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CAN ISCHEMIA MODIFIED ALBUMIN LEVEL BE REGARDED AS AN INDICATIVE MARKER OF ULCERATIVE COLITIS AND ITS ACTIVITY?

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Abstract

Objectives: We studied the effectivity of serum ischemia-modified albumin (IMA) levels in the diagnosis and clinical activity of patients suffering from Ulcerative Colitis (UC).

Materials and Methods: Eighty-eight clinically and pathologically confirmed UC patients and 48 age- and sex-matched healthy volunteers were included in the study. The patients were classified according to the Rachmilewitz Score [Endoscopy activity index (EAI)], and those with a score below five were considered in the remission group, and those above five were considered as active disease group. The IMA levels were calculated by the colorimetric method.

Results: When UC patients were compared to the control group, higher IMA levels were observed in the patient's serum (0.48±0.25 g/L *vs.* 0.28±0.08 g/L), and the difference was statistically significant ($p<0.001$). Among UC patients, higher IMA levels were found in the active group (n:36) compared to the remission group (n:52) (0.72±0.20 g/L vs. 0.32±0.12 g/L, and $p<0.001$). Positive and statistically significant correlations between serum IMA levels and EAI scores ($r:0.81$, $p<0.001$) were detected.

Conclusion: Serum IMA level may be a suitable biomarker for the diagnosis and the clinical and endoscopic activity of UC disease. It may have diagnostic and prognostic features in UC disease.

Keywords: Endoscopic activity index, ischemia-modified albumin, serum marker, ulcerative colitis.

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Introduction

Ulcerative colitis (UC) is an inflammatory disease of the colon causing diffuse fragility and superficial erosions of the colonic membrane associated with blood loss of unknown origin. It is the most common type of inflammatory bowel disease involving the inflammation limited to the colonic mucosa and submucosa. Typically, the disease starts in the rectum and spreads to the proximal colon without interruption.[1, 2] Although the etiology of UC is unknown, environmental and genetic factors, immune system diseases and oxidative stress may play a role in the etiopathogenesis. The increase in reactive oxygen/nitrogen species (ROS/RNS) is believed to take part in the oxidative stress in the UC. As a product of standard cellular metabolism, the excessive production of ROS/RNS causes oxidative stress, ischemia and tissue hypoxia. ROS/RNS corresponding to hydroxyl radicals were generated almost in every ischemic disease and adjusted the N-terminus of serum albumin leading to ischemia-modified albumin (IMA) formation. It is known that IMA formed in this way is considered an indirect marker of oxidative stress.[3-5] Since it has been shown that IMA was associated with oxidative stress and tissue perfusion, we designed this study considering that IMA may play a role in the pathogenesis of UC.

We aimed to assess serum IMA level as a diagnostic marker in UC patients and determine whether it is efficient in assessing the disease severity or not.

Materials and Methods

Study population

This study was conducted in our hospital between August 2017 and January 2020. Eighty-eight patients with UC and 48 healthy volunteers were enrolled in the study. UC and the control group were older than 18 years. The control group consisted of volunteers without any disease who applied to our outpatient clinic for control purposes and were similar to UC patients in terms of age and gender. Patients with any chronic systemic disease, ischemic disease or a history of ischemic diseases, such as myocardial infarction and pulmonary embolism, patients with hepatic and renal failure or infectious disease, were excluded from the study because IMA levels may be affected.

Endoscopic evaluation

To evaluate the degree of the disease, the history of the patients at the time of admission and all blood values, including inflammatory markers, were investigated. All procedures were performed by the same experienced endoscopist under the same conditions to calculate the endoscopic activity index (EAI) of Rachmilewitz scoring

(MC). Colonoscopy evaluation was performed by the same clinician using a high-definition white-light colonoscope (Olympus Medical Systems, Tokyo, Japan), each lasting approximately 15-20 minutes, by evaluating the colonic mucosa and calculating the EAI.

