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Original Article

The clinical significance of serum uric acid in patients with Takayasu arteritis

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Abstract: Objective: The study aims to evaluate the association between serum uric acid (UA) and inflammatory markers in patients with Takayasu arteritis (TA), and investigate the change in serum UA concentrations after prednisone therapy in TA patients with active disease. Methods: A total of 117TA patients were divided into active disease groups and inactive disease groups, and forty-eight active patients with TA were followed with standard TA treatment protocol. Results: Serum UA levels in active TA patients were significantly higher than in inactive TA patients (274.9±77.11 μmol/L Vs. 238.3±70.10 μmol/L, P=0.008). Elevated serum levels of UA showed a positive correlation with C-reactive protein (CRP) in active and inactive TA patients, respectively (r=0.394, P=0.004; r=0.570, P<0.001). In stepwise multiple linear regression analysis, serum UA still remained a positive correlation with CRP in all TA patients after adjustment for multiple confounders (β=1.445, P<0.001). Serum concentrations of UA were found to be decreased after achieving clinical remission in active patients (274.4±73.22 μmol/L vs. 232.1±45.41 μmol/L, P=0.001). Conclusions: The present results suggest that serum UA is correlated with CRP in TA patients, and may be a useful tool to assess prednisone treatment effects in active TA patients.

Keywords: Takayasu arteritis, serum uric acid, c-reactive protein

Introduction

Takayasu arteritis (TA), as a rare, chronic and idiopathic inflammatory disease, primarily affects aorta, pulmonary artery and their main branches, and mainly attacks young women. Some signs and symptoms that derive from vascular inflammation may occur such as claudication, pain, loss of blood pressure, vascular bruit and light headedness [1]. Clinical and laboratory characteristics are variably correlated with disease activity in patients with TA [2]. Clinically, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been suggested as common inflammatory markers for the evaluation of disease severity in patients with TA, despite of the relative absence of sensitivity and specificity. Angiographic also has been used to examine vascular enhancement and progression of TA patients, these imaging examinations, however, are inconvenient and costly for use in routine clinical practice. Thus, it may be interesting to investigate some available markers to reflect inflammatory and therapeutic conditions in patients with TA.

Uric acid (UA), an end product of purine metabolism, is an antioxidant and iron scavenger in human body. It is well known that excessive UA crystals lead to presence of gout [3]. Very recently, serum UA has been found to be a strong antioxidant in inflammatory response process [4]. Recent studies have shown that UA can promote production of inflammatory cytokines such asinterleukin-6 (IL-6) and tumor necrosis factor (TNF) and interleukin-1β (IL-1β) in mononuclear cells [4]. Previous evidences have suggested that serum UA is associated with some oxidative stress and inflammation-linked diseases such as parkinson's disease, post stroke depression and acute ischemic stroke [5-7]. Moreover, increased levels of UA have been reported in some rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis [8-10]. However, reliable evidences regarding the relation-

Table 1. Demographic and laboratory characteristics in active and inactive patients with TA

	Active patients N=52	Inactive patients N=65	Statistical value	*P*-value
Gender (Female)	52 (100%)	63 (96.9%)	0.379	0.123
Age (yr)	27.2±10.38	29.8±11.20	1.250	0.214
Body mass index (kg/m^2)	25.7±2.49	25.0±2.54	-1.429	0.159
Disease duration, (yr)	5.4±7.48	6.1±6.17	0.576	0.566
Hypertension, n (%)	28 (53.8%)	30 (46.2%)	0.684	0.408
Diabetes mellitus, n (%)	1 (1.9%)	3 (4.6%)	0.672	0.413
Medication history (prednisone), n (%)	43 (82.7%)	52 (80.0%)	0.137	0.711
C-reactive protein (mg/L)	19.1±20.63	6.1±6.59	-4.387	<0.001
Erythrocyte sedimentation rate (mm/h)	34.9±12.90	12.0±5.38	-22.900	<0.001
Alanine transaminase (U/L)	24.8±17.22	19.9±11.99	-1.731	0.087
Aspertate aminotransferase (U/L)	20.0±10.03	17.6±5.60	-1.567	0.121
Total protein (g/L)	66.8±9.72	69.7±5.70	1.934	0.057
Creatinine (μmol/L)	63.8±15.07	63.3±16.66	-1.105	0.917
Urea nitrogen (mmol/L)	5.2±3.21	5.4±1.90	0.299	0.766
Uric acid (μmol/L)	274.9±77.11	238.3±70.10	-2.688	0.008

ship between serum UA and TAis so far lacking. Therefore, the study aims to evaluate the associations between UA and inflammatory markers in patients with TA, and investigate the change in serum UA concentrations after prednisone therapy in TA patients with active disease.

