

PAPER DETAILS

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PAGES: 639-645

ORIGINAL PDF URL: <https://dergipark.org.tr/tr/download/article-file/1910372>

Evaluation of the relationship between disease activity and serum bilirubin, albumin, and uric acid levels in Crohn's disease

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Cite this article as: Bedir Keser G, Ekmen N. Evaluation of the relationship between disease activity and serum bilirubin, albumin, and uric acid levels in Crohn's disease. J Health Sci Med 2021; 4(5): 639-645.

ABSTRACT

Objective: Oxidative stress and antioxidant deficiency play key roles in the pathogenesis of gastrointestinal damage associated with Crohn's disease (CD). Serum bilirubin, uric acid (UA) and albumin are non-enzymatic antioxidants that play a role in oxidative stress control. In this study, it was aimed to evaluate the change in serum bilirubin, UA and albumin levels due to disease activity.

Material and Method: This study was designed as a single-center, cross-sectional and retrospective. The clinical and demographic data of the patients, disease activity, as well as serum albumin, UA, and bilirubin values were recorded from the hospital database. Study variables were statistically analyzed between patient and control groups based on disease activity.

Results: A total of 234 people, 114 with CD and 120 with controls, were included in the study. Total bilirubin, direct bilirubin and albumin levels were found to be significantly lower in the CD than in the health control ($p=0.045$, $p<0.001$, $p<0.001$). There was a significant difference in total bilirubin, direct bilirubin, indirect bilirubin and albumin levels between the control group and active CD ($p=0.009$; $p=0.001$; $p=0.037$; $p<0.001$); no significant difference with the UA level ($p=0.992$). There was a significant difference in direct bilirubin levels between the control group and remission CD ($p=0.005$); no difference in total bilirubin, indirect bilirubin, albumin, and UA levels ($p=0.263$; $p=0.440$; $p=0.112$; $p=0.365$, respectively).

Conclusion: Antioxidant capacity reaches levels similar to the healthy population in patients who achieve remission with medical treatment.

Keywords: Albumin, bilirubin, Crohn's disease, oxidative stress, uric acid

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease that can affect the gastrointestinal tract from mouth to rectum (1). Its annual incidence varies according to geographical region, environmental factors, genetic predisposition and lifestyle (2). With the increasing incidence of inflammatory bowel disease, the diagnosis and treatment of CD has gained importance in terms of gastroenterology (3). Since the etiology of the disease has not been fully elucidated, the goal of treatment is to convert the disease from active to remission. Multiple laboratory indices are used to diagnose and evaluate the activity of CD. Some laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), red cell distribution width (RDW), tumor necrosis factor, and fecal calprotectin were found to be associated with the activity of the disease (4).

Such laboratory tests not only show the activity of the disease, but may also be indicative of existing bacterial infection. Therefore, there is a need for low-cost and non-invasive tests that can evaluate the activity of the disease, with high patient compliance.

Bilirubin, the end product of heme metabolism, is a potent endogenous antioxidant (5). While bilirubin was previously considered as a cytotoxic waste with potential toxicity, it has recently come to the fore with its strong antioxidant, anti-inflammatory and immunosuppressive properties (5). The antioxidant property of bilirubin has been demonstrated in patients with systemic lupus erythematosus (6) and polymyositis (7). Uric acid (UA) is the end product of purine catabolism and has been shown to scavenge more than half of the free radicals in

the blood as an antioxidant (8). The antioxidant role of UA was demonstrated in a study conducted with patients with myasthenia gravis (9). Serum albumin is known as an antioxidant against oxidative damage.

Considering the role of serum bilirubin, UA and albumin in inflammatory diseases, we aimed to investigate the relationship between these values and the activity of CD.

MATERIAL AND METHOD

The study was approved by Gazi University Faculty of Medicine, Clinical Research Ethics Committee (Date: 7/12/2020, Decision No: 834). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

This study is a single-center retrospective cohort study, and patients with CD who applied to the gastroenterology outpatient clinic between 1 October 2015 and 1 October 2020 were included. When the sample was calculated with 95% confidence interval and 80% power of analysis, the sample size was calculated as 87 people. Our study included patients aged 18 years and older, who were diagnosed with Crohn's disease based on medical history, clinical features, endoscopic, histopathological, imaging methods and laboratory tests, and whose follow-up and medical treatment continued. The healthy control group was selected from the patients who applied to the general internal medicine outpatient clinic in the same period.

