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CASE CONTROL STUDY

Serum beta 2-microglobulin as a biomarker in inflammatory bowel disease

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Abstract

AIM: To investigate the diagnostic utility of beta 2 microglobulin (B2-M) levels and analyze this correlation with the activity of inflammatory bowel disease (IBD).

METHODS: Overall, 78 IBD patients and 30 healthy controls were enrolled in the study. We examined B2-M serum levels in 43 ulcerative colitis (UC) patients, 35 with Crohn's disease (CD) and 30 control subjects, using an enzymatic method. Patients were divided into two groups according to two disease types: active and in remission. Subjects were also divided into two subgroups according to extent of the disease: left-side and pancolitis for UC and ileitis and ileocolitis for CD. All groups were compared for mean serum B2-M levels and also examined to see whether there was a correlation between serum B2-M levels and other inflammatory markers.

RESULTS: The mean serum B2-M levels in the control group, UC and CD were 1.71, 2.41 and 2.24 respectively. B2-M values $\geqslant$ 1.96 mg/L had a 62% sensitivity, 76% specificity, a 79% positive predictive value, and a 58% negative predictive value for UC patients. B2-M values $\geqslant$ 1.70 mg/L had 80% sensitivity, 53% specificity, 66% positive predictive value, and 69% negative predictive value for CD patients. Mean B2-M values were significantly higher in ulcerative colitis and Crohn's disease patients than in healthy controls (UC 2.41 ± 0.87 *vs* 1.71 ± 0.44, $P = 0.002$; CD 2.24 ± 1.01 *vs* 1.71 ± 0.44, $P = 0.033$). Also, mean B2-M values were significantly higher in active disease when compared to patients in remission (UC 2.66 ± 0.92 *vs* 1.88 ± 0.41, $P = 0.004$; CD 2.50 ± 1.15 *vs* 1.73 ± 0.31, $P = 0.033$). The difference between groups (UC and CD) in terms of serum B2-M levels was statistically insignificant (2.41 ± 0.87 *vs* 2.24 ± 1.01, $P > 0.05$ respectively).

CONCLUSION: Serum B2-M levels may be used as an activity parameter in IBD.

Key words: Beta 2 microglobulin; Ulcerative colitis; Crohn disease; Inflammatory bowel disease

Core tip: Endoscopy has been the gold standard for diagnosing and following patients with inflammatory bowel disease (IBD). However, it is still an expensive and invasive method. Beta 2 microglobulin levels of intestinal inflammation represent an easy, non-invasive, cheap and objective diagnostic biomarker for active IBD.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are characterized by idiopathic and chronic inflammation of the intestinal

tract and consist of ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis. Disease activity in IBD is determined using both direct and non-invasive laboratory markers. However, endoscopic examination is still the gold-standard diagnostic test, even though it is invasive and expensive[1,2]. Laboratory markers such as C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC) and platelet count, albumin, fecal calprotectin and acid glycoprotein (orosomucoid) have been investigated in IBD with different aims including diagnosis, disease activity, response to therapy, and estimate of relapse with a wide range of sensitivity and specificity[3-6]. Unfortunately, an ideal marker for IBD that is easy, cheap, rapid to perform, disease specific, and having prognostic merit against relapse or recurrence of the disease has not yet been identified[7].

Beta 2 microglobulin (B2-M) is a low-molecular-weight protein released by activated T and B lymphocytes. The estimated half-lifetime is short (2 h)[8]. B2-M has been shown to increase in several inflammatory and hematologic disorders, such as systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome, multiple myeloma, lymphoma and leukemia[9-12]. To our knowledge, only a few studies have investigated B2-M in IBD, and the results are conflicting[13-16]. The aim of the present study is to evaluate B2-M levels in patients with UC and CD and to compare their validity with the other tests used in clinical practice.

MATERIALS AND METHODS

Patients

A total of 108 subjects were included in the study. Seventy-eight patients had IBD (43 UC and 35 CD patients). The diagnosis of IBD was based on standard clinical, radiological, endoscopic and histological criteria. All enrolled IBD patients had normal renal function and had no other disease that could influence serum levels of B2-M.

