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Decreased Serum Bilirubin Levels and Increased Uric Acid Levels are Associated with Ulcerative Colitis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: In recent years, emerging evidence has suggested that ulcerative colitis occurs as a consequence of an imbalance between oxidative stress and antioxidant capacity. The objective of this study was to investigate whether serum total bilirubin and serum uric acid levels were associated with ulcerative colitis.

Material/Methods: We conducted a retrospective case-control study which included 170 patients with ulcerative colitis and 200 healthy individuals. Concentrations of serum total bilirubin and serum uric acid were obtained from biochemical information and segregated into quartiles. Logistic regression analysis was adopted to explore the correlations between levels of the 2 biochemical markers and the risk of ulcerative colitis.

Results: Compared with healthy controls, patients with ulcerative colitis exhibited lower levels of serum bilirubin (9.30 umol/L versus 12.49 umol/L respectively, $P<0.001$). Multivariate logistic regression showed that the lowest quartile of total serum bilirubin was independently associated with the occurrence of ulcerative colitis (OR=2.56, 95%CI: 1.54–4.25, $P<0.001$). Similarly, ulcerative colitis patients exhibited higher concentrations of serum uric acid (338 umol/L versus 300 umol/L respectively, $P=0.041$). Multivariate logistic regression showed that the highest quartile of serum uric acid was independently associated with ulcerative colitis risk (OR=1.20, 95%CI: 1.05–1.77, $P=0.045$). Furthermore, a negative association was observed between serum total bilirubin and serum uric acid in patients with ulcerative colitis.

Conclusion: Lower levels of serum total bilirubin and higher levels of serum uric acid are associated with ulcerative colitis patients compared to healthy controls.

MeSH Keywords: **Bilirubin • Colitis, Ulcerative • Oxidative Stress • Uric Acid**

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Background

Ulcerative colitis (UC) is an idiopathic, chronic, and nonspecific inflammatory bowel disease which usually affects the colon [1]. Although its exact pathogenesis remains elusive, the etiology of UC is related to genetic predisposition, environmental factors, and immune system dysfunction. In recent years, the literature has suggested the UC as a consequence of an imbalance between oxidative stress and antioxidative capacity. Chronic inflammation resulting from oxidative stress plays a critical role in the intestinal injury among UC patients.

Bilirubin is an endogenous metabolic product and has long been recognized for its antioxidative and anti-inflammatory properties [2,3]. Serum total bilirubin (sTB) possesses a protective effect against metabolic syndrome and diabetes [4]. Quite a few studies have demonstrated the correlation between reduced levels of sTB with several diseases such as cardiovascular disease [5,6], rheumatoid arthritis [7], and inflammatory bowel disease (IBD) [8]. In a retrospective case-control study, Schieffer et al. [8] found that patients with UC exhibited lower levels of sTB compared with healthy individuals. However, the relationship between sTB and clinical stage of UC has not been established yet.

Recently, uric acid, the inert product of purine nucleotides metabolism, has been the focus of attention due to its contribution to oxidative stress. A number of studies have reported that serum uric acid (sUA) is not just limited to the accumulation of the urate crystal, but also responsible for the pathogenesis of multiple diseases such as chronic kidney disease [9,10], coronary heart disease [11–13], chronic obstructive pulmonary disease [14], and metabolic syndrome [15]. As far as we know, the correlation between sUA and the risk of UC has not been elucidated. Therefore, our study aimed to investigate the association between levels of sTB, as well as sUA, and UC, and also aimed to explore the correlations between the levels of the 2 biochemical markers and the clinical stage of UC.

Material and Methods

Patients and controls

In this retrospective case-control study, we included a total of 170 patients with UC who were admitted to the Department of Gastroenterology and Gastrointestinal Surgery at Renmin Hospital of Wuhan University from January 2014 to January 2018. The participants who visited Renmin Hospital of Wuhan University for routine physical examination at the same given period were assigned to the control group. The control group consisted of 200 healthy individuals who were free from chronic diseases. This study was approved by the Ethical Committee of Renmin Hospital of Wuhan University.

