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Research Article

Long Pentraxin PTX 3 and Faecal Calprotectin as a Non Invasive Biomarkers for Ulcerative Colitis

Abstract

Background and Study Aims: as there is no single golden rule for the diagnosis and activity of ulcerative colitis disease, this study is going to discuss the clinical relevance of calprotectin and PTX 3 in cases of ulcerative colitis and their roles as non-invasive methods to diagnose UC and determine disease activity.

Patients and Methods: Patients were classified into two groups; group 1 include 40 patients of different phases of activity of UC. Group 2 included 20 healthy volunteers as a Controls. Measurement of feacal calprotectin by using the ELISA (enzyme-linked immunosorbent assay) kit. Measurement of serum Pentraxin3 (PTX 3) by enzyme-linked immunosorbent assay (ELISA).

Results: PTX 3 levels were significantly different between mild, moderate and sever patients with UC which the same as calprotectin level. Moreover, PTX 3 was significantly increased more than calprotectin in mild and severe UC patients.

Conclusions: PTX 3 is directly produced from the inflamed gut in UC. Plasma PTX 3 concentration is thought to be a useful marker for understanding the disease activity in patients with UC. PTX 3 was found to be more sensitive and specific than faecal calprotectin as a marker for inflammation and disease activity in UC.

Introduction

Ulcerative colitis (UC), one of the inflammatory bowel diseases (IBD), is characterized by recurring episodes of inflammation of the mucosal layer of the large bowel not related to an intestinal infection or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) [1].

The cause of UC is still unknown, however, many etiologies have been postulated and studied [2]. There is no single rule model for the diagnosis of UC, however the diagnosis is confirmed by clinical evaluation and a cooperation among endoscopy, histology, radiology, and/or biochemistry [3].

Traditional colonoscopic picture of UC is usually limited to the rectum and may involves part of or the colon. Normal mucosa may begin anywhere from the rectum to the caecum .The mucosa may be hyperemic or nodular .Erosions and ulcerations maybe seen with blood, pus or mucus may overlie the mucosa [4].

On microscopic examination, UC is not a transmural process and inflammation remains limited to the mucosa. On the other hand the submucosa, muscularis propria and serosa remain normal [5].

If there is no gastrointestinal infection, faecal markers of inflammation seems to be more specific for IBD than serological markers. Calprotectin one of these fecal markers, was first isolated from granulocytes in 1980 [6].

It is a calcium-binding neutrophil protein and remains unchanged during intestinal transit, so it is considered a sensitive biomarker of bowel inflammation [7].

Pentraxin 3 (PTX 3) is known as tumor necrosis factor-stimulated gene 14 (TSG-14). It belongs to the pentraxin super family of multifunctional conserved proteins [8] that are involved in the acute immunological responses [9]. The pentraxins are divided into short pentraxins (e.g., CRP, serum amyloid P) and long pentraxins [10].

Not as CRP which is produced by hepatocytes, PTX 3 is produced by innate immunity and endothelial cells in response to inflammatory cytokine [11].

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PTX 3 has been suggested as a rapid disease activity biomarker for primary local inflammation [12]. PTX 3 levels are an independent biomarker of disease activity produced at the site of inflammation because of their extrahepatic synthesis. PTX 3 activates complement and innate immunity and playing an essential rule in tissue and vascular inflammation [13-15].

Aim of the work

The aim of this study is to assess the increased level of PTX 3 and faecal calprotectin to be used as a non-invasive investigations for diagnosis and assessment of disease activity in UC (Figure 1).

Patients and Methods

The patients of this study were retrieved from gastroenterology outpatient clinic at initial presentation, or UC patients scheduled for follow up from GIT endoscopy unit of the Internal Medicine Department in a University Hospital. At the period from January 2015 to January 2016.

Patients divided into two groups; 40 patients in group 1 of different phases of activity of UC. Group 2 included 20 healthy volunteers as a Controls.

Inclusion criteria were as the following; for group 1; patients were diagnosed with colonoscopy, biopsies underwent histopathological examination confirmed the diagnosis. In group 2, this study included 20 volunteers of matched age and sex with no history suggested of IBD and their colonoscopy examination confirmed the absence of a disease.

Exclusion criteria were: patients with chronic renal failure, acute or chronic heart disease, liver diseases, rheumatoid arthritis, Crohn's disease, colorectal carcinoma and pregnant females.

