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Non-invasive Tests as an Indicator of IBD Activity and Severity

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic inflammatory and destructive disease of the gastrointestinal tract. Chronic inflammation causes ulcerations, stricture formations, and perforations and is a risk factor for dysplasia and cancer. To reduce these longstanding complications, the current treatment goal for patients with IBD is mucosal healing. A treat-to-target approach and close monitoring of disease status improve the outcomes for these patients. The cornerstone and gold standard for monitoring patients with inflammatory bowel disease is endoscopy, which is time consuming, expensive, and invasive. In addition, pre-procedural bowel cleansing is uncomfortable and inconvenient. Serological biomarkers, such as ESR, CRP, fecal calprotectin have been widely used as noninvasive parameters for inflammatory bowel disease. in our study we compare the inflammatory bowel disease activity according to Montreal classification which depend upon endoscopy to the level of serological markers as (FC and ESR, Platelet, Total protein, HB level and Albumin) which can be used instead of endoscopy as a marker of activity and the initial level of FC as an Predictor of dysplasia in Ulcerative patient.

Aim: The aim of the study is to (a) determine the mean level of Fecal Calprotectin (FC) at the time of diagnosis and in remission (b) determine the laboratory markers which correlate to IBD activity (c) correlate the initial level of FC as one of predictors for occurrences of early dysplasia.

Methods: This prospective study enrolled 96 patients newly diagnosed as inflammatory bowel disease in outpatient clinic at Kafrelsheikh University Hospital after complete clinical and laboratory evaluation followed by endoscopic assessment then histopathological examination and follow up of the patient till clinical remission followed by re-evaluation of the patient.

Results: Ninety-six patients, 78 (81%) ulcerative colitis and 18 (18.8) crohn's, the mean age about 34.40 years and 30.94 years with p-value 0.380, the mean fecal calprotectin level at the time of diagnosis (823.61+545.457 µg/g) and after remission 165.18+202.255 µg/g with P-value 0.000.

Conclusion: The mean level of Fecal Calprotectin (FC) at (823.61+545.457 µg/g) at the remission was (165.18+202.255). Fecal Calprotectin, ESR, Platelet, Total protein, HB level and albumin which can be used as a marker of activity. the initial level of FC as an Predictor of dysplasia in ulcerative patient. Presence of parasitic infestation may retard the remission of IBD.

Keywords: Crohn's disease; Ulcerative colitis; Fecal calprotectin

Abbreviations: IBD: Inflammatory Bowel Disease; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; FC: Fecal Calprotectin

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory and destructive disease of the gastrointestinal tract. Chronic inflammation causes ulcerations, stricture formations, and perforations and is a risk factor for dysplasia and cancer [1]. To reduce these longstanding complications, the current treatment goal for patients with IBD is mucosal healing. A treat-to-target approach and close monitoring of disease status improve the outcomes for these patients [2]. The gold standard for monitoring patients with IBD is endoscopy, which is time consuming, expensive, and invasive. In addition, pre-procedural bowel cleansing is uncomfortable and inconvenient. Serological biomarkers, such as ESR, CRP, fecal calprotectin have been widely used as non-invasive parameters for IBD [3,4].

In our study we compare the IBD activity according to Montreal classification which depend upon endoscopy to the level of serological markers as (FC and ESR, Platelet, Total protein, HB level and Albumin) which can be used instead of endoscopy as a marker of activity and the initial level of FC as an Predictor of dysplasia in Ulcerative patient [5]. Calprotectin is a calcium binding protein that is found mainly in neutrophils and to a lesser extent in monocytes and reactive macrophages. It belongs to a sub group of proteins of the S100 family (calgranulin A, S100A8; calgranulin B, S100A9 and calgranulin C, S100A12) that is associated with acute/chronic inflammatory disorders and a number of malignancies [6,7].

Aim

The aim of the study is to evaluate the prevalence of IBD in addition to age and sex prediction; Estimate prevalence of parasitic infection in IBD; To determine the mean level of FC at the time of diagnosis and in remission; To investigate the laboratory markers that correlate of IBD

activity; Use of FC as prognostic marker and correlate it with endoscopic activity.

Patients and Methods

Participants

In this prospective study, ninety-six patients coming to Kafrelsheikh University Hospital were diagnosed to have IBD (Ulcerative colitis or crohn ' s disease) after complete laboratory investigation and endoscopic diagnosis confirmed by histopathological examination.

Baseline evaluation

All patients subjected to detailed medical history and complete clinical examination. Blood samples will be tested for Erythrocyte Sedimentation Rate (ESR), C-reactive Protein (CRP), Fecal Calprotectin (FC), Platelet, total protein, HB level and Albumin. Patients also undergo abdominal ultrasound and endoscopic examination and biopsies were taken from suspected lesions for confirmation by histopathology.