IBD patients and the control group were tested for complete blood count, ESR, CRP and albumin at the time of entry. All IBD patients underwent a total colonoscopic examination. The terminal ileum was also examined in patients with CD. All IBD patients were divided into two groups according to disease activity: either active or in remission. Patients were also divided into two subgroups according to the extent of the disease: left and extensive for UC, or ileitis and ileocolitis for CD. On the initial examination, two patients had proctitis and these were included in the left-sided group for comparison. All groups were compared for mean serum B2M levels.

The extent of UC was classified according to the Montreal classification[17]. Involvement up to the splenic flexure was defined as left-sided colitis, and disease extension to the proximal part of the splenic flexura was defined as extensive UC. Clinical disease activity was evaluated using a modified Truelove-Witts severity index (MTWSI). Clinically active disease was defined as having an estimated MTWSI score of 4 or higher; patients with a score lower than 4 were considered to be in remission (inactive)[18]. The disease activities of CD patients were classified according to the Harvey-Bradshaw index[19].

B2M assay

In the ADVIA 2400 Chemistry B2-M assay, a sample is diluted and reacted with a buffer that contains latex particles coated with an antibody specific for B2-M. The formation of the antibody-antigen complex during the reaction results in an increase in turbidity, the extent of which is measured as the amount of light adsorbed at 545 nm. The B2-M concentration in a sample is determined by constructing a standard curve from the absorbance of a reagent blank and a single-level calibrator. Blood samples were collected from a peripheral vein after an overnight fast and were subjected to centrifugation at the speed of 3000 revolutions per minute for 10 min at 4 ℃, to obtain serum. All blood samples were stored at -20 ℃ immediately after separation from peripheral blood prior to analysis.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 13 software (SPSS Inc., Chicago, IL, United States). Values are presented in the study as mean ± SD. Continuous variables were analyzed using unpaired Student *t* tests or a 1-way analysis of variance. χ^2 analysis was used for categorical variables. The Pearson correlation coefficient was utilized to analyze the correlation between B2-M and other markers. The sensitivity and specificity of B2-M, CRP, ESR and WBC levels for the evaluation of patients were calculated with various cut-off ranges, and the receiver operating characteristic (ROC) curves were drawn. A "*P*" value of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of patients and control subjects are summarized in Table 1. Gender and age were comparable for IBD patients and the control group. The mean serum B2-M levels in the control group, UC and CD were 1.71, 2.41, and 2.24 respectively. Mean B2-M and ESR values were significantly higher in UC and CD patients than in healthy controls. The difference between groups (UC and CD) in terms of serum B2-M, ESR and albumin levels was statistically insignificant. Mean albumin and hemoglobin values were significantly lower in UC and CD patients than controls. Mean CRP and WBC levels were statistically insignificant in comparing patients and controls (Table 1). No correlation was found between B2-M and other inflammation markers for UC patients (CRP: $r = 0.281$, $P = 0.079$, ESR: $r = 0.14$, $P = 0.383$, WBC: $r = 0.222$, $P = 0.162$). However, there was a correlation for B2-M with CRP and ESR for CD patients (CRP: $r = 0.79$, $P = 0.001$, ESR: $r = 0.76$, $P = 0.001$).

Table 1 Demographic characteristics and comparison of serum Beta 2 microglobulin levels with other laboratory markers between patients and controls *n* (%)

	Controls	UC	CD	*P* value	
	n = 30	*n* = 43	*n* = 35		
Mean age	38.90 ± 11.05	42.72 ± 13.52	38.28 ± 13.15	0.254	
Gender (F/M)	18 (60)/12 (40)	17 (40)/26 (60)	19 (54)/16 (46)	0.188	
Duration (yr)		5.04 ± 5.81	4.50 ± 3.70	0.729	
Inactive/active		14 (33)/29 (67)	12 (34)/23 (66)		
Disease location		Left type 29 (67) Extensive 14 (33)	Ileal type 24 (69) Ileocolonic 11 (31)		
B2-M	1.71 ± 0.44	2.41 ± 0.87	2.24 ± 1.01	0.002	UC *vs* C 0.002 CD *vs* C 0.033 UC *vs* CD 0.642
CRP	0.57 ± 0.83	1.82 ± 2.94	1.59 ± 2.79	0.188	
ESR	10.18 ± 11.31	21.21 ± 18.37	22.76 ± 22.81	0.021	UC *vs* C 0.047 CD *vs* C 0.026 UC *vs* CD 0.931
WBC ($\times 10^3$)	7.09 ± 1.75	7.52 ± 2.84	7.48 ± 3.91	0.190	
Albumin	4.43 ± 0.24	4.00 ± 0.62	4.05 ± 0.63	0.005	UC *vs* C 0.006 CD *vs* C 0.023 UC *vs* CD 0.916

Data are expressed as absolute numbers (percentage), mean ± SD or median (interquartile range). UC : Ulcerative colitis; CD : Crohn Disease; F: Female; M: Male; B2-M: Beta 2 microglobulin; CRP: C reactive protein; WBC: White blood count; C: Control; ESR: Erythrocyte sedimentation rate.

