growth factor- b (TGF-b) in the lung tissue of patients with ILD, since the induction of XO was suppressed by treatment of TGF-b in rat cardiac cells (27). Thus, it is speculated that serum UA levels are not elevated in patients with COPD and ILD, even coexisting with pulmonary hypertension. Consequently, serum UA level can be a useful indicator distinguishing SLE-associated PH from lung disease associated pulmonary hypertension.

In SSc patients, uric acid levels have been correlated with sPAP and functional capacity and were independent predictors of the presence of PH in asymptomatic patients with SSc (28). However, its levels have not been evaluated as a screening biomarker or predictor in SLE-associated PH.

In this study serum UA levels were independently increased in SLE patients with PH and with the use of a cutoff point of 6.5 mg/dL, the serum UA had reasonable accuracy for predicting the presence of PH in SLE patients. Therefore, if a variety of common causes of hyperuricemia such as decreased renal function, hypertension, use of drugs like diuretics, salicylate and cyclosporine are ruled out, and then unexplained increase of UA would carry clinical relevance for detecting PH in SLE patients with better specificity.

Conclusion

Given a long asymptomatic period before clinically overt disease and the nonspecific symptoms and subtle physical signs, particularly in the early stages of PH in SLE patients a high clinical index of suspicion is necessary to detect the disease before irreversible pathophysiologic changes occur. In this regard, serum UA may be useful as a surrogate marker for screening of PH

in SLE patients since its level has a significant correlation with sPAP and offers reasonable diagnostic values. Moreover, UA measurement is more useful because it is inexpensive and it can be repeatedly and easily performed in a variety of clinical settings. Therefore, it is worth consideration that echocardiography would be performed on SLE patients with unexplained high UA levels

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