Selection

Patient selection was randomized from the outpatient clinic at Kafrelsheikh University Hospital after medical history and complete clinical examination.

Fecal calprotectin measurement

Calprotectin was measured, using quantitative Enzyme-Linked Immunosorbent Assay (ELISA) (Genova Diagnostics, Asheville, NC). Laboratory personnel, who were blinded from the current clinical and endoscopic disease activity of the patients, performed the analyses.

Endoscopic technique

Patients were treated under sedation with intravenous administration of fentanyl and propofol, in spontaneous breathing with oxygen mask support. The colonoscopy model number (EC38-i10L) used with complete examination was done up to the cecum with illeal intubation and biopsy from ileum to exclude any histopathological disease, also upper endoscopy (EG29-i10) done for patients with Crohn's Disease to determine the Montreal classification.

Histology

Random mucosal biopsies were obtained from each colon segment, targeting the area of most significant mucosal disease activity. Two pathologists assess all biopsies and report histology utilizing a standardized scale that includes histologically normal, quiescent, mild, moderate or severe disease. Histologically normal is defined as completely normal mucosa with no features of chronicity present.

Histologically quiescent is defined as having features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses or focal neutrophil infiltration. Histologically active is defined as presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration and is further classified into mild, moderate or severe [7,8].

Follow up after the intervention

Reassessment of the patient monthly till the patient enter into remission clinically and laboratory and endoscopically. Blood samples for complete blood count, Erythrocyte Sedimentation Rate (ESR), C-reactive Protein (CRP), Fecal Calprotectin (FC), Platelet, Total protein, HB level and Albumin. We included endoscopic and histopathological proven cases of IBD. Patients previously diagnosed to have IBD and already started treatment, patients who took NSAIDs or aspirin within the 4 weeks prior to the measurement of calprotectin were not included.

Inclusion criteria

Endoscopic and histopathological proven cases of IBD and patients accepted to participate and to do the follow up only at Kafrelsheikh University Hospital.

Exclusion criteria

Patients previously diagnosed to have IBD and already started treatment and coming for follow up; Patients who refuse follow up and evaluation; Failure to obtain the consent; Pregnant patients because potential risks to the patient and/or fetus to do complete colonoscopy during pregnancy.

Ethics and Consents

The survey will be approved by the faculty's ethics committee and permission will be obtained from all department heads who will be assured that confidentiality would be maintained and ethical principles would be followed. Before distribution of the study, a background about the study and its reason will be explained, the targeted population will be encouraged to participate without any undue pressure, and written informed consent will be obtained.

Statistical Analysis

Data collected and entered in spread sheets of Microsoft Excel before being transferred to the Statistical package for social Sciences (SPSS) software (SPSS Inc., Chicago, IL, USA) version 16 for Windows 7 (Microsoft Corp., Redmond, WA) to be analyzed.

Wilcoxon's test and Paired Student's t-test will be used to compare paired data, whereas Chi-Square test, Fisher's exact test and Mann-Whitney U-test will be used to compare unpaired data.

Factors that will be found to be significant on univariate analysis ($P<0.05$) will then be included in a multiple logistic regression analysis to evaluate the role of contrast enhanced ultrasound in the diagnosis and follow up of HCC.

Results

During the period of the study, a total of One hundred patients recently diagnosed as IBD that fulfilled the inclusion criteria were enrolled in the study about 78 (81%) ulcerative colitis and 18 (18.8%) Crohn's. Of the hundred patients, follow up was done in 96 cases only because of 2 cases not done the follow up at arranged time, 2 cases refuse to continue in the study.

So, 96 cases (9 females and 31 males) were enrolled and followed up and statistical analysis was done for them (Table 1a).

Variables	No	Percentage (%)
Ulcerative Colitis	78	81.20
		18.80
Crohn's disease	18	48

Table 1a: Type of IBD and age difference of the studied population.

The mean age was (34.40) for patient diagnosed as ulcerative colitis and (30.94) for patient diagnosed as Crohn's (Table 1b) with no statistical significant difference as (p-value 0.380).

Variables	Mean Age	P-Value
Ulcerative Colitis	34.40	0.38
Crohn's disease	30.94	

Table 1b: Calculative measures of mean age and p-value.

Sex differences between patients of both types of IBD is shown in Figure 1.

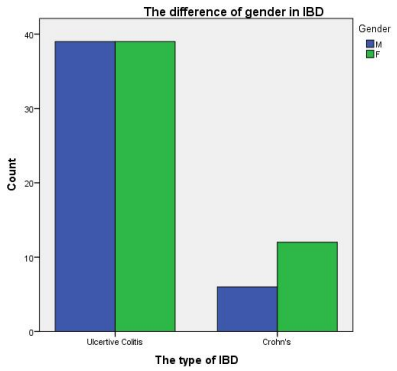

Figure 1: Sex differences between patients between both types of IBD.