Table 2 Overall accuracy and receiver operating characteristic analyses of beta 2 microglobulin and other inflammation markers to differentiate active from inactive ulcerative colitis

	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
B2-M (cut off: 2.02)	0.757	79.3	78.6	88.5	64.7
CRP (cut off: 0.55)	0.731	67.9	75.0	86.4	50.0
WBC ($\times 10^3$) (cut off: 6.50)	0.656	72.4	58.3	80.8	46.7
ESR (cut off: 14.5)	0.677	69.0	58.3	80.0	43.8

AUC: Area under the curve; B2-M: Beta 2 microglobulin; CRP: C reactive protein; WBC: White blood count; ESR: Erythrocyte sedimentation rate; NPV: Negative predictive value; PPV: Positive predictive value.

Table 3 Comparison of serum beta 2 microglobulin levels with other laboratory markers between active and inactive ulcerative colitis patients

	Inactive CD	Active CD	*P* value
	n = 14	*n* = 29	
B2-M	1.88 ± 0.41	2.66 ± 0.92	0.004
CRP	0.41 ± 0.27	2.43 ± 3.34	0.046
ESR	14.00 ± 7.85	24.20 ± 20.65	0.106
WBC ($\times 10^3$)	6.41 ± 1.47	7.96 ± 3.16	0.119
Albumin	3.99 ± 0.50	4.01 ± 0.67	0.948

B2-M: Beta 2 microglobulin; CRP: C reactive protein; WBC: White blood count; ESR: Erythrocyte sedimentation rate.

Table 4 Comparison of serum beta 2 microglobulin levels with other laboratory markers between active and inactive Crohn's disease patients

	Inactive CD	active CD	*P* value
	n = 12	*n* = 23	
B2-M	1.73 ± 0.31	2.50 ± 1.15	0.033
CRP	0.24 ± 0.12	2.23 ± 3.22	0.050
ESR	11.45 ± 11.21	28.17 ± 25.08	0.044
WBC ($\times 10^3$)	7.81 ± 2.28	7.33 ± 4.53	0.742
Albumin	4.50 ± 0.42	3.83 ± 0.60	0.002

CD: Crohn's disease; B2-M: Beta 2 microglobulin: CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; WBC: White blood count.

Ulcerative colitis

B2-M values ⩾ 1.96 mg/L had a 62% sensitivity, 76% specificity, a 79% positive predictive value (PPV), and a 58% negative predictive value (NPV) for UC patients. ROC curve analysis suggested that the optimum B2-M cut-off point for active UC was 2.02 mg/L, with a sensitivity, specificity, PPV, and NPV of 79%, 78%, 88%, and 64% respectively (Table 2). The same analyses for other inflammation markers are summarized in Table 2. Serum B2-M and CRP levels of the active UC patients were significantly higher than those of inactive patients (Table 3). There was not a significant correlation between B2-M levels and other inflammatory markers in patients with UC. Fourteen patients were classified as having pancolitis and 29 patients as having left-sided pancolitis, according to endoscopic examination upon study entry. There was no significant difference between B2-M and UC extension ($P = 0.694$).

Table 5 Overall accuracy and receiver operating characteristic analyses of beta 2 microglobulin and other inflammation markers between active and inactive ulcerative colitis patients

	AUC	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
B2-M (Cut off: 1.84)	0.828	78.3	75.0	85.7	64.3
CRP (Cut off: 0.35)	0.903	78.3	81.8	90.0	64.3
WBC ($\times 10^3$) (Cut off: 6.80)	0.379	47.8	56.5	68.8	33.3
ESR (Cut off: 13.5)	0.761	78.3	72.7	85.7	61.5

AUC: Area under the curve; B2-M: Beta 2 microglobulin; CRP: C reactive protein; WBC: White blood count; ESR: Erythrocyte sedimentation rate; NPV: Negative predictive value; PPV: Positive predictive value.