Materials and methods

Patients and healthy controls

Our study included 117 consecutive TA patients from The First Affiliated Hospital, Xinjiang Medical University between January 2014 and May 2016. All patients with TA met diagnostic criteria of the American College of Rheumatology classification criteria [11]. Of all patients, those patients with cardiovascular disease, hyperuricemia, gout, dyslipidemia, hepatic or renal insufficiency, infectious disease, malignancy and other rheumatic diseases were excluded. Our study was reviewed and approved by the Ethics Committee of The First Affiliated Hospital, Xinjiang Medical University, and all patients provided informed consent.

Collection of laboratory data

Laboratory data were collected from the medical records. Fasting blood samples of all patients were used to measure laboratory parameters. Routine laboratory markers such as UA, creatinine (Cr), urea nitrogen (UN), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), CRP and ESR were extracted, and the medical and following-up data of patients was recorded. All biochemical parameters were carried out by identical biochemical analyzer, and CRP and ESR were measured by using immunonephelometry and westergren method, respectively.

Assessment of disease activity

We used the national institutes of health criteria to estimate the disease activity of patients [12]. Active disease of TA patients was determined when patients met following features at least two: (1) typical systemic symptoms; (2) vascular insufficiency signs, such as asymmetry of pulses or blood pressure, vascular pain, claudication and vascular bruit; (3) increased ESR with no infection; (4) typical angiographic characteristics.

Statistical analysis

Statistical analyses were evaluated by SPSS 16.0 statistical package (SPSS Inc., Chicago, IL, USA). Descriptive parameters were presented as mean ± standard deviation or percentages. Student's t test, Mann-Whitney U test and Chi-square test were used to compare the differences for continuous variables and percentages when appropriate. Spearman approach was used to examine the correlations between the two continuous variables. Multiple linear

Table 2. The correlations between UA and laboratory parameters in patients with TA

	All patients		Active TA patients		Inactive TA patients	
	r	*P*-value	r	*P*-value	r	*P*-value
C-reactive protein	0.451	<0.001	0.394	0.004	0.570	<0.001
Erythrocyte sedimentation rate	0.333	<0.001	0.237	0.090	0.281	0.024
Alanine transaminase	0.123	0.188	0.218	0.120	-0.078	0.534
Aspertate aminotransferase	0.102	0.272	0.209	0.137	-0.149	0.236
Total protein	-0.347	<0.001	0.265	0.058	-0.049	0.701
Creatinine	0.568	<0.001	0.591	<0.001	0.673	<0.001
Urea nitrogen	0.512	<0.001	0.432	0.002	0.393	0.001

Table 3. The correlation between serum UA and CRP in all TA patients in multiple linear regression analysis

	Unstandardized coefficients				
	β	Standard error	β	t-value	*P*-value
Gender	-5.227	43.931	-0.009	-0.119	0.906
Age	-1.810	1.123	-0.268	-1.612	0.110
Body mass index	2.141	2.123	0.074	1.008	0.316
Disease duration	2.431	1.812	0.221	1.342	0.183
Hypertension	-1.756	11.108	-0.012	-0.158	0.875
Diabetes mellitus	1.252	29.818	0.003	0.042	0.967
Medication history	-21.046	14.005	-0.113	-1.503	0.136
C-reactive protein	1.445	0.524	0.312	2.757	0.001
Erythrocyte sedimentation rate	0.162	0.532	0.033	0.305	0.161
Urea nitrogen	4.530	3.324	0.159	1.362	0.176
Creatinine	1.075	0.288	0.403	3.738	<0.001

regression was performed with adjustment for multiple confounders. In addition, pair t test was applied to compare the change in serum UA levels before and after prednisone therapy. A *P* value of <0.05 was significant.

Results

Clinical characteristics in patients with TA

Cumulative results for laboratory and clinical characteristics were reviewed for TA patients. Average age was 28±10.87 years, mean values of disease duration were 5.8 years, and mean serum UA concentrations were 254.5±75.23 (μmol/L) in all patients with TA. Most TA patients had hypertension 49.6% (58/117) and prednisone history 81.2% (95/117).

Serum UA in patients with TA

All patients were grouped into active and inactive patients in **Table 1**. Values of CRP and ESR were significantly increased in active TA patients as compared with inactive TA patients. Of note, serum UA in active TA patients were significantly higher than in inactive TA patients (274.9±77.11 μmol/L Vs. 238.3±70.10 μmol/L, P=0.008). However, there were no statistical differences for ALT, AST, UN, Cr and TP between the two groups.

Correlation analysis

Increased serum concentrations of UA were found to be positive correlated with Cr, UN, ESR and CRP, and negative TP in all patients with TA. Serum UA concentrations were positive correlated with serum Cr and UN in active patients with TA, and positive correlated with Cr, UN, and ESR in inactive TA patients. Interesting, elevated serum levels of UA showed a positive correlation with CRP in active and inactive TA patients, respectively, as shown in **Table 2**.