Clinical and endoscopic values were used for the staging of the disease. Endoscopic activity index values were calculated for UC activity using the Rachmilewitz scoring system, and values of 5 and above were accepted as active disease.[6]

Ischemia-modified albumin evaluation

For the measurement of IMA levels, 5 ml of blood was taken from all patients and controls between 08.00 and 10.00 a.m. after at least 12 hours of fasting, using the antecubital vein. Then the blood was centrifuged at 4000 rpm for 10 minutes, and the serum samples were placed in Eppendorf tubes and stored in -80-degree cabinets until the day of the procedure. All the IMA measurements were done by the same operator throughout the study period via Shimadzu UVmini-1240 spectrophotometry, including cobalt chloride, dithiothreitol, and sodium chloride 0.9%, by the spectrophotometric method reported by Bar-Or et al.[7]

Biochemical parameters evaluation

Complete blood count, alanine aminotransferase (ALT), (aspartate aminotransferase (AST), total protein, albumin, C-reactive protein (CRP) levels and erythrocyte sedimentation rates (ESR) were evaluated in the morning of the colonoscopy procedure and then recorded as data for analysis. ALT, AST, total protein, and albumin were calculated by using Roche Cobas Integra 800 (Roche Diagnostic Corp., Indianapolis, Indiana, USA) autoanalyzer. CRP was assessed by using a Hitachi Modular P800 analyzer. Also, ESR was evaluated by Alifax Test 1 THL (Alifax s.p.a Comp. Polvera, Italy) machine.

Statistical analysis

All statistical analysis was performed using SPSS (Statistical Program for Social Sciences) version 26 software. To assess the normality of data Kolmogorov-Smirnov/Shapiro–Wilk tests were used. Quantitative factors with normal distribution were indicated as mean ± standard deviation (SD), while those with non-normally distributed were indicated as median (IQR). Categorical factors were presented by numbers and percentages. In two group comparisons of normally distributed quantitative variables, the Student t-test was used, while for comparison of non-normally distributed quantitative variables, the Mann–Whitney U test was used. Comparison of categorical data was made by chi-square/ Fisher's exact tests where appropriate. The correlation analysis was done using Pearson/Spearman correlation analysis tests among quantitative variables. A $p<0.050$ was considered statistically significant.

Results

There were 88 patients at UC and 48 volunteers in the control group. No statistically significant difference was found when the control group and the UC group were compared in terms of age, sex and body mass index (BMI). There was no significant difference between the groups regarding hemoglobin, platelet, white blood cells (WBC), glucose, total protein, albumin and ESR. CRP levels were significantly higher in the UC group compared with the control group (1.5 (6.3) mg/L *vs.* 0.43 (0.2) mg/L) respectively, and p<0.001. When compared in terms of IMA levels, it was determined that there were higher levels in the UC group than in the control group, and the difference was statistically significant (0.48 ± 0.25 g/L *vs.* 0.28 ±0.08 g/L, respectively) and p<0.001. Comparisons of demographic characteristics and laboratory findings of control and UC patients are represented in Table1. The comparison of IMA levels between the control and UC group is shown in Figure 1.

Table 1. Comparison of Demographic and Clinical Factors of Ulcerative Colitis and Control Groups.

Factors	Control group (n:48)	UC group (n:88)	p
Gender, F (%)	16 (33.33%)	33 (37.50%)	0.629
Age, years	43 (21-77)	43 (18-77)	0.726
BMI (kg/m^2)	24.9 (3.48)	25.78 (3.59)	0.841
Hemoglobin (g/dl)	13.8 (1.8)	14.05 (1.2)	0.350
Platelet (x10^3 µL)	271.0 (68)	264 (96)	0.784
WBC (x10^3 µL)	7640 (3100)	7095 (2500)	0.071
Glucose (mg/dl)	94.62 ± 17.2	97.10 ± 16.3	0.752
T protein (g/L)	7.40 ± 0.43	7.31 ± 0.44	0.831
Albumin (g/L)	4.64 ± 0.36	4.36 ± 0.29	0.324
ESR (mm/h)	12 (9)	13 (20)	0.494
CRP (mg/L)	0.43 (0.2)	1.5 (6.3)	<0.001
IMA (g/L)	0.28 ± 0.08	0.48 ± 0.25	<0.001

Factors were expressed as mean ± SD (Standard deviation) for normally distributed and median (Interquartile range) for non-normally distributed factors. Categorical factors were defined as numbers (%).
(BMI; body mass index, CRP; C-reactive protein, EAI; endoscopic activity index, ESR, erythrocyte sedimentation rate, F; female, IMA, ischemia modified albumin; NS, non-significant; UC, ulcerative colitis; WBC, white blood cell)