Determination of Study Variables and Disease Activity

In the anamnesis form obtained from the hospital database of the patients diagnosed with Crohn's disease; gender, age, date of diagnosis, localization of the disease, presence of systemic disease, extraintestinal findings, documentation of current and past medical treatment were recorded. Serum total bilirubin, direct bilirubin, indirect bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, UA, CRP, ESR, RDW, globulin, hemoglobin, hematocrit, white blood cell, lymphocyte, neutrophil, monocytes, ferritin, mean platelet volume (MPV) values were examined. Disease activity was determined at the time of admission to the hospital using the information in the anamnesis form obtained from the database, clinical features and laboratory parameters, and the CD activity index (CDAI) score. Patients with a CDAI score below 150 were considered in remission, 150-220: mild-moderate, 221-450: moderate-severe, >450: severe fulminant Crohn's disease. Age at diagnosis, site of involvement, type of disease and presence of perianal disease were determined according to the Montreal classification.

Statistical Analysis

Statistical analyzes were performed using the SPSS for Windows Version 22. Frequencies were stated for the variables in the categorized data (qualitative), and for the numerical data (quantitative) variables, the means \pm standard deviation if appropriate for the normal distribution, and the median (min-max) values if not for the normal distribution. Whether the variables fit the normal distribution or not was evaluated with the Kolmogorov Smirnov test. Parametric tests (Independent Sample t Test) were used for the variables showing normal distribution, and nonparametric tests (Chi-Square, Mann Withney U Test) were used for those that did not. Kruskal Wallis Test was used for comparison of triple numeric data. Spearman correlation test was used for the correlation between continuous variables. The statistical significance of this study was accepted as $p \leq 0.05$.

RESULTS

A total of 234 people, 114 with CD and 120 with controls, were included in the study. 49% (n=56) of CD and 39% (n=47) of the healthy control group were male. There was no statistically significant difference between the two groups by gender ($p=0.125$). There was no statistically significant difference in the mean age of the CD (39.36 ± 12.26) and control group (39.12 ± 13.63) ($p=0.886$). While 28.9% (n=33) of CD were in the active period, 71.1% (n=81) were in remission, and the clinical demographic characteristics of the entire group are summarized in **Table 1**.

There was a statistically significant difference in total bilirubin, direct bilirubin, albumin, globulin, ALP, ferritin, hemoglobin, neutrophil, lymphocyte, platelet, RDW and MPV values between the CD and control group ($p < 0.05$) (**Table 2**). There was no statistically significant difference between indirect bilirubin, UA, AST, ALT, GGT, leukocytes, monocytes, and hematocrit values ($p > 0.05$) (**Table 2**).

A statistically significant difference was found between CRP and albumin levels between remission and active CD ($p < 0.001$, $p < 0.001$). No statistically significant difference was found between gender, age, total bilirubin, direct bilirubin, indirect bilirubin and UA levels ($p=0.361$, $p=0.476$, $p=0.170$, $p=0.280$, $p=0.233$, $p=0.478$, respectively) (**Table 3**).

There was a statistically significant difference between the control group and active CD, levels of total bilirubin, direct bilirubin, indirect bilirubin, and albumin ($p=0.009$, $p=0.001$, $p=0.037$, $p < 0.001$, respectively). There was no statistically significant difference between the UA level ($p=0.992$) (**Table 4**). There was a statistically significant difference between direct bilirubin levels

between control and remission CD ($p=0.005$). No statistically significant difference was found between total bilirubin, indirect bilirubin, albumin, and UA levels ($p>0.05$) (Table 4).

There was a statistically significant difference in terms of disease activity severity (mild, moderate and severe), albumin and CRP ($p<0.001$, $p<0.001$, respectively). There was no statistically significant difference between total bilirubin, direct bilirubin, indirect bilirubin and UA levels ($p=0.300$, $p=0.378$, $p=0.340$, $p=0.173$, respectively).

