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Serum Beta 2-Microglobulin as a Biomarker of Activity in Ulcerative Colitis

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ABSTRACT

Background: ulcerative colitis (UC) is a chronic, idiopathic, inflammatory bowel disease that causes inflammation and ulcers in the innermost layers of the large intestine (colon) and rectum. Assessment of intestinal inflammation in UC is crucial and still remains a difficult challenge for the clinician. Although endoscopic modalities with biopsy sampling seem to be the most reliable method for estimating disease severity, they are invasive and costly. Apart from endoscopic interventions, disease severity can be assessed using both laboratory studies and non-invasive imaging tests. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBCs), acid glycoprotein, platelet count and albumin are in common use but have only modest accuracy in reflecting UC disease activity. Therefore, adjunctive use of additional serum markers that will be more sensitive and specific for determination of disease activity and achieving diagnostic accuracy is strongly needed in daily clinical practice. **Aim of the Work:** to investigate the diagnostic utility of beta 2 microglobulin (B2-M) levels and analyze this correlation with the activity of ulcerative colitis disease. **Patients and Methods:** a case control study that was conducted at the Gastroenterology Clinic, Internal Medicine Department, Ain Shams University during the period of January to July 2018. 60 patients were recruited for the study. They were divided as follows; Group "A": 40 patients newly diagnosed as ulcerative colitis based on colonoscopy and biopsy, subdivided as follows; 20 patients with active ulcerative colitis and 20 patients with inactive ulcerative colitis. Group "B": 20 healthy individuals free from any systemic diseases serving as a control group. **Results:** in this study, the serum levels of serum B2-microglobulins were highest in patients with active ulcerative colitis compared to those with inactive ulcerative colitis and the control groups. Also B2-microglobulins values become higher with higher number of presenting symptoms and endoscopic activity, which becomes higher in severe disease. **Conclusion:** our results revealed that serum B2-microglobulin was simple and non-invasive marker that could be helpful for differentiating active UC from inactive disease. Moreover, it was more helpful when used together with serum laboratory inflammatory indices (ESR and CRP).

Keywords: Serum Bet2-Microglobulins, Ulcerative Colitis, ESR, CRP, Endoscopy.

INTRODUCTION

Ulcerative colitis is characterized by idiopathic and chronic inflammation of the intestinal tract. Disease activity of ulcerative colitis 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)]. Laboratory markers such as C reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood count (WBC) and platelet count 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 [(2)]**.** Beta 2 microglobulin (B2-M) is a low-molecular-weight protein released by activated T and B lymphocytes. The estimated half-lifetime is short. 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 [(3)] **.** 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 elevated in several benign condition such as chronic inflammation.

AIM OF THE WORK

To investigate the diagnostic utility of beta 2 microglobulin (B2-M) levels and analyze this correlation with the activity of ulcerative colitis disease.

PATIENTS AND METHODS

1-Patients: A case control study that was conducted at the Gastroenterology Clinic, Internal Medicine Department, Ain Shams University during the period of January to July 2018. **The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.** 60 patients were recruited for the study. They were divided as follows; Group A: 40 patients newly diagnosed as ulcerative colitis based

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on colonoscopy and biopsy, subdivided as follows; a. 20 patients with active ulcerative colitis, b. 20 patients with inactive ulcerative colitis. Group B: 20 healthy individuals free from any systemic diseases serving as a control group. **2- Methods: All subjects and controls were subjected to:** -Detailed medical history, - Full clinical and abdominal examination with assessment of disease activity according to modified Truelove-Witts severity index (MTWSI). **Laboratory investigations:** 1) Complete blood count (CBC) with differential count by automated count technology, 2) Erythrocyte sedimentation rate (ESR): Estimation will be done by the Westregren method recorded in mm/hour .the reading of the first hour will be taken, 3) C-reactive protein(CRP): using fully automated ELISA, 4) Serum B 2-microglobulin:using fully automated ELISA , 2 samples will be drawn ,one in patient with disease activity and the other one will be drawn after induction of remission one month apart in the same patient. 5) Colonoscopy with biopsy. ***Sample preparation***: Specimen was allowed to clot completely at room temperature. serum or plasma from cells ASAP was separated within 2 hours of collection. 1 mL s plasma was transferred to an ARUP Standard Transport Tube. (Min: 0.3 mL). ***Statistical Calculation of results:*** Data were analyzed using IBM SPSS (Statistical Package of Social Sciences) version 23, USA. Normality of numerical data distribution was examined using the Shapiro-Wilk test. Non-Normally distributed numerical data were presented as median and interquartile and intergroup differences were compared using the Wlicoxon rank sum test (for two-group comparison) or the Jonckheere-Terpstra trend test. The Conover post hoc test was used for post hoc comparison with application of the Bonferroni correction whenever the Jonckheere-Terpstra test showed statistically significant difference among the groups. Categorical data were presented as number and percentage or ratio and differences that were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Receiver-operating characteristic (ROC) curve analysis was used to examine the diagnostic value of serum b2-miroglobulin . The area under the ROC curve (AUC) was interpreted as follows:

Table (1): Area under the ROC curve interpretation

Area under ROC curve (AUC)	Diagnostic / predictive value
0.9 – 1.0	Excellent
0.8 – 0.89	Good
0.7 –0.79	Fair
0.6 –0 .69	Poor
<0.6	Fail

RESULTS

The results obtained from the study were as follow:

Table (2) Comparison of serum B2-microglobulins level between active IBD, inactive IBD and control groups

Groups	B2-microglobulins					ANOVA	
	Range			Mean	± SD	F	P-value
Active IBD	2	-	5.7	4.275	± 0.965	60.779	<0.001*
Inactive IBD	0.8	-	3.8	2.530	± 0.890		
Control	1.3	-	2.1	1.630	± 0.252		
TUKEY'S Test							
A&I				**A&C**		**I&C**	
<0.001*				<0.001*		0.001*	

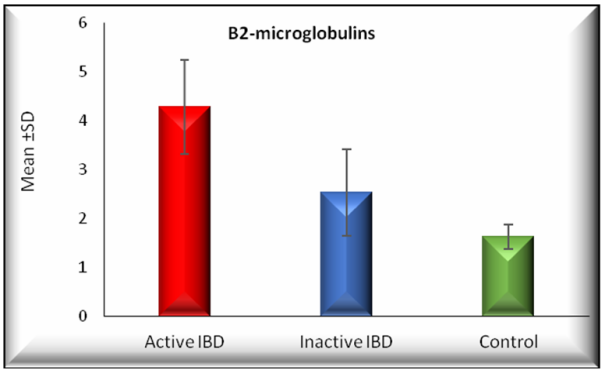

Figure (1): There was statistical significant difference as regards serum B2-microglobulin level between active, inactive UC patients and control group, which became higher in active UC.

Table (3): Comparison between serum Beta2-microglobulins levels as regard presenting symptoms and disease involvement

Presenting symptom	**One symptoms**	9	4.667 ± 0.618	5.549	0.008*	
	Two symptoms	6	4.467 ± 0.273			
	Three symptoms	4	2.950 ± 1.320			
	Four symptoms	1	4.900 ± 0.000			
Disease involvement	**Proctosigmoid**	6	3.817 ± 1.102	2.114	0.151	
	Left sided	6	4.067 ± 1.044			
	Extensive	8	4.775 ± 0.614			

There was statistical significant difference as regards serum B2-microglobulin level and number of presenting symptoms, which became higher with higher number of presenting symptoms. In addition, there was statistical significant difference as regards serum B2-microglobulin level and endoscopic activity (mild, moderate and severe) which became higher in severe disease.

Table (4): The cut-off point of different inflammatory markers based on comparison between different groups of activity

ROC curve between Cases and Control						
	Cutoff	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
B2-microglobulins (mg/l)	>1.9	92.50	90.00	94.9	85.7	91.4%
ESR mm/ hour	>16	77.50	95.00	96.9	67.9	93.9%
CRP (mg/dL)	>1	85.00	80.00	89.5	72.7	91.4%

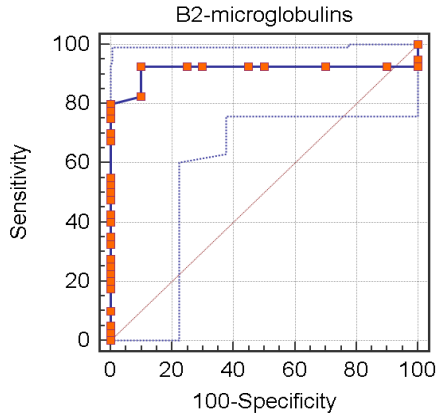

Figure (2): As regard B2_microglobulins, the cut off value for determining active disease was 1.9 mg/l with sensitivity 92.5% & specificity 90 %.