Patients with a diagnosis of UC were classified as having an EAI < 5 in remission (n:52) and those with a score of greater than five as an active disease (n:36). There was a good positive correlation between IMA levels and EAI scores (r:0.81 and p<0.001) and CRP levels (r:0.37 and p<0.001). There was no statistically significant difference regarding age, gender, BMI, hemoglobin, platelet, WBC, ALT, AST, total protein, Albumin and ESR between the remission and active groups. There was a significant difference among remission and active groups regarding CRP levels (1.46 ± 1.04 mg/dL *vs.* 10.34 ± 9.6 mg/dL, respectively) and p<0.001. When the remission and active UC groups were compared in terms of IMA levels, a statistically significant difference was calculated (0.32 ± 0.12 g/L *vs.* 0.72 ± 0.20 g/L, respectively) and p<0.001. A comparison of demographic and

clinical factors among remission and active UC group are demonstrated in Table 2. Figure 2 represents the comparison of IMA levels between remission and active UC groups.

Table 2. Comparison of Demographic and Clinical Factors of Remission and Active Ulcerative Colitis Groups.

Factors	Remission group (n:52)	Active group (n:36)	P
Gender F (%)	17 (32.69%)	16 (44.44%)	0.263
Age, years	55 (32-68)	47 (20-66)	0.365
BMI (kg/m^2)	24.43 ± 3.51	26.68 ± 3.30	0.203
Hemoglobin (g/dl)	12.86 ± 3.35	13.8 ± 0.63	0.519
Platelet (x10^3 µL)	323 ± 256	267 ± 70.4	0.783
WBC (x10^3 µL)	5720 ± 3900	6620 ± 1290	0.368
ALT (IU/L)	10 ± 3.6	17 ± 9.2	0.663
AST (IU/L)	16.67 ± 3.21	16.29 ± 3.1	0.974
T protein (g/L)	7.40 ± 1.10	6.98 ± 0.36	0.191
Albumin (g/L)	4.16 ± 0.90	4.3 ± 0.29	0.691
ESR (mm/h)	15 ± 15.7	10.43 ± 7.77	0.212
CRP (mg/L)	1.46 ± 1.04	10.34 ± 9.6	<0.001
IMA (g/L)	0.32 ± 0.12	0.72 ± 0.20	<0.001

Factors were expressed as mean ± SD (Standard deviation) for normally distributed and median (Interquartile range) for non-normally distributed factors. Categorical factors were defined as numbers (%).
(ALT; alanine aminotransferase, AST; aspartate aminotransferase, BMI; body mass index, CRP; C-reactive protein, EAI; endoscopic activity index, ESR, erythrocyte sedimentation rate, F; female, IMA, ischemia modified albumin; NS, non-significant; UC, ulcerative colitis; WBC, white blood cell.)

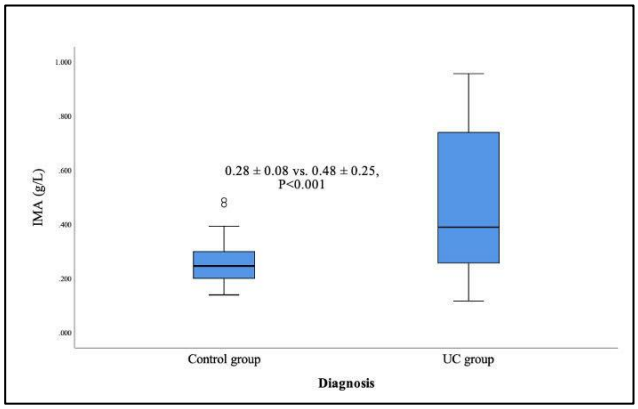

Figure 1. The Comparison of IMA Levels Between the Control and the UC Groups

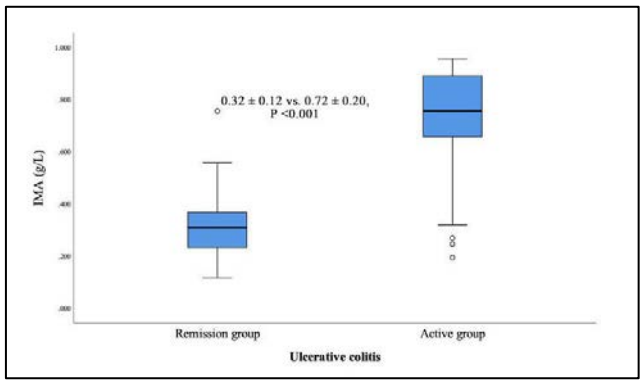

Figure 2. The Comparison of IMA Levels Between Remission and Active UC Groups.