Table 1. Demographic and clinical characteristics of CD		
	CD, n=114	
Disease activity	n	%
Active	33	28.9
Remission	81	71.1
Gender		
Male	56	49
Female	58	51
Comorbidities		
Yes	30	26.4
No	84	73.6
Age at diagnosis		
<16 years (A1)	7	6.1
17-40 years (A2)	78	68.4
>40 years (A3)	29	25.5
Disease localization		
Ileal (L1)	32	29.6
Colonic (L2)	36	33.3
Ileocolonic (L3)	38	35.2
Upper GIS involvement (L4)	2	1.9
Disease Behaviour		
Inflammatory (B1)	62	54.85
Obstructive/stenosing (B2)	19	16.85
Penetrating/fistulizing (B3)	20	17.65
Perianal (P)	12	10.65
Extraintestinal symptom		
Yes	24	20.5
No	90	79.5
Disease activity (CDAI score)		
<150 remission	81	71.1
150-220 mild moderate	23	20.2
220-450 moderate-severe	10	8.8
>450 fulminant	0	0
Type of treatment		
Vedolizumab/Certolizumab	13	11.4
5-ASA	19	16.6
Azathioprine±anti TNF	37	32.4
Prednol or unknown	8	7.0
Azathioprine±5-ASA	37	32.4
Only azathioprine treatment	18	15.7
Other treatments	96	84.2

CD=Crohn's disease,

When the laboratory parameters of CD patients who received only azathioprine treatment and those who received other treatment types were compared, no statistically significant difference was found between total bilirubin, direct bilirubin, indirect bilirubin, albumin, and UA values ($p>0.05$) (Table 5).

No correlation was found between the duration of treatment and serum total bilirubin, direct bilirubin, indirect bilirubin, UA, and albumin values ($p=0.845$, $r=0.019$; $p=0.728$, $r=0.033$; $p=0.997$, $r=0.000$; $p=0.894$, $r=0.013$; $p=0.965$, $r=0.004$, respectively).

Table 2. Comparison of demographic characteristics and laboratory parameters in the study group			
	CD, n=114	Control, n=120	P
Gender n (%)			0.125
Male	56 (49%)	47 (39%)	
Female	58 (51%)	73 (61%)	
Age (years)*	39.36±12.26	39.12±13.63	0.886
CRP, mg/L**	7.30 (1-206)		
Total bilirubin, mg/dL	0.52 (0.13-2.45)	0.58 (0.26-2.37)	0.045
Direct bilirubin, mg/dL	0.10 (0.03-0.37)	0.13 (0.05-0.51)	<0.001
Indirect bilirubin, mg/dL	0.42 (0.05-2.14)	0.46 (0.11-1.86)	0.128
Albumin, g/dL	4.30 (1.50-8.40)	4.50 (3.60-5.10)	<0.001
UA, mg/dL	4.85 (2.20-8.80)	4.70 (2.20-8.30)	0.481
AST, U/L	19.00 (10-225)	20.00 (11-42)	0.477
ALT, U/L	16.00 (2-271)	17.00 (7-69)	0.486
ALP, U/L	90.00 (47-230)	77.50 (38-164)	0.003
GGT, U/L	22.00 (7-277)	18.00 (8-127)	0.054
Globulin, g/dL	3.15 (2.30-4.70)	2.90 (2.30-3.90)	<0.001
Ferritin, ng/mL	35.00 (2-595)	21.00 (2-175)	0.007
Hemoglobin, g/dL	13.60 (7.40-18.10)	13.95 (10.00-18.30)	0.007
Leukocyte, $\times 10^3/\mu\text{L}$	7380.00 (3110-22620)	7100.00 (3790-12720)	0.140
Neutrophil, $\times 10^3/\mu\text{L}$	4425.00 (1150-18450)	3960.00 (670-7170)	0.002
Lymphocyte, $\times 10^3/\mu\text{L}$	2035.00 (300-4550)	2275.00 (990-4770)	0.002
Monocyte, $\times 10^3/\mu\text{L}$	560.00 (120-1610)	560.00 (230-1140)	0.488
Platelet, $\times 10^3/\mu\text{L}$	303000.00 (110000-766000)	276500.00 (163000-439000)	0.001
RDW, %	13.65 (12-32)	13.00 (11-19)	<0.001
MPV, fL	9.70(8.10-21.70)	10.20 (8.40-12.90)	0.002
Hematocrit, %	41.50 (22-53)	42.05 (34-54)	0.174
Sedimentation, mm/h	20.50 (2-105)		