All patients were subjected to a history and clinical examination with special emphasis on signs of malnutrition or dehydration, abdominal examination (tenderness or abdominal masses) and extra intestinal manifestations of U.C. Investigations included, laboratory Investigations (complete blood picture, blood urea, serum creatinine, serum albumin, alanine aminotransferase, aspartate aminotransferase, quantitative CRR and ESR) and endoscopic examination namely colonoscopy with mucosal biopsies and assessment of disease extension and activity using Baron Score [16].

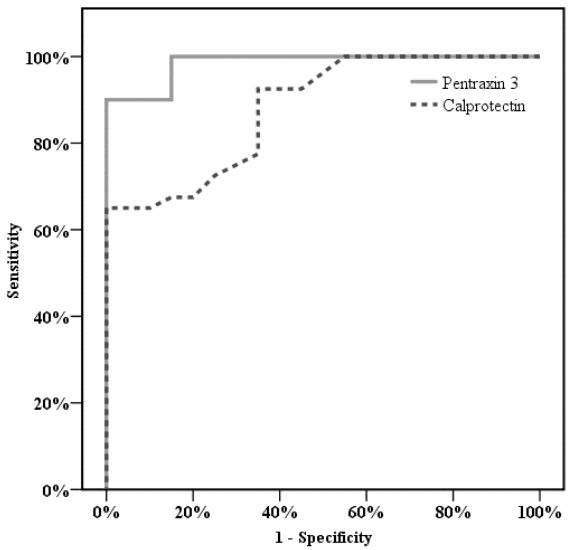

Figure 1: ROC curve for PTX 3 and Calprotectin to diagnose patient.

Measurement of feacal calprotectin by using the ELISA (enzyme-linked immunosorbent assay) kit which is intended for the quantitative determination of feacal calprotectin (neutrophil cytoplasmic protein A100AB/AG) concentration based on sandwich principle [17].

Measurement of serum PTX 3 by enzyme-linked immunosorbent assay (ELISA) [18].

Assay principle

The OmniKine™ Human PTX 3 ELISA Kit contains the components necessary for quantitative determination of natural or recombinant hPentraxin-3 concentrations within any experimental sample including cell lysates, serum and plasma. This particular immunoassay utilizes the quantitative technique of a "sandwich" enzyme-linked immunosorbent assay (ELISA).

An informed consent was taken from all patients and controls. The ethics research committee, at authors' faculty of medicine, has approved conduction of this study.

Statistical analysis

The collected data were organized, tabulated and statistically analyzed using Statistical Package for the Social Sciences software (SPSS, version 13, SPSS Inc. Chicago, IL, USA).

Results

The present study included 40 patients with UC during different phases of activity, also, 20 healthy persons as a control group were included. In group 1 males were 25 (62.5%) and females were 15 (37.5%) with a mean age of 28.55 ±7.72. However, in group 2, males were 15 (75.00%) and females were 5 (25.0%) with a mean age of 30.80 ±6.68 years. There were no statistical significant differences between the two studied groups regarding the age or sex.

In table 1, there was significant decrease in Hb value (8.45 ± 1.0 mg/dl) for UC patients compared to the control group (13.17 ± 0.94mg/dl). White blood cell count for UC patients was significantly higher than the control group (8.25±2.23, 7.39 ±1.52 × 103 cell/mm3) respectively. ESR1 level for UC was (19.02 ± 9.33 mm/hr) which was significantly higher than the control group (8. 25 ± 1.25mm/hr. CRP level for UC was significantly higher (12.65 ± 6.68 mg/l) than control group (3.75 ± 2.0 mg/l). SGPT level for UC patients was significantly higher than the control group (41.0 ± 8.66, 22.40±2.21 IU/L) respectively. Serum albumin was significantly lower in UC patients than

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Table 1: Laboratory data of the studied population.