Discussion

According to the results of our present work, when IMA levels were compared between the control group and UC group, statistically significantly higher levels were found in the UC group. A good positive correlation was found between IMA levels, CRP and EAI scores among patients in the UC group. The reason for the increased level of IMA may be due to tissue hypoxia developing after intestinal microvascular ischemia in the classical UC pathology. Therefore, a significant difference was observed between UC and healthy controls, and as the endoscopic activity of the disease increased, the detection of increased IMA levels revealed its relationship with tissue hypoxia.[8-10]

The IMA level, which has a valuable role in both diagnosis and disease severity in UC patients, gains value in the diagnosis and follow-up of the UC as a non-invasive serum biomarker. It has been reported that IMA levels have a significant role in some diseases, such as sepsis and cholestatic jaundice, both at the diagnostic and prognostic level. [11] Our results also confirm these studies and support the usability of IMA in the diagnosis and prognostic evaluation of UC.

Inflammatory bowel diseases are chronic inflammatory disorders and may also have the gastrointestinal system and extraintestinal involvement, which are not clarified in terms of etiology. [12] Although the onset of the deterioration of the immune system response and how the damage to the colonic mucosa occurs has not been clarified; it has been proven that reactive oxygen radicals, redox modules, nitrogen particles (ROS/RNS) and subsequent oxidative stress molecules may take part in its physiopathology. [9, 13] Recently, it has been reported that colonic oxidative stress may stimulate the formation of colitis.[9] It has been shown that the IMA level was an indirect marker of oxidative stress.[14-16] In our study, the presence of higher serum IMA levels was demonstrated in patients with UC compared to controls. Furthermore, higher levels were found in UC patients with active disease compared to those in remission, which is important in terms of showing that this hypothesis was proven in our study.

Several studies have shown that the proinflammatory cascade that causes the creation of reactive oxygen species (ROS) is induced by ischemia.[17, 18] In addition, the role of IMA in inflammation-related diseases has been shown recently.[14, 19] As a result of our study, we indirectly showed that serum IMA level could be obtained both diagnostically and prognostically in UC disease which has chronic inflammatory pathophysiology.

Although IMA levels were associated with acute coronary syndrome, liver ischemia, and ischemic conditions in organs such as the brain, kidney and intestine in adults, the association between IMA levels and UC disease and activity has not been demonstrated.[14-16] In the previous studies, the relationship between IMA levels and inflammatory bowel diseases was investigated, but different results were found.[15, 20] In our study, the

relationship between serum IMA levels and UC was important because it was significant both in diagnosis and prognosis. With this study, we obtained results that support the studies showing that there is a relationship between the level of ima and the UC.

Normally, IBD patients have more oxidative stress than healthy people. Due to ongoing chronic oxidative stress, antioxidants that increase in the inflamed tissue decrease over time, and this causes an increase in oxidative stress in the tissue due to the decrease in antioxidants.[21] It is acknowledged that oxidative DNA damage is very effective in the pathophysiology of UC and in the carcinogenesis that may develop in the later stages of the disease.[22] Therefore, patients with UC are at risk of developing colon carcinoma.[23] This is thought to be due to the increase in unmet oxidative stress. Consequently, we thought that high IMA levels in active UC patients were due to oxidative stress.

Since some serum biomarkers are involved in severe inflammation as acute phase reactants, they have been accepted for use in inflammatory diseases such as UC. Therefore, the good positive correlation between IMA levels and CRP reinforces the usability of this marker in the diagnosis and prognosis of UC.[24, 25]

In conclusion, serum IMA level may be a suitable biomarker for the diagnosis and the clinical and endoscopic activity of UC disease. It may have diagnostic and prognostic features in UC disease.

Ethical considerations: The work was designed according to the Helsinki declaration, and the local ethics committee confirmed with the number 10022015.03.12. All applicants signed the consent form before being recruited into the study.

Conflict of Interest: The authors declare no conflict of interest.

