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Research Article

Increased Serum Uric Acid Level is Positively Associated with Ulcerative Colitis: A Retrospective Case-Control Study

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1. Abstract

1.1. Objective: Recent studies have found that elevated uric acid in intestine during an inflammatory response could exacerbate intestinal disease. The aim of this study was to investigate the association of serum uric acid level with Chinese ulcerative colitis.

1.2. Methods: Serum uric acid level was acquired from the blood biochemical examination and divided them into quartiles. Serum uric acid level was compared between ulcerative colitis patients and controls. Relationship between serum uric acid level and characteristics of ulcerative colitis were evaluated. Logistic regression analysis was used to evaluate serum uric acid level and the risk of ulcerative colitis.

1.3. Results: Higher serum uric acid level was identified in ulcerative colitis patients compared to healthy controls(259.14 ± 85.17 umol/L versus 235.55 ± 50.26 umol/L respectively, P < 0.001), the result was the same when stratified by gender. After stratification by disease stage of ulcerative colitis, higher serum uric acid level was also identified in ulcerative colitis patients in active stage compared to ulcerative colitis patients in remission stage (262.32 ± 83.75umol/L versus 236.28 ± 53.23 umol/L respectively, *P*=0.036).There was no difference in SUA level between UC patients and healthy controls according to smoking status, existence of extra intestinal symptoms, and disease localization. Multivariate logistic regression showed that the highest quartile of serum uric acid was independently associated with ulcerative colitis risk (OR = 1.87 95% CI: 1.35 – 2.89, *P* ≤ 0.001). After adjusting for gender and age, the highest quartile of serum uric acid was still independently associated with ulcerative colitis risk (OR = 1.62, 95% CI: 1.24 – 2.55, *P*=0.002).

1.4. Conclusion: Serum uric acid level is significantly associated with ulcerative colitis, and elevated serum uric acid level is an independent risk factor for ulcerative colitis.

2. Keywords: Serum uric acid; Ulcerative colitis; Association; Oxidative stress

3. Introduction

Ulcerative Colitis (UC) is an chronic, idiopathic and nonspecific inflammatory disorder of the colonic mucosa [1]. Although the pathogenesis of UC remains unknown, genetically susceptible individuals seem to have a dys regulated mucosal immune response to commensal gut flora, which leads to bowel inflammation [2].

Uric Acid (UA) is the end product of nucleic acid, other purine compounds and the purine in food decomposed by xanthine oxidoreductase [3]. Allopurinol, a drug that can lower uric acid lever, has been report edinmany studies that it can improve the efficacy of azathioprine and 6-thioprine in treating IBD [4, 5] found that UA supplementation can increase intestinal mucosal permeability and aggravate inflammation. Allopurinol reduced UA and improved intestinal inflammation in mice [6]. However, related mechanisms were unclear. Besides, high concentration of UA can increase the level of reactive oxygen species (ROS) [7] which can reduce the cellular antioxidant capacity and activate the oxidative stress response and thus serve a vital role in the development and maintenance of colonic inflammation [8-10], and excessive oxidative stress plays a

key factor in the pathogenesis and perpetuation of mucosal damage in UC [8, 11].

Therefore, we conducted a retrospective case-control study, aiming to investigate the correlation between the increasing level of SUA and UC and its clinical stages.

4. Material and Method

4.1. Study Design and Subjects

In patients with UC were recruited from the department of gastroenterology, the first affiliated hospital of Zhejiang University. The diagnosis of UC were based on the clinical, endoscopic and histological features according to the criteria of the European Crohn's and Colitis Organization guideline [12]. Gender and age matched healthy controls were recruited from the Health management center of the first affiliated hospital of Zhejiang University. As for the clinical stages of UC, Mayo score system was adopted, according to which, active stage was defined if the total score<2, and remission stage was defined if total score≥3.This study recruited 257 UC patients who were first diagnosed and no medication was given and they also had no history of taking hypouricemic agents and were free from primary gout, chronic kidney disease and other diseases, 211 age and gender-matched controls who were free from any chronic diseases. Medical records and blood biochemical markers of patients with UC or controls were obtained from electronic health records.

4.2. Ethics Statement

All participants were informed verbally about the purpose and design of the study, written informed consent was not required because of the observational nature of the investigation, and the procedures were approved by the Ethics Committee of Zhejiang University School of Medicine.

This study was approved by the ethical committee of the first affiliated hospital of Zhejiang University (approved number 20191443).

4.3. Statistical Analysis

Statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, United States). All tests were 2-sided, and P<0.05 was considered to be statistically significant result. Mann Whitney rank sum test was used to compare between two groups and Kruskal-Wallis H nonparametric test was used to compare among three or more groups. The correlation between SUA and clinical data was evaluated using Spearman's rank test. SUA level was categorized into quartiles using the 25th, 50th, and 75th percentiles, quintile 1,≤207 mmol/L; quintile 2, 208–249mmol/L; quintile 3, 250–287 mmol/L; quintile 4, ≥288mmol/L. Multiple regression analysis was used to assess the association of SUA level and UC risk, association of SUA level and the stage of UC using the lowest SUA values as the reference group. Besides, we also adjusted the logistic regression for age and gender.