	Patients (n=40)	Control (n=20)	T test	P value
Hb (g/dl)				
Min. – Max.	6.0 – 10.0	12.0 – 15.0		<0.001*
Mean ± SD.	8.45 ± 1.0	13.17 ± 0.94	17.621*	
Median	8.65	12.95		
PLT (× 10^3 /cmm)				
Min. – Max.	200.0 – 400.0	150.0 ± 350.0		
Mean ± SD.	280.90 ± 51.44	267.20 ± 63.94	0.896	0.374
Median	274	281.5		
RBCs (×106/cmm)				
Min. – Max.	2.90 – 4.20	4.50 – 5.30		
Mean ± SD.	3.59 ± 0.37	4.90 ± 0.28	13.913*	<0.001*
Median	3.6	5		
WBCs (×103/cmm)				
Min. – Max.	5.40 – 14.0	6.10 – 9.70		
Mean ± SD.	8.25 ± 2.23	7.39 ± 1.52	2.053*	0.05*
Median	8.65	6.3		
CRP(mg/l)				
Min. – Max.			Z- test	P value
Mean ± SD.				
Median	6.0 – 27.0	1.0 – 7.0		
	12.65 ± 6.68	3.75 ± 2.0	5.818*	<0.001*
	10	3		
ESR 1(mm/h)				
Min. – Max.	10.0 – 42.0	6.0 – 10.0		
Mean ± SD.	19.02 ± 9.33	8.25 ± 1.25	5.913*	<0.001*
Median	15	8		
ESR 2(mm/h)				
Min. – Max.	20.0 – 60.0	10.0 – 20.0		
Mean ± SD.	32.63 ± 10.67	15.0 ± 4.68	6.182*	<0.001*
Median	35	13.5		
SGPT(IU/L)				
Min. – Max.			T- test	P value
Mean ± SD.				
Median	30.0 – 60.0	20.0 – 28.0		
	41.0 ± 8.66	22.40 ± 2.21	12.771*	<0.001*
	37.5	22		
SGOT(IU/L)				
Min. – Max.	29.0 – 65.0	22.0 – 35.0		
Mean ± SD.	44.80 ± 10.66	27.65 ± 4.73	8.618*	<0.001*
Median	43	28		
Albumin(mg/l)				
Min. – Max.	20.0 – 31.0	35.0 – 40.0		<0.001*
Mean ± SD.	26.68 ± 3.18	36.95 ± 1.70	16.294*	
Median	28	36.5		
Creatinine(mg/dl)				
Min. – Max.	0.80 – 2.10	0.60 – 1.20		
Mean ± SD.	1.46 ± 0.49	0.86 ± 0.22	4.415*	<0.001*
Median	1.45	0.8		
Blood Urea(mg/dl)				
Min. – Max.	16.0 – 50.0	15.0 – 22.0		
Mean ± SD.	28.43 ± 12.90	16.80 ± 2.07	4.478*	<0.001*
Median	20	16		

Z: Z for Mann Whitney test
*: Statistically significant at p ≤ 0.05

the control group (26.68 ±3.18, 36.95±1.70 mg/l) respectively. Creatinine level was significantly higher in UC patients than control group (1.46 ± 0.49, 0.86 ±0.22 mg/dl) respectively.

In table 2, faecal calprotectin was significantly higher in UC patients (229.93 ± 279.37) compared to controls (35.40 ± 12.46 mg/kg) p value<0.001. PTX 3 was significantly higher in UC patients (5612.8 ± 640.41) compared to the control group (553.8 ± 113.6 pg/ml) p value<0.001.

In Table 3, a positive correlations were positive and statistically different regarding WBCS, SGOT, SGPT, Creatinine, urea, CRP and ESR but were negative with statistical difference in serum albumin for both PTX 3 and fecal calprotectin.

It was noticed in table 4, 5 that PTX 3 levels were significantly different between mild, moderate and sever patients with UC which the same as calprotectin level. Moreover, PTX 3 was significantly increased more than calprotectin in mild and severe UC patients.

	AUC	p
Pentraxin 3	0.985*	<0.001
Calprotectin	0.881*	<0.001

Discussion

Faecal calprotectin which is a faecal marker of inflammation seems to be more specific for IBD in absence of enteric infection than serological markers. It is a calcium-binding neutrophil protein and is stable during intestinal transit, it is a sensitive marker of bowel inflammation which correlate with relapse of quiescent disease [6].

PTX 3 is rapidly released at sites of inflammation, in response to primary inflammatory signals as tumor necrosis factor α (TNFα) and interleukin IL-1β by mononuclear phagocytes, endothelial cells, dendritic cells, and smooth muscle cells [19].

PTX 3 playing a role in complement activation, pathogen recognition by phagocytes and apoptotic cell clearance [20].

PTX 3 is stored in a ready-made form in neutrophils inside granules and is released in response to recognition of pathogens and inflammatory signals, whereas released PTX 3 can partially localize in neutrophil extracellular traps (NETs) [21].

This study is going to discuss the clinical relevance of calprotectin and PTX 3 in cases of ulcerative colitis and their roles as non-invasive methods to diagnose UC and determine disease activity.

In the present study, male patients were about 62.5% in (ulcerative colitis), and 75% in control group with the mean age of ulcerative colitis was 28.55 ± 7.72 and in healthy controls was 30.80± 6.68 years, with no significant difference in between the two studied groups as regard age or sex .