* mean ±standard deviation. **median (min-max). CD=Crohn's disease, ALT=alanine aminotransferase. ALP=alkaline phosphatase. AST=aspartate aminotransferase. CRP=C reactive protein. GGT=gammaglutamyl transferase. MPV=mean platelet volume. RDW= red cell distribution width. UA=uric acid

Table 3. Comparison of laboratory parameters according to activity in CD

	Remission CD, n=81	Active CD, n=33	P
Gender n (%)			
Male	42 (51.9)	14 (42.4)	0.361
Female	39 (48.1)	19 (57.6)	
Age (years)*	39.77±12.03	38.36±12.95	0.476
CRP, mg/L**	47.37 (1-73)	78.36 (12-105)	<0.001
Total bilirubin, mg/dL	0.52 (0.13-2.45)	0.50 (0.26-0.83)	0.170
Direct bilirubin, mg/dL	0.11 (0.03-0.37)	0.09 (0.06-0.19)	0.280
Indirect bilirubin, mg/dL	0.42 (0.05-2.14)	0.40 (0.20-0.66)	0.233
Albumin, g/dL	4.40 (1.50-8.40)	4.00 (2.90-7.80)	<0.001
UA, mg/dL	4.95 (2.30-8.80)	4.45 (2.20-7.70)	0.478

*mean ±standard deviation. **median(min-max). CD=Crohn's disease, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CRP=C reactive protein, UA=uric acid.

Table 4. Comparison of laboratory parameters of control group and active and remission CD

	Control, n=120	Active CD, n=33	P	Remission CD, n=81	P
Total bilirubin,mg/dL*	0.58 (0.26-2.37)	0.50 (0.26-0.83)	0.009	0.52 (0.13-2.45)	0.263
Direct bilirubin,mg/dL	0.13 (0.05-0.51)	0.09 (0.06-0.19)	0.001	0.11 (0.03-0.37)	0.005
Indirect bilirubin,mg/dL	0.46 (0.11-1.86)	0.40 (0.20-0.66)	0.037	0.42 (0.05-2.14)	0.440
Albumin, g/dL	4.50 (3.60-5.10)	4.00 (2.90-7.80)	<0.001	4.40 (1.50-8.40)	0.112
UA, mg/dL	4.70 (2.20-8.30)	4.45 (2.20-7.70)	0.992	4.95 (2.30-8.80)	0.365

*median(min-max), CD=Crohn's disease, UA=uric acid

Table 5. Comparison of laboratory parameters in CD receiving azathioprine only and other treatments

	Only azathioprine treatment, n=18	Other treatments, n=96	P
Total bilirubin mg/dL*	0.52 (0.23-1.35)	0.52 (0.13-2.45)	0.887
Direct bilirubin mg/dL	0.10 (0.05-0.26)	0.11 (0.03-0.37)	0.832
Indirect bilirubin mg/dL	0.40 (0.09-0.66)	0.42 (0.05-2.14)	0.657
Albumin g/dL	4.30 (3.90-4.80)	4.30 (1.50-8.40)	0.617
UA, mg/dL	4.50 (2.60-6.90)	4.90 (2.20-8.80)	0.317

*median(minimum-maximum), CD=Crohn's disease, UA=uric acid

DISCUSSION

To the best of our knowledge, our study is the first reported from Turkey to examine the relationship between serum bilirubin, albumin and UA which are non-enzymatic antioxidant molecules and disease activity in patients with CD followed up with medical treatment.