Clinical data

All the patients with UC were diagnosed according to the combination of clinical, endoscopic, and histopathologic criteria. We used the Mayo score system to determine the clinical stages of UC, which were categorized into active phase (total scores ≥3) and remission phase (total scores <2). The exclusion criteria for all study participants included the presence of hepatobiliary disease, cholelithiasis, hemolytic anemia, hemochromatosis, malignant tumor, primary gout, and chronic kidney disease.

All the biochemical data, such as sTB and sUA, were retrieved from the electronic medical record system. Moreover, clinical information of UC patients was also collected from the electronic medical record system, which includes age, sex, symptoms, and colonoscopy and histopathological results.

Statistical analysis

SPSS 20.0 (IBM Inc., Chicago, IL, USA) software program was used to perform all the statistical analyses. Kolmogorov-Smirnov tests were used to check for the normality of continuous variables. Variables with normal distribution are represented as the means ± standard deviation and variables with skewed distribution as the median (interquartile range [IQR]). Non-continuous variables are denoted by the numbers and percentages. Variance on ranks or Mann-Whitney rank sum test was employed to assess the differences between UC patients and healthy controls due to an asymmetric distribution of the sTB and sUA levels. Both sTB and sUA were categorized into quartiles using the 25th, 50th, and 75th percentiles. Logistic regression was performed to evaluate the association between sTB levels and the risk of UC, using the last quartile (highest sTB values) as the reference. Similarly, logistic regression was conducted to evaluate the correlation between sUA levels and UC risk, using the first quartile (lowest sUA values) as the reference. Moreover, we also adjusted the logistic regression for sex, age, and biochemical indicator (sTB or sUA). In addition, a Pearson's correlation analysis was performed to assess the relationship between sUA and sTB in UC patients. All tests were 2-sided, and $P<0.05$ was regarded as a statistically significant result.

Results

Clinical characteristics of included participants

In all, 170 patients with UC and 200 healthy controls were included in this study. We considered sTB levels in the 2 groups, using quartiles of sTB levels: Q1 <8.14 umol/L, Q2 8.14–11.01 umol/L, Q3 11.02–14.77 umol/L, and Q4 >14.77 umol/L. Likewise, we regarded sUA concentrations in the 2 groups using quartiles of sUA: Q1 <249 umol/L, Q2 249–297 umol/L, Q3 298–378 umol/L,

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Table 1. Levels of sUA in UC patients and controls.

Groups		UC (n=170)			Con (n=200)		
		Median (IQR**)		P value	Median (IQR**)		P value
Sex	Male	381	(261–451)	<0.0001*	367	(296–413)	<0.0001*
	Female	358	(167–395)		285	(259–320)	
Age group (years)	<30	325	(247–398)	0.073	345	(278–354)	0.518
	30–50	279	(225–385)		290	(258–364)	
	>50	293	(237–337)		304	(266–342)	
Total		338	(256–391)	–	300	(265–341)	0.041*

Serum uric acid levels were compared by Mann-Whitney rank sum test. * Stands for P<0.05; ** stands for interquartile range.

Table 2. Levels of sTB in UC patients and controls.

Groups		UC (n=170)			Con (n=200)		
		Median (IQR**)		P value	Median (IQR**)		P value
Sex	Male	9.6	(6.5–13.45)	0.456	14.03	(11.23–19.18)	0.17
	Female	9.1	(7.0–11.77)		13.46	(8.92–16.00)	
Age group (years)	<30	9.4	(6.12–18.17)	0.061	16.13	(12.05–24.17)	0.35
	30–50	8.2	(5.6–10.87)		12.12	(9.30–16.14)	
	>50	11.0	(8.27–13.5)		12.42	(9.70–17.57)	
Total		9.3	(6.65–12.15)	–	12.49	(9.66–17.46)	<0.0001*

Serum total bilirubin levels were compared by Mann-Whitney rank sum test. * Stands for P<0.05; ** stands for interquartile range.

Table 3. Association between levels of sTB and UC risk.