5. Results

5.1. Serum Uric Acid Level in Patients with UC

This study recruited 257 UC patients (median age= 48 years, 95% Confidence Interval [CI] 39–64 years, male to female ratio [M:F]= 1.40) and 211 age and gender-matched controls (median age =49 years, 95% CI 36–59 years, M:F ratio =1.40).

As (Table 1) showed, higher SUA level was identified in UC patients compared to healthy controls (259.14 ± 85.17 umol/L versus 235.55 ± 50.26 umol/L respectively, P< 0.001). We found the similar results when stratified by gender, with significant gender difference in the SUA levels between both groups (274.36 ± 79.62 umol/L versus 251.98 ± 48.20 umol/L respectively, P = 0.004,237.46 ± 88.45 umol/L versus 212.15 ± 43.61, P = 0.011). When stratified by age, no difference was found in SUA levels in two groups.

According to the Mayo Scoring System, 25 UC patients were in the active stage and 232UC patients were in the remission stage. After stratification by disease stage of UC, higher SUA level was identified in active stage compared to those in remission stage (262.32 ± 83.75 umol/L versus 236.28 ± 53.23 umol/L respectively, P=0.036).

Furthermore, no difference was found in SUA level between UC patients and healthy controls according to smoking status, existence of extra intestinal symptoms, and disease localization (Table 2).

Table 1: SUA level in UCpatients and healthy controls.

	N	SUA (μmol/L)	*P*
Totalcontrols	211	235.55 ± 50.26	<0.001*
TotalUC	257	259.14 ± 85.17	
Male controls	124	251.98 ± 48.20	0.004*
Male UC	151	274.36 ± 79.62	
Female controls	87	212.15 ± 43.61	0.011*
Female UC	106	237.46 ± 88.45	
Agebetween 30-50 of controls	99	253.45 ± 43.32	0.341
Agebetween 30-50 of UC	119	251.12 ± 46.76	
Age＞50 of controls	112	224.13 ± 50.23	0.225
Age＞50 of UC	138	221.37 ± 49.88	
Active stage of UC	25	262.32 ± 83.75	0.036*
Remission stage of UC	232	236.28 ± 53.23	
Ulcerative colitis, UC; Serum uric acid, SUA;Data are expressed as mean (SD). * Stands for P<0.05.			

Table 2: Relationship between SUA level and characteristics of UC

	N (%)	SUA (μmol/L)	*P*
Sex			
Male	151 (58.8)	274.36 ± 79.62	0.025*
Female	106 (41.2)	237.46 ± 88.45	
Smoking			
Yes	16 (6.2)	253.56 ± 77.26	0.965
No	241 (93.8)	260.78 ± 82.51	
Extraintestinal symptoms			
Yes	23 (8.9)	255.99 ± 81.38	0.794
No	234 (91.1)	262.12 ± 85.17	
Disease localization			
Ulcerative proctitis (E1)	51 (19.8)	253.56 ± 79.37	0.129
Left sided UC (E2)	119 (46.3)	257.61 ± 83.34	
Extensive UC (E3)	87 (33.9)	263.49 ± 86.99	
Ulcerative colitis, UC; Serum uric acid, SUA. Phenotype assessed according to the Montreal classification. * Stands for P<0.05;			

5.2. Association of SUA Level and UC Risk

As it was showed in (Table 1), when comparing with the control group, UC patients exhibited significantly higher SUA levels. Univariate and multivariate logistic regression models were conducted respectively to investigate SUA levels and UC risk in Q2–Q4, with Q1 serving as reference. Univariate logistic regression displayed that participants in Q4, which was the highest quartile of SUA, revealed a positive association with UC risk (OR=1.87, 95% CI: 1.35-2.89, $P \leq 0.001$) compared to participants in Q1, which was the lowest quartile. Participants in Q3 also showed a positive association with UC risk (OR = 1.62 95% CI: 1.09 – 2.34, $P = 0.025$*) compared to participants in Q1. After adjusting for gender and age**,** SUA levels were still independently associated with UC risk when compared patients in Q4 with patients in Q1(OR=1.62, 95% CI: 1.24–2.55, $P=0.002$) and compared patients in Q3 with patients in Q1 (OR = 1.54, 95% CI: 1.01 – 2.23, $P=0.049$) (Table 3).