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It was important to say that diarrhea or bloody diarrhea and abdominal pain were the predominant gastrointestinal symptoms of UC among patients of this study.

Regarding laboratory data there was significant difference between patients and controls in the mean hemoglobin level. The patients' values appear to be lower than those of control. Gasche et al. [22], mentioned that one third of IBD patients have hemoglobin levels below 12g/dl. Wilson et al. [23], reported similar data that patients with long lasting inflammation in IBD are often anaemic, and this was related to the inflammatory activity in their patients. The mean WBC count for (UC) patients have significantly higher values than controls. Mpofu et al. [24], reported that moderately elevated leukocytic count is indicative of disease activity.

In the current study, the mean erythrocyte sedimentation rate (ESR1) level appears to be higher in UC cases than controls and there was significant statistical difference between the two studied groups. A study of Desai et al. [7], reported that ESR is an indirect measurement of plasma acute phase protein concentration and is influenced by the morphology of erythrocytes as well as some plasma constituents as immunoglobulins. In addition, Shine and Colleagues [25] reported that ESR proved to be the second best marker after CRP for IBD activity.

In the present study, the mean CRP level was significantly higher in patients than control group. In a recent study by Solem et al. [26], In UC patients, elevation of serum CRP level was significantly associated with severe clinical activity and active disease at colonoscopy and there was a good correlation between CRP and other biomarkers of inflammation.

This study reveals that albumin is significantly lower in cases than controls. Vermeire et al. [27], mentioned that decreased serum albumin level may be found during active inflammation. However, other conditions such as malnutrition and malabsorption also cause low serum albumin levels.

Regarding liver enzymes (SGOT, SGPT) there was statistical differences between UC group and control group. Wieser V et al. [28], mentioned that liver complications are observed

Table 2: Comparison between both studied groups regarding calprotectin and Pentraxin 3.

	Patients (n=40)	Control (n=20)	Z	P value
Calprotectin(mg/kg)				
Min. – Max.	38.0 – 900.0	10.0 – 49.0		
Mean ± SD.	229.93 ± 279.37	35.40 ± 12.46	4.779*	**<0.001***
Median	57.5	38		
Pentraxin 3(pg/ml)				
Min. – Max.	680.0 – 20000.0	400.0 – 750.0		
Mean ± SD.	5612.8 ± 640.41	553.8 ± 113.6	6.089*	**<0.001***

Z: Z for Mann Whitney test
*: Statistically significant at p ≤ 0.05

Table 3: Correlation between pentraxin 3 and calprotectin with different studied parameters in patients group.

	Pentraxin 3		Calprotectin	
	rs	p	rs	p
HB	-0.155	0.340	-0.070	0.669
RBCs (×106)	0.160	0.325	0.111	0.497
PLT (×103)	-0.108	0.507	-0.055	0.737
WBCs (×103)	0.672*	<0.001	0.578*	<0.001
SGPT	0.680*	<0.001	0.654*	<0.001
SGOT	0.663*	<0.001	0.585*	<0.001
Creatinine	0.725*	<0.001	0.822*	<0.001
Blood Urea	0.866*	<0.001	0.875*	<0.001
Albumin	-0.619*	<0.001	-0.683*	<0.001
CRP	0.905*	<0.001	0.857*	<0.001
ESR 1	0.730*	<0.001	0.771*	<0.001
ESR 2	0.627*	<0.001	0.698*	<0.001

rs: Spearman coefficient
*: Statistically significant at p ≤ 0.05

Table 4: Correlation between Endoscopic findings with pentraxin 3 and Faecal calprotectin in patients group.

	Endoscopic findings			KWx2	p
	Baron score 1 (n = 24)	Baron score 2 (n = 6)	Baron score 3 (n = 6)		
Pentraxin 3					
Min. – Max.	680.0 – 2350.0	3900.0 – 12800.0	15400.0 – 20000.0	29.955*	<0.001*
Mean ± SD.	1587.92 ± 559.77	7420.0 ± 3777.14	18700.0 ± 1720.47		
Median	1625.0	4850.0	19200.0		
Sig. bet. stages	p1<0.001*, p2 <0.001*, p3= 0.001*				
rs(p)	0.876* (<0.001*)				
Calprotectin					
Min. – Max.	38.0 – 60.0	176.0 – 500.0	700.0 – 900.0	29.913*	<0.001*
Mean ± SD.	47.96 ± 7.52	324.60 ± 136.72	800.0 ± 89.44		
Median	45.0	275.0	800.0		
Sig. bet. stages	p1<0.001*, p2 <0.001*, p3= 0.001*				
rs(p)	0.876* (<0.001*)				
	P4<0.0001*	P5<0.1926	P6<0.0001*		