In the current study, found that serum total bilirubin and albumin levels, which reflect the change in serum antioxidant capacity due to the increase in inflammation-related oxidative stress, were significantly lower in CD compared to the healthy controls. But there was no significant difference in indirect bilirubin and UA levels.

In the study of Su et al. (10) serum bilirubin, albumin, and UA levels were found to be lower in newly diagnosed Crohn's patients who had not yet received medical treatment compared to the healthy controls, and this was associated with excessive consumption and destruction of serum bilirubin, albumin, and UA.

In a study by Zhu et al. (11) UA levels were found to be higher in inflammatory bowel disease compared to healthy controls, similar to present study, and it was observed that UA level increased with disease activity. UA is a parameter

that undergoes renal elimination and is affected by renal functions. UA is a parameter that undergoes renal elimination and is affected by renal functions. Creatinine, on the other hand, is a biochemical parameter that changes depending on muscle mass and dietary protein, and it is a test that is affected by both kidney functions and nutritional status. For these reasons, in the same study, they evaluated the UA level, which is one of the parameters that will show the decrease in the endogenous antioxidant capacity of the patients, as the UA/creatinine ratio in order to minimize the interpretation errors. The lack of significant difference in UA level between the healthy controls and CD in the current study may be related to the medical treatment, the possible effect of medical treatment on the redox balance, or the fact that UA is a parameter affected by the nutritional status. In addition, oxidative stress management in the body is provided by enzymatic and non-enzymatic mechanisms, and the net effect of medical treatment on the enzymatic antioxidant system is unknown.

In the current study, a statistically significant difference was found between albumin and CRP levels and disease activity, but no significant difference was found between

disease activity and total bilirubin, direct bilirubin, indirect bilirubin and UA levels. Kekilli et al. (12) found no difference in serum albumin levels between newly diagnosed active CD and CD patients in remission. The reason for this different result compared to the current study may be due to the low number of patients in remission in this study.

Albumin is a negative acute phase reactant and decreases as disease activity increases, while CRP level increases in line with the severity of inflammation. At the same time, albumin can be affected by the nutritional status of patients.

In the study of Su et al. (10) similar to present study, no significant difference was found between disease activity and UA level. They showed that as the severity of the disease increased, serum bilirubin, albumin and UA levels decreased, and CRP levels increased. The difference of this study from the current study is that newly diagnosed patients who have not yet received medical treatment were included in the study. The lack of a significant difference between disease activity and serum bilirubin and UA levels in the current study may be due to the small number of active patients. The fact that the patients were under medical treatment, and the different effects of the drugs used on the redox balance (10).

In the current study, in the comparison between remission and active Crohn's patients, CRP level was significantly higher and albumin level was significantly lower in patients with active disease. In contrast, no statistically significant difference was found between serum bilirubin and UA levels. The reason for these results is that all patients are receiving medical treatment and the number of active patients is relatively low. Serum bilirubin and albumin levels were found to be significantly lower in active Crohn's disease compared to healthy controls, but there was no statistically significant difference between UA values. If there is no difference between UA levels, it can be considered that all Crohn's patients should be under medical treatment. While there was a significant difference only in direct bilirubin levels between healthy controls and CD in remission, there was no significant difference in serum total bilirubin, indirect bilirubin, albumin, and UA levels.

In the light of this information, it can be concluded that redox balance is established in the body and serum antioxidant capacity reaches levels similar to the healthy population in patients who are in remission with medical treatment.

There is increased oxidative stress and decreased antioxidant capacity in active CD, and serum antioxidant capacity reaches levels similar to the healthy controls in patients with remission (13-15).

In the study of Szczeklik et al. (16) serum bilirubin and albumin levels were found to be significantly lower in active CD compared to healthy controls and inactive CD patients, and present values were negatively correlated with disease severity. Lenicek et al. (17) reported that each 1 mmol/L decrease in serum bilirubin is associated with a 13% increase in the risk of developing CD. Schieffer et al. (18) suggested that the decrease in serum bilirubin is due to inflammation and that this phenomenon is observed not only in CD but also in various inflammatory diseases.