Serum UA and inflammatory parameters in multiple linear regression analysis

Other potential confounders may have influence on the relationship between UA and CRP in all patients with TA. The multiple linear regression analysis was used to further illustrate the correlation UA and CRP in all TA patents. In multiple linear regression analysis (The presence of hypertension, diabetes mellitus and medication history was defined as “1”, otherwise as “0” in this regression mode), serum UA still remained a positive correlation with

Table 4. Laboratoryparameters of active patients before and after prednisonetherapy

	Before treatment	After treatment	t value	*P*-value
Alanine transaminase (U/L)	26.6±17.94	20.9±12.50	1.675	0.101
Aspertate aminotransferase (U/L)	20.9±10.62	18.0±5.26	1.710	0.094
Total protein (g/L)	66.6±9.38	70.3±5.79	-2.571	0.014
Creatinine (μmol/L)	57.3±16.32	62.2±17.47	-1.271	0.211
Urea nitrogen (mmol/L)	5.2±1.87	5.5±1.84	-0.784	0.437
Uric acid (μmol/L)	274.4±73.22	232.1±45.41	3.670	0.001
C-reactive protein (mg/L)	19.9±21.79	7.1±7.42	4.343	<0.001
Erythrocyte sedimentation rate (mm/h)	35.8±12.92	13.8±3.52	14.827	<0.001

CRP in all TA patients (β=1.445, P<0.001) after adjustment for gender, age, body mass index, disease duration, medication history (prednisone), diabetes mellitus, hypertension, Cr, UN and ESR, as shown in **Table 3**.

Serum UA levels and treatment

To investigate the change in serum UA concentrations after prednisone therapy, a total of 48 active patients with TA were followed with standard TA treatment protocol (prednisone, 1 mg/kg per day), mean follow-up times were 50±8.59 days. The primary end points of the follow-up were to achieve following clinical remission criterion: (1) typical clinical symptoms disappeared or decreased; (2) no significant disease progress in vascular imaging findings; (3) decreased ESR within normal values. Forty-four patients with active period achieved clinical remission after prednisone therapy. We compared the change in laboratory data before and after treatment, values of CRP and ESR were decreased, and serum concentrations of UA were found to be decreased in patients during clinical remission stage (274.4±73.22 μmol/L vs. 232.1±45.41 μmol/L, P=0.001) (**Table 4**).

Discussion

Up to now, there is no information available regarding serum UA levels in active and inactive patients with TA. The present study found that serum concentrations of UA were increased in active TA patients compared to those with inactive phase, and serum concentrations of UA were positive correlated with CRP in patients with TA. Remarkably, serum UA concentrations in active TA patients were decreased after receiving prednisone therapy.

The serum concentrations of UA are mainly regulated by purine metabolism and renal excretion. Accumulating data have indicated that serum UA plays an important role in inflammatory response modulation [13]. Elevated serum levels of UA are an independent risk factor in the development of atherosclerosis, and tend to increase the cardiovascular risk in general population [14]. In fact, serum UA, as a powerful physiological antioxidant, has been demonstrated to be associated with arterial hypertension, cardiovascular disease and acute coronary syndrome [15, 16]. Serum UA presents greater ability to predict alteration in the concentrations of CRP in healthy population [17]. Spahić E et al. reported a relationship between serum UA and CRP in patients with acute coronary syndrome [16], and Demir Ş et al. provided an evidence that increased serum UA is linked to CRP in patients with coronary artery ectasia [18]. Currently, we notified a positive correlation between serum UA and CRP in patients with TA, and the serum concentrations of UA in active patients were increased compared to those with inactive phase, indicating that serum UA may be influenced by inflammation in TA patients. Previous research has shown that serum UA has a property to eliminate free radicals, and exhibits a compensatory mechanism against inflammation [14]. Nevertheless, systemic inflammatory milieu is a crucial factor in arterial wall remodeling of TA patients [21], a number of studies have documented that inflammation is involved with pathogenesis in patients with TA, and some inflammatory cytokines such as IL-2, IL-6 and TNF are increased in TA patients [19, 20], these inflammatory cytokines enhance inflammation response of the vascular wall in patients with TA, which accelerate their synthesis and increase concentrations in peripheral circulation.

On the other hand, serum UA as an objective biochemical parameter is available compared with angiography. Our study also examined whether the serum levels of UA could be considered as a potential marker to assess medications treatment. The results demonstrated that serum UA was decreased after receiving anti-inflammatory therapy in active TA patients. The interesting phenomenon may attribute toreducedsystemic inflammatory burden in active TA patients. Obviously, our results also suggested that serum concentrations of UA may be a useful tool to assess prednisone treatment effects in active TA patients.

There are several limitations in the current study. Our patient sample groups were small for this relatively rare disease. In addition, there was no analysis for the association between serum UA and disease classification in TA patients. Finally, some other confounders associated with UA such as diet, exercise and alcohol consumption were not included in multiple linear regression analysis. In conclusion, our present results suggest that serum concentrations of UA are correlated with CRP in TA patients, and may be a useful tool to evaluate prednisone treatment effects in active TA patients.

Disclosure of conflict of interest

None.

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