TBIL (umol/L)	OR (95%CI)	P value	OR_a (95%CI)	P_a value
<8.14	2.95 (1.80–4.84)	<0.0001*	2.56 (1.54–4.25)	<0.0001*
8.14–11.01	2.35 (1.42–13.92)	0.001*	2.42 (1.44–4.07)	0.011*
11.02–14.77	1.74 (1.02–2.98)	0.042*	1.52 (0.97–2.51)	0.051
>14.77	Reference	–	Reference	–

Logistic regression was conducted to evaluate the association between sTb and UC using the last quartile as the reference. OR was adjusted for sex,age and levels of sUA. * Stands for P<0.05.

and Q4 >378 umol/L. The data were stratified by age and sex; we found significant gender difference in the sUA levels between both groups (*P*<0.001). We found that male individuals had higher concentrations of sUA compared with female individuals (Table 1). However, there was no significant gender difference noticed in the sTB levels of both groups (Table 2).

sTB levels between the UC group and the control group

Patients with UC exhibited significantly lower levels of sTB compared to the control group (median 9.3 umol/L versus 12.49 umol/L, *P*<0.001). Univariate and multivariate logistic regression models were used to evaluate the odds ratio (OR) between sTB levels and UC in Q1–Q3, while Q4 was considered a reference. Univariate logistic regression analysis revealed that UC patients in the lowest quartile of sTB had a significantly positive association with UC risk (OR=2.95, 95%CI: 1.80–4.84, *P*<0.0001) compared with patients in the highest quartile. After adjustment for sex, age, and sUA levels, the results were not obviously altered (OR=2.56, 95%CI: 1.54–4.25, *P*<0.0001) (Table 3).

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Table 4. Association between levels of sUA and UC risk.

UA (umol/L)	OR (95%CI)	P value	OR_a (95%CI)	P_a value
<249	Reference	–	Reference	–
249–297	1.5 (0.97–2.31)	0.066	1.18 (0.76–1.86)	0.474
298–378	0.68 (0.43–1.10)	0.118	0.67 (0.41–1.08)	0.102
>378	1.63 (1.27–2.48)	0.024*	1.20 (1.05–1.77)	0.045*

Logistic regression was conducted to evaluate the association between sUA and UC using the fist quartile as the reference. OR was adjusted for sex,age and levels of sTB. * Stands for P<0.05.

Table 5. Association between levels of sTB and stage of UC.

TBIL (umol/L)	OR (95%CI)	P value
<8.14	1.16 (0.61–2.20)	0.66
8.14–11.01	0.81 (0.40–1.62)	0.54
11.02–14.77	0.85 (0.40–1.77)	0.67
>14.77	Reference	–

Logistic regression was conducted to evaluate the association between sTb and UC stage using the last quartile as the reference. OR was adjusted for sex,age and levels of sUA.

Table 6. Association between levels of sUA and stage of UC.

UA (umol/L)	OR (95%CI)	P value
<249	Reference	–
249–297	1.07 (0.61–1.87)	0.81
298–378	0.91 (0.48–1.73)	0.77
>378	0.83 (0.46–1.47)	0.51

Logistic regression was conducted to evaluate the association between sUA and UC stage using the fist quartile as the reference. OR was adjusted for sex,age and levels of sTB.

sUA levels between the UC group and the control group

UC patients displayed significantly higher levels of sUA compared to the control group (median 338 umol/L versus 300 umol/L, *P*=0.041). Univariate and multivariate logistic regression models were conducted to explore the OR between sUA and UC in Q2–Q4, with Q1 serving as reference. Univariate logistic regression demonstrated that UC patients in the highest quartile of sUA exhibited a positive association with UC risk (OR=1.63, 95% CI: 1.27–2.48, *P*=0.024) compared to participants in the lowest quartile. After controlling for sex, age, and sTB, we found that sUA levels were independently associated with UC risk (OR=1.20, 95% CI: 1.05–1.77], *P*=0.045) (Table 4).

Association between the 2 biochemical indicators and clinical stages

According to the Mayo Scoring System, among the 170 UC patients included in this study, 94 patients were in the active phase and 76 patients were in the remission stage. Although the patients in the active phase had lower sTB levels than those in remission stage, no significant difference was detected through statistical analysis (9.0 umol/L versus 9.48 umol/L, *P*=0.127). After univariate logistic regression, we found no significant association between the lowest quartile of sTB and the active stage of UC (OR=1.16, 95% CI: 0.61–2.20], *P*=0.66) compared with participants in the highest quartile (Table 5). Moreover, patients in the active stage had higher levels of sUA than patients in the remission stage. However, no significant difference was observed after the Mann-Whitney rank sum test (301 umol/L versus 278 umol/L, *P*=0.116). In addition, there was no significant association observed difference between the highest quartile of sUA and the clinical stage of UC (OR=0.83, 95% CI: 0.46–1.47, *P*=0.51) compared with the lowest quartile (Table 6).