KWx2: Chi square for Kruskal Wallis test
p1: p value for Mann Whitney test for comparing between mild and moderate
p2: p value for Mann Whitney test for comparing between mild and severe
p3: p value for Mann Whitney test for comparing between moderate and severe
p4: p value for Mann Whitney test for comparing between PTX 3 and Calprotectin in mild cases
p3: p value for Mann Whitney test for comparing between PTX 3 and Calprotectin in moderate cases
p3: p p value for Mann Whitney test for comparing between PTX 3 and Calprotectin in severe cases
rs: Spearman coefficient
*: Statistically significant at p ≤ 0.05

Table 5: Agreement (sensitivity, specificity and accuracy) for pentraxin 3 and faecal calprotectin.

	Cut off Value	Sensitivity	Specificity	PPV	NPV	Accuracy
Pentraxin 3	**>750**	90.0	85.0	92.31	80.95	88.33
Calprotectin	**>49**	72.50	65.0	75.29	57.69	69.33

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in 10.20% of IBD patients and they mentioned that primary sclerosing cholangitis (PSC), drug induced hepatotoxicity and non- alcoholic fatty liver disease (NAFLD) are the most frequent liver complications in IBD.

Concerning faecal calprotectin, it was significantly higher in UC patients than that for control group. Schoepfer et al. [29] , found that calprotectin levels can be used in discriminating irritable bowel syndrome from organic diseases of the colon, especially inflammatory bowel disease. They also reported that calprotectin levels were significantly higher in the group with moderate to severe endoscopic activity. Xiang et al. [30], conducted a similar study and found faecal calprotectin concentrations were significantly higher in the patients with active UC than in the patients with inactive UC and in the controls. In addition, they showed that faecal calprotectin concentration had a significant correlation with Mayo Score / Disease Activity Index (DAI) for Ulcerative Colitis which is the mostly commonly used assessment tool to help evaluate symptom severity and response to treatment and these findings were consistent with the results of the present study.

Regarding serum pentraxin 3 levels there was significant difference between the UC group and the control group. Kato et al. [31], mentioned that plasma pentraxin3 (PTX 3) levels were significantly higher in patients with UC than in normal subjects.

Correlations of clinical disease activities with PTX 3 concentrations in patients with UC were shown to be statistically significant by spearman's rank correlation tests. This was in agreement of previous studies. Jaillon S et al. [32], studied PTX 3 expression in neutrophils. They showed that colonization of PTX 3 with lactoferrin granules that are rapidly released upon stimulation and associated with Neutrophils generate NETs. Lactoferrin serves as an intrinsic inhibitor of NETs release into the circulation. Mitasuyamak et al. [33], and Waugh DJJ et al . [34], mentioned that IL8 plays an important role as a major neutrophil chemo attractant and activating substance, and it correlated with the degree of neutrophil infiltration of the colonic tissue of patients with UC.

Savchenko et al. [35], studied the mechanism of PTX 3 expression in neutrophils under stimulation. They found that medium increase of PTX 3 was significant in the presence of IL8.

In this study, a positive statistically significant correlation between both biomarkers PTX 3 and faecal calprotectin and the activity of UC, thus we can use each of them as marker for follow up of activity of the disease non-invasively without the need of endoscopy.

Moreover, these results revealed that PTX 3 is more sensitive, specific and accurate than faecal calprotectin. Increased level of faecal calprotectin is not specific for IBD, as any inflammation inside the gastrointestinal tract will result in the release of calprotectin. Faecal calprotectin has been shown in studies to be elevated in many conditions including infection, colorectal cancer, coeliac disease, microscopic colitis and diverticulitis [36,17].

PTX 3 is released from inflamed tissues in response to IL1, TNF-a and lipopolysaccharide (LPS) [37,38]. The plasma PTX 3 maximum level achieved within 12 hours [39]. These findings may indicate that PTX 3 is a good diagnostic biomarker for disease activity in patients with UC.

In conclusion, PTX 3 is directly produced from the inflamed gut in UC. Plasma PTX 3 concentration is thought to be a useful biomarker for understanding the disease activity in patients with UC. PTX 3 was found to be more sensitive and specific than faecal calprotectin as a biomarker for inflammation and disease activity in UC.

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