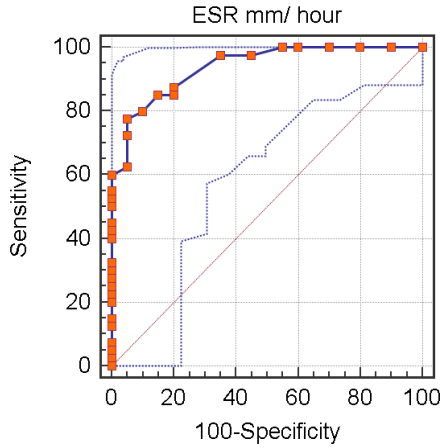

Figure (3): As regards ESR, the cut off value for determining the presence of the disease was 16 mm/h with sensitivity 77.5 % & specificity 95 %.

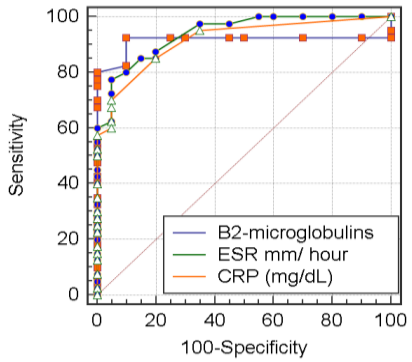

Figure (5): As regards CRP, the cut off value for determining active disease was 1 mg /dl with sensitivity 85 % & specificity 80 %.

DISCUSSION

In our study, results demonstrated that the serum b2-microglobulins was higher in patients with active UC compared with inactive UC patients and controls with mean value of 2.69 ± 0.48, 1.63 ± 0.25, 1.43 ± 0.19 respectively. The cut-off value of 1.9mg/l indicating the presence of active disease, with a sensitivity of 92% and a specificity of 90%. Our cut off value for determining active disease is out of the range mentioned by the studies. This could be due to our small sample size, which will need further investigations with a larger sample. After adjusting for the other inflammatory markers (WBCs, ESR, and CRP. Our results were in line with **zissis and colleagues** who conducted retrospective study, which included 87 UC patients with active disease, 47 patients inactive UC (who had not received corticosteroid or immunosuppressive drugs within a defined period of time) and gender matched healthy subjects as the control group. In the active UC group, serum B2-microglobulins values were found to be elevated compared to inactive UC patients and controls (3.22 ± 1.29, 1.84 ± 0.69 and 2.01 ± 0.64, respectively). Using ROC statistics, a cut-off value of 2.16 indicated the presence of active disease with a sensitivity of 81.8% and a specificity of 80.5% (positive predictive value [PPV] 86.8%, negative predictive value [NPV] 73.8%). Serum B2-microglobulin values were found to be correlated with WBC and ESR levels. Also, there was statistical insignificance as regard serum b2-microglobulins between proctosigmoid & left side colon, and between pancolitis patients. The mean of proctosigmoid and left side colon was 3.817 ± 1.12 compared to pan colitis 4.7 ± 0.55 with p-value of

0.15. However in contrast to our study, they found significant difference between inflammation parameters, disease extension, and disease activity[(4)]. As regard comparing the ratios and endoscopic disease activity in active disease, there was statistical significance in serum beta 2-microcglobulins. For determining disease activity as mild, moderate and severe, with the mean for them 4.35, 4.23 and 2.4 respectively, with p-value of 0.0005. **Zissis and colleagues** found significant difference between serum B2-microglobuins and endoscopic disease activity in active disease[(5)]. In our study, also there was statistical significance as regard serum b2-microglobulins and number of presenting symptoms with mean values of one symptom 4.667 ± 0.618, two symptoms 4.467 ± 0.273, three symptoms 2.950 ± 1.320 and four symptoms 4.900 ± 0.000 with p value less than 0.008. In current daily practice, the most commonly used noninvasive serum biomarkers to assess active disease are ESR and CRP[(6)]. The limited correlation of ESR and CRP with endoscopic activity was also reported by several other studies [(5)].However, looking at clinical disease activity, our results were found to have similar to slightly higher sensitivities and specificities compared with ESR and CRP with the benefit of being more common, readily available, having a lower cost , more safe [(7)] and for prognosis after treatment[(8)]. We reported an elevation of serum beta 2-microglobulins in clinically and endoscopically active UC. Serum beta 2-micro globulins are promising biomarkers in UC. They can add to the other tools that clinicians use in daily practice. They offer the advantage of being routinely available, rapidly obtained. Future work to prospectively assess these biomarkers is needed.

CONCLUSION

Our results revealed that serum B2-micro globulin was simple and non-invasive marker that can be helpful for differentiating active UC from inactive disease. In addition, it was more helpful when used together with serum laboratory inflammatory indices (ESR and CRP).

CONFLICTS OF INTEREST

There are no conflicts of interest.

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