Correlation between sUA and sTB in UC patients

Pearson correlation analysis was performed to evaluate the correlation between sUA and sTB in patients with UC, and a negative correlation was observed between sUA and sTB in patients with UC (R=–0.19, *P*=0.013) (Figure 1).

Discussion

To the best of our knowledge, this is a novel clinical report delineating the positive relationship between levels of sUA and UC risk. Furthermore, for the first time, our study reports that there was no association between sTB or sUA levels and UC clinical stage. Moreover, this study was unique in that it evaluated the correlation between sUA and sTB in UC patients.

It is a well-known fact that sTB is a useful marker for the diagnosis of hepatic disease, hemolytic disease, and biliary tract disease. Recent studies have revealed that higher levels of sTB

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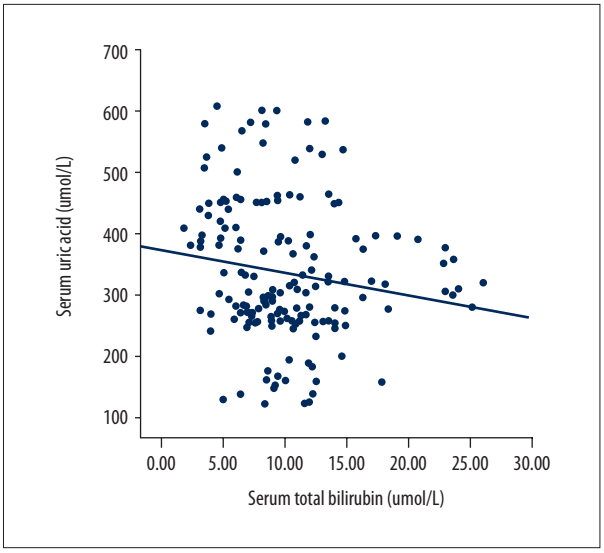

Figure 1. Scatter plot shows the correlation between sTB and sUA in patients with UA (n=170).

could protect against the incidence of diabetes mellitus and metabolic syndrome. Moreover, several clinical studies reported that bilirubin levels were negatively correlated with the risk of coronary heart disease, ischemic stroke, and even IBD. As bilirubin is an essential metabolite with antioxidative properties, lower levels of bilirubin will lead to a decrease in systemic antioxidative capability [16]. It is reasonable to speculate that lower levels of sTB in UC patients may compromised the defense mechanisms against oxidative stress. This could be explained by the ability of bilirubin to inhibit NADPH oxidase, a well-known culprit in superoxide product [17], which could potentially induce oxidant injury and inflammatory response in the intestinal mucosa [18]. Recent studies have also demonstrated that bilirubin is not just limited to its antioxidative property but also possess the ability to affect the differentiation of the regulatory T cells [19,20], which could be implicated in the pathogenesis of UC.

Studies have shown that intestinal microbiota plays an important role in the pathogenesis of IBD [21]. Barnich et al. [22] successfully isolated adherent invasive *E. coli* (AIEC) from the ileum of patients with Crohn disease (CD) and discovered that the detection rate of AIEC in CD patients was significantly higher than in healthy individuals. AIEC has strong β-glucuronidase activity, which could breakdown conjugated bilirubin in the intestinal lumen. Ruminococcus bacteria has been proven to be another kind of genus that participates in the intestinal dysbiosis of IBD and also produces large amounts of β-glucuronidase activity, leading to the degradation of conjugated bilirubin [23]. Furthermore, gut microbiota is reported to participate in the catabolism of UA. Zhang et al. [24] found that gut microbiota of patients with gout were highly different compared to healthy controls. Synthesis of uricase was found in Lactobacillus and Pseudomonas, which were generally located in human intestinal mucosa [25]. Prevotellaceae, which appears to be undervalued in IBD, is correlated with higher levels of sUA [26]. The expansion of uricase-possessing flora represents an adaptive response of the gut microbiome to lower urate [27]. Thus, the gut dysbacteriosis not only participates in the pathogenesis of IBD, but also affects the metabolic pathway of bilirubin and urate, causing a decrease in sTB and increase in sUA.