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References

1. Tate MC. Surgery for gliomas. Cancer Treat Res. 2015;163:31-47.
2. Jackson B, De Cruz P. Algorithms to facilitate shared decision-making for the management of mild-to-moderate ulcerative colitis. Expert Rev Gastroenterol Hepatol. 2018;12(11):1079-100.
3. Vera JC, Rosen OM. Functional expression of mammalian glucose transporters in Xenopus laevis oocytes: evidence for cell-dependent insulin sensitivity. Mol Cell Biol. 1989;9(10):4187-95.
4. Roy D, Quiles J, Gaze DC, Collinson P, Kaski JC, Baxter GF. Role of reactive oxygen species on the formation of the novel diagnostic marker ischaemia modified albumin. Heart. 2006;92(1):113-4.
5. Oh BJ, Seo MH, Kim HS. Insignificant role of the N-terminal cobalt-binding site of albumin in the assessment of acute coronary syndrome: discrepancy between the albumin cobalt-binding assay and N-terminal-targeted immunoassay. Biomarkers. 2012;17(5):394-401.
6. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82-
7. Bar-Or D, Winkler JV, Vanbenthuysen K, Harris L, Lau E, Hetzel FW. Reduced albumin-cobalt binding with transient myocardial ischemia after elective percutaneous transluminal coronary angioplasty: a preliminary comparison to creatine kinase-MB, myoglobin, and troponin I. Am Heart J. 2001;141(6):985-91.
8. Yakut I, Tayman C, Oztekin O, Namuslu M, Karaca F, Kosus A. Ischemia-modified albumin may be a novel marker for the diagnosis and follow-up of necrotizing enterocolitis. J Clin Lab Anal. 2014;28(3):170-7.
9. Pavlick KP, Laroux FS, Fuseler J et al. Role of reactive metabolites of oxygen and nitrogen in inflammatory bowel disease. Free Radic Biol Med. 2002;33(3):311-22.
10. Grisham MB. Oxidants and free radicals in inflammatory bowel disease. Lancet. 1994;344(8926):859-61.
11. Erdem SS, Yerlikaya FH, Cicekler H, Gul M. Association between ischemia-modified albumin, homocysteine, vitamin B(12) and folic acid in patients with severe sepsis. Clin Chem Lab Med. 2012;50(8):1417-21.
12. Williams J, Bergmann T. Probable inflammatory bowel disease in a child: assessment and conservative management. J Chiropr Med. 2003;2(4):157-62.
13. Zhu H, Li YR. Oxidative stress and redox signaling mechanisms of inflammatory bowel disease: updated experimental and clinical evidence. Exp Biol Med (Maywood). 2012;237(5):474-80.
14. Ellidag HY, Bulbuller N, Eren E et al. Ischemia-modified albumin: could it be a new oxidative stress biomarker for colorectal carcinoma? Gut Liver. 2013;7(6):675-80.
15. Kaplan M, Yuksel M, Ates I et al. Is ischemia modified albumin a disease activity marker for inflammatory bowel diseases? J Gastroenterol Hepatol. 2016;31(6):1120-5.

16. Gunduz A, Turkmen S, Turedi S et al. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. Acad Emerg Med. 2009;16(6):539-43.
17. Kotur-Stevuljevic J, Memon L, Stefanovic A et al. Correlation of oxidative stress parameters and inflammatory markers in coronary artery disease patients. Clin Biochem. 2007;40(3-4):181-7.
18. Vassalle C, Pratali L, Boni C, Mercuri A, Ndreu R. An oxidative stress score as a combined measure of the pro-oxidant and anti-oxidant counterparts in patients with coronary artery disease. Clin Biochem. 2008;41(14-15):1162-7.
19. Achitei D, Ciobica A, Balan G, Gologan E, Stanciu C, Stefanescu G. Different profile of peripheral antioxidant enzymes and lipid peroxidation in active and non-active inflammatory bowel disease patients. Dig Dis Sci. 2013;58(5):1244-9.
20. Guntas G, Sahin A, Duran S, Kahraman R et al. Evaluation of Ischemia-Modified Albumin in Patients with Inflammatory Bowel Disease. Clin Lab. 2017;63(2):341-7.
21. Balmus IM, Ciobica A, Trifan A, Stanciu C. The implications of oxidative stress and antioxidant therapies in Inflammatory Bowel Disease: Clinical aspects and animal models. Saudi J Gastroentero*l.* 2016;22(1):3-17.
22. Pereira C, Gracio D, Teixeira JP, Magro F. Oxidative Stress and DNA Damage: Implications in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21(10):2403-17.
23. Annese V, Beaugerie L, Egan L et al. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. J Crohns Colitis. 2015;9(11):945-65.
24. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55(3):426-31.
25. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. Am J Gastroenterol. 2015;110(3):444-54.