An Australian study (16) suggested that bilirubin levels are significantly lower in severe asthma, while inflammation affects antioxidant vitamins and bilirubin levels in asthmatics. This study shows the relationship between the changing serum concentration of bilirubin and albumin and oxidative imbalance in inflammation, similar to our study. In the study by Yang et al. (9) serum bilirubin, UA, albumin and creatinine levels were found to be lower in patients with myasthenia gravis, an autoimmune disease, when compared to the healthy controls. In the same study, when grouped according to the degree of disease progression, no significant difference was found in serum bilirubin levels, and serum UA, albumin and creatinine levels were negatively correlated with disease progression.

Peng et al. (19) found that serum total bilirubin, indirect bilirubin, UA and albumin levels were significantly lower in patients with neuromyelitis optica compared to healthy controls. Li et al. (20), found significantly lower serum bilirubin, UA and albumin levels in patients with newly diagnosed pemphigus vulgaris that also known as a autoimmune severe bullous dermatosis compared to healthy controls. Albumin levels when compared to healthy controls.

Since CD is an inflammatory disease, it has been suggested that decreased antioxidant reserve is probably the pathogenic mechanism in the disease. Oxidative stress and antioxidant deficiency are thought to play a key role in the pathogenesis of CD-related gastrointestinal damage (15).

In the current study, did not find a significant difference in serum bilirubin, UA, and albumin levels between patients treated with azathioprine alone and those receiving other treatments. Neubauer et al. (20) investigated the possible relationship between non-enzymatic antioxidants and azathioprine treatment. In this study, no significant difference was found in serum UA levels between patients who received and did not receive azathioprine. Azathioprine may have opposite effects on systemic antioxidants. On the one hand, it causes an increase in systemic hydrogen peroxide, leading to cytotoxicity

mediated by drug-induced oxidative stress in hepatocytes or T lymphocytes. On the other hand, azathioprine, which can undergo biotransformation through three different enzymatic systems and is metabolized by xanthine oxidase, produces thioric acid. Thioric acid is a compound equipped with a free sulfhydryl group, which has antioxidant capacity like UA. It has been shown in studies that sulfur derivatives of UA have neuroprotective effects and reduce ischemic brain damage (21).

Lemarachel et al. (22) measured protein oxidation levels in patients with rheumatoid arthritis who were treated with infliximab, and it was interpreted that redox balance was achieved due to the decrease in serum protein carbonyl groups after infliximab treatment. Monoclonal antibodies (anti-TNF- α) inhibit the production of activated macrophage and other proinflammatory cytokines that increase T cell infiltration. A potent anti-inflammatory effect appears, including lysis of activated immune cells and induction of apoptosis by TNF- α neutralization (23).

Bednarek et al. (24) conducted a study on oxidative stress parameters in patients treated with corticosteroids for infiltrative Graves' ophthalmopathy. They found that oxidative stress parameters decreased during treatment and concluded that corticosteroids can temporarily reduce oxidative load. Corticosteroids are drugs that have anti-inflammatory and immunosuppressive effects by reducing lymphocyte proliferation and inhibiting inflammatory mediators secreted by macrophages. Thus, corticosteroids prevent the production of reactive free radicals. With the reduction of immune cells and mediators, the formation and release of free radicals is reduced, and oxidative stress is prevented.

There are some limitations in the current study. First, this is a retrospective study of patients with CD and has a small sample size. Secondly, due to the small number of patients with active CD, it was prevented to reach clear conclusions in evaluating the relationship between bilirubin, albumin, UA and disease activation. Third, the relationship between some antioxidant enzymes (SOD, GSH-Px, catalase) and disease activity was not evaluated in the present study. Finally, a proportion of patients with CD have been treated with azathioprine, and the impact of this drug on outcomes cannot be excluded.

CONCLUSION

Albumin, bilirubin and UA, which are cost-effective tests that are routinely used in clinical practice, may be useful biomarkers in the detection of antioxidant status in Crohn's disease and may guide the early diagnosis of the disease. Larger-scale studies are needed for the use of these biomarkers for the evaluation of disease activity and treatment response.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Gazi University Faculty of Medicine, Clinical Research Ethics Committee (Date: 7/12/2020, Decision No: 834).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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