Crohn's disease

B2-M values ⩾ 1.70 mg/L had 80% sensitivity, 53% specificity, 66% PPV, and 69% NPV for CD patients. Serum B2-M, CRP, and ESR levels of the active CD patients were significantly higher than those of inactive patients (Table 4). ROC curve analysis suggested that the optimum B2-M cutoff point for active CD was 1.84 mg/L, with a sensitivity, specificity, PPV, and NPV of 78%, 75%, 86%, and 64% respectively (Table 5). B2-M levels were correlated with CRP, ESR, PLT, and age in patients with CD, but not with WBC and disease duration. Twelve patients were classified with the ileal type and 23 patients with the ileocolonic type, according to endoscopic examination upon study entry. There was no significant difference between B2-M and CD location ($P = 0.165$).

DISCUSSION

The clinical courses of UC and CD are characterized by exacerbations and remissions, which occur spontaneously or in response to medical treatment[20-23]. Disease flares occur in an indiscriminate way and are mostly unpredictable. Inflammatory markers have been investigated in IBD for diagnosis, disease activity and prediction of relapse. As an inflammatory marker, B2-M has been investigated in patients with IBD in several studies. However, the results were conflicting and not all authors were able to confirm a correlation.

Among the laboratory markers used in IBD practice, CRP is the most studied and the most popular one. It is accepted as a good predictor of disease activity in IBD. However, the CRP assay correlates better for CD than for UC[4,24,25]. Other laboratory markers, including WBC, platelets, albumin, sialic acid, orosomucoid, fibrinogen, lactoferrin and serum amyloid have variable associations with the disease activity of IBD. Similarly, we also detected a positive correlation between CRP and disease activity in the present study.

A recent study by Zissis *et al*[13] investigated B2-M serum levels in 87 UC patients, 74 with CD and 68 healthy control subjects. Twenty two (90%) of the severe CD patients were found to have elevated serum B2-M levels. B2-M levels were significantly higher in all CD patients. However, such a correlation could not be assessed in UC patients. The researchers claimed that B2-M serum levels could prove to be a useful marker in assessing the activity, severity, extent of CD, and treatment efficacy.

To investigate the clinical significance of B2-M in other inflammatory diseases, Kim *et al*[26] searched for B2-M in the serum of 100 SLE patients and found a positive correlation between B2-M serum levels and disease activity. Aygündüz *et al*[27] investigated the relative efficiency of B2-M levels as a marker of disease activity in 43 patients with Behçet's disease. In that study, serum B2-M levels could be regarded as a discriminative marker of activation in Behçet's disease.

Searching Pubmed for relevant studies, we did not find a positive correlation between B2-M serum levels and UC activity. In the present study, we demonstrated that active IBD patients had elevated serum B2-M levels in comparison with inactive patients and the control group. Serum B2-M activity had higher sensitivity, specificity, and predictive values in active IBD patients. Increased B2-M activity in patients with active IBD may support the role of activated macrophages and T-lymphocytes in the disease pathophysiology.

In summary, our study demonstrates that in patients with IBD, serum B2-M level is associated with active disease. B2-M level may be considered a useful marker of IBD and could be a potential indicator of disease activation. B2-M serum level provides additional data to supplement existing markers such as CRP and ESR.

COMMENTS

Background

There are controversies regarding the role of beta 2 microglobulin (B2-M) in inflammatory bowel disease (IBD). In this study we examined B2-M serum levels in patients suffering from the disease to assess its extent, and the possible correlation between serum levels and disease activity.

Research frontier

There is currently increasing interest in research focused on new, more effective, non-invasive biochemical markers for evaluating endoscopic activity in patients with IBD. This study analyzes the association between B2-M levels and disease activity in IBD patients.

Innovations and breakthroughs

This was an original study assessing the relationship between B2-M level and activity of IBD. This question was not described thoroughly enough in the medical literature.

Applications

These findings suggest that B2-M can be used as surrogate marker for activity in IBD patients. B2-M is a simple, inexpensive and objective tool for the assessment of mucosal inflammation.

Terminology

Clinical IBD activity is difficult to assess objectively because of several subjective components. Serum B2-M levels are elevated in diseases associated with increased cell turnover, and they are also elevated in several benign condition such as chronic inflammation.

Peer review

This manuscript contains potentially interesting observations, and should be received for publication.

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