Table 3: Association between levels of SUA and UC risk

SUA (μmol/L)	OR (95%CI)	*P*	ORa (95%CI)	*P*a
Quartile 1	Reference	-	Reference	-
Quartile 2	0.59(0.45-1.23)	0.102	0.54 (0.41-1.15)	0.053
Quartile 3	1.62(1.09-2.34)	0.025*	1.54 (1.01-2.23)	0.049*
Quartile 4	1.87(1.35-2.89)	<0.001*	1.62 (1.24-2.55)	0.002*
Ulcerative colitis, UC; Serum uric acid, SUA;* Stands for P<0.05				

5.3. Association of SUA Level and Clinical Stages of UC

As it was showed in (Table 1), UC patients in the active stage displayed significantly higher levels of SUA compared to patients in the remission stage (262.32 ± 83.75 μmol/L versus 236.28 ± 53.23 μmol/L, $P=0.036$). Univariate and multivariate logistic regression models were conducted to explore the OR between SUA and the stage of UC in Q2–Q4, with Q1 serving as reference. We found no significant association between the highest quartile of SUA and the active stage of UC (Table 4).

Table 4: Association between levels of SUA and stage of UC

SUA (μmol/L)	OR (95%CI)	*P*	ORa (95%CI)	*P*a
Quartile 1	Reference	-	Reference	-
Quartile 2	0.33 (0.14-1.03)	0.07	0.29(0.09-0.87)	0.09
Quartile 3	0.89 (0.63-1.56)	0.1	0.72(0.51-1.41)	0.12
Quartile 4	0.62 (0.46-1.31)	0.09	0.49(0.28-1.13)	0.1
Ulcerative colitis, UC; Serum uric acid, SUA				

6. Discussion

The correlation between elevation of SUA levels and UC and its clinical activity has been rarely studied. In this study, we provided evidence that the SUA level is significantly associated with UC. Firstly, SUA levels were higher in UC patients than in healthy controls, the result was the same when stratified by gender. Secondly, after stratification by disease stage of UC, higher SUA level was also identified in ulcerative colitis patients in active stage compared to ulcerative colitis patients in remission stage. Thirdly, univariate and multivariate logistic regression indicated that highest quartile of SUA level serum uric acid was independently associated with UC risk though no significant association between the highest quartile of SUA and the active stage of UC was found.

One of the possible explanations for an association between SUA level and UC is that gut microbiota seem to participate in the catabolism of UA and in the pathogenesis of IBD. It was reported that prevotellaceae, which appears to be undervalued in IBD, is correlated with higher levels of SUA [13] found that UA could mediate intestinal inflammation caused by saccharomycete targeting in UC animal model. UA supplementation can increase intestinal mucosal permeability and aggravate inflammation. Allopurinol reduced UA and improved intestinal inflammation in mice [14]. Hsieh C Y et al found that synthesis of uricase exists in Pseudomonas and Lactobacillus, and those microbiota were generally found to be located in intestinal mucosa [15].

Many studies have shown that NLRP3 inflammasome involved in mediating dextran sodium sulfate (dextran sulfate sodium, DSS) induced colitis in mice. After inhibiting the activation of the NLRP3 inflammasome, intestinal inflammation in mice relieved [16]. There are literatures reported UA can mediate inflammasome NLRP3 activation, thus, participating in the inflammatory reaction, immune responses and the onset of a variety of disease processes [17, 18]. Normal serum UA level is a natural antioxidant in human body, but elevated serum UA level can change its antioxidant role into pro-oxidant and cause damage to human body [19,20]. High concentration of UA can increase the level of intracellular Reactive Oxygen Species (ROS), and ROS can affect intestinal inflammation by regulating the expression of NLRP3 inflamosome. These results suggest that UA may be involved in the occurrence and development of UC by regulating ROS level and regulating NLRP3 inflammasome expression.

Lower levels of serum total bilirubin and higher levels of serum uric acid were associated with UC patients compared to healthy controls [21] in Huhan, Hubei province, which located in central China. We conducted this retrospective case-control study which included 257 UC patients and 211 healthy individuals in Zhejiang province which lies on the southeast coast of China, seafood seems to be a part of People's Daily diet in Zhejiang Province, thus may increasing the SUA level. Our results showed that SUA levels were higher in UC patients than in healthy controls and were correlated with the PR% of UC, hyper uricemia was an independent risk factor for UC and highest quartile of SUA level serum uric acid was independently associated with UC risk.

There were a few limitations in our current study. Firstly, a cause-and-effect relationship could not be elucidated due to the inherent limitation of a retrospective study, and we fail to collect feces to investigate the association between SUA and intestinal microbiota. Secondly, the sample was not sufficiently representative, only 257UC patients who were admitted to the Department of Gastroenterology, The First Affiliated Hospital of Zhejiang University School of Medicine were

included, which may impair the reliability of the results. Lastly, due to the relative small samples, we cannot do further analysis according to Mild activity stage Moderate activity stage and heavy activity stage of UC.

We are planning a randomized prospective study to determine whether UC can be controlled by lowering SUC level and further studies are also necessary to understand thoroughly the mechanisms mediating this relationship and help to clarify the key point of disease prevention and treatment.

7. Conclusions

In summary, our results demonstrated a significant correlation between SUA level and UC. However, for different stage of UC, this correlation was not so obvious. Further studies on the involvement of uric acid in UC will not only expand our understanding of its specific mechanism, but also contribute to the renewal of prevention and treatment strategies for the disease.

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