A literature search revealed that several studies investigated the role of sTB in IBD patients. Leníček et al. [28] performed an exploratory case-control study that included 90 cases of CD and 229 healthy controls, and they concluded that CD was associated with obviously lower levels of sTB, which resulted in an increased level of oxidative stress. Moreover, the study conducted by Kathleen et al. [8] evaluated the relationship between sTB and UC at 2 medical centers and found a reduction of sTB in UC patients compared with healthy individuals. However, in contrast to our study, Sen et al. [29] suggest that sTB levels were raised in CD patients compared to controls, and patients with active stage disease exhibited higher levels of sTB compared to patients in a remission phase. However, due to the small size of this retrospective study (30 CD patients and 66 healthy controls), the quality of evidence is limited. Thus, large-scale clinical studies are needed to elucidate the association between sTB and the risk of IBD.

UA was once thought to be an intracellular free radical scavenger [30] which possessed antioxidative properties [31,32]. However, increasing epidemiological evidence suggests that a role for hyperuricemia in the occurrence and progression of cardiovascular diseases [12,13], chronic kidney disease [10,33], diabetes mellitus [34], metabolic syndrome [35], malignant neoplasms [36,37] and even IBD [38]. The association of UA with the risk of suffering the aforementioned diseases could be partly explained by its pro-oxidant and proinflammatory properties. Moreover, some studies [39–41] have documented the stimulatory role of UA in the secretion of inflammatory cytokines produced by mononuclear cells such as TNF-α, IL-1β, and IL-6. Furthermore, Zhang et al. [42] suggest that raised UA contributes to oxidative stress by activation of the ROS and RAS pathway.

The level of sUA is maintained by the balance between uric acid production and excretion, and hyperuricemia results from an alteration of this balance [43]. Renal excretion accounts for two-thirds of the total uric acid and the remaining urate is excreted through gut mucosa [44]. The excretion of UA is mainly regulated by several types of UA transporters, and the primary UA transporter is ABCG2 (ATP-binding cassette transporter superfamily G2), which is expressed not only in the proximal tubule but also in the intestine membrane [45]. ABCG2 plays

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a central role in both renal and intestinal excretion of urate. Recent studies demonstrated that the dysfunction of ABCG2 leads to a decrease of urate excretion and results in hyperuricemia [46]. Ichida et al. [45] observed that a reduction of intestinal UA excretion resulted in an increase in sUA in ABCG2 knockout mice. In addition, ABCG2 protein was one of the most common components of the intestinal barrier and the ABCG2 gene serves as an attractive candidate gene for the development and progression of IBD. Deuring et al. [47] found that the expression of ABCG2 protein was downregulated in IBD patients during the active disease stage. Englund et al. [48] noticed that ABCG2 protein expression was significantly decreased in UC patients with active inflammation compared with controls and the levels of ABCG2 protein were negatively related to IL-6 mRNA. Based on this evidence, we speculate that decreased ABCG2 in the intestine due to the impairment of oxidative stress leads to reduced urate excretion and increased sUA.

There were a few limitations in our current study. First, this study was a retrospective study, and thus did not collect feces to investigate the association between intestinal microbiota and sUA or sTB. We could not determine whether higher levels of sUA and lower levels of sTB caused UC, or UC led to the alteration of sUA or sTB. Second, only 170 patients with UC were included in our study, which may impair the quality of the evidence. Last, in this retrospective study, we did not consider all possible confounding factors in the multivariate logistic analysis. Medications, such as amino salicylic acid, glucocorticoid, and immunosuppressive agents, given to UC patients might skew the inflammatory status and alter the levels of sUA and sTB. Hence, there is a need for high quality studies in the near the future to determine the cutoff values of sUA and sTB in UC patients.

Conclusions

This current study reports on the association of higher levels of sUA and lower levels of sTB in UC patients compared to healthy controls. However, we were unable to report on results in patients during an active phase in contrast to patients during a remission phase. Furthermore, our study demonstrated a negative correlation existed between sUA and sTB levels in patients with UC.

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Conflicts of interest

None.

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