Table 2 showed the laboratory investigation (Fecal calprotectin level, platelet count, total Protein, Albumin, ESR (First Hour) and hemoglobin level) correlate with IBD activity of the patient enrolled in the study at the time of the diagnosis and at the time of remission with significant difference.

The mean fecal calprotectin level in correlation to endoscopic severity of IBD according to Montreal classification (Table 3) in both types, which showed that the highest mean fecal Calprotectin level in Ulcerative colitis (E3) was (1006+513) and the highest mean fecal Calprotectin level in patient crohn's disease the highest mean level in A1L3B2 (less than 17 years with ileocolonic and structuring pattern) was (1540+0).

Variables	At time of diagnosis	After Remission	P-value
Fecal calprotectin level (µg/g)	823.61+545.457	165.18+202.255	0.000
PLT (mg/dl)	350 +120.54	242.7+73.02	0.019
Total Protein (gm/l)	69.64+4.67	57.13+4.77	0.001
Albumin (gm/dl)	3.54+.501	3.75+0.481	0.010
ESR (First Hour)	51.21+31.186	17.10+12.3	0.009
HB (mg/dl)	11.52+2.12	12.65+1.91	0.001

Table 2: Laboratory investigation correlates with IBD activity.

Type of IBD	Montreal Classification	Mean	% of Total N	P-value
Crohn's disease	A1L2B1	150+0	1.00%	0.005**
	A1L3B1	1039.5+819.158	12.50%	
	A1L3B2	1540+0	1.00%	
	A2L3B2	795+341.8	12.50%	
	A2L3B3	1000+0	1.00%	
Ulcerative Colitis	E1	439.55+248.5	22.90%	
	E2	910+541.4	28.10%	
	E3	1006+513	20.80%	

Table 3: Fecal calprotectin as key indicator of severity in IBD [**statistically significant difference ($p<0.05$)].

Figure 2 show that initial higher fecal calprotectin level associated with early occurrence of low grade dysplasia as the mean fecal calprotectin for patient with early dysplasia was 978.76 and the mean fecal calprotectin for patients who didn't develop dysplasia after three years was 742.35.

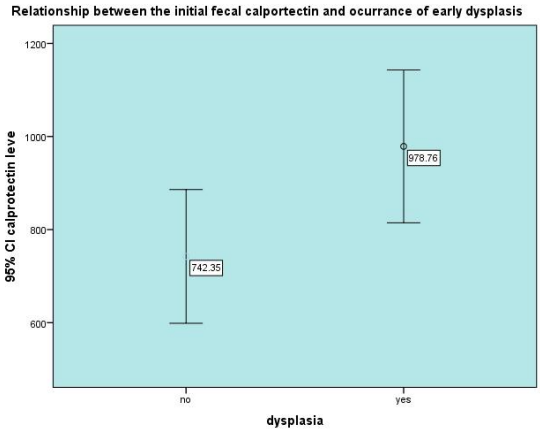

Figure 2: Relationship between the initial fecal calprotectin and occurrence of early dysplasis.

Discussion

Still estimation of severity and activity of the gastrointestinal inflammation in IBD is a problematic dilemma. Endoscopy with biopsy remain the most reliable method [4]. However, the fact that the endoscopic interventions are invasive and frequently disturbing, and

the symptoms are usually not conclusive, has led to the use of laboratory investigations in the assessment of disease activity in IBD [5]. Among these, acute phase reactants, ESR, platate, Albumin and fecal calprotectin are the most frequently used laboratory markers. A number of studies have reported that fecal calprotectin can be used as diagnostic aid, here we try to get mean level to fecal calprotectin in disease remission and exacerbation. It's the first study to correlate it with endoscopic severity and estimate the initial level as a predictor of early dysplasia [9].

Previous study done by Vermeire and its colleague show that some acute phase reactants increase in active inflammatory conditions and CRP is among the most commonly used acute phase reactants. In our study we noticed that there is significant difference between the level of (HB, ESR (First hour), Albumin, Total Protein, PLT) in patient at the time of diagnosis and after remission [10]. Our study showed that the mean level of Fecal calprotectin level at time of diagnosis 823.61+545.457 μg/g and was 165.18+202.255 μg/g at Remission and this disconcordent with the result of Costa and it is colleagues who demonstrated a 14-fold greater risk of relapse in UC patients if the calprotectin was more than 150 g/g, but this did not hold true for CD patients. The difference in the mean level may be due to poor sanitation and frequent intestinal infections in developing countries than developed country [11].

This study shown that the highest fecal calprotectin level in (crohn's A1L3B2) was 1540+0 Who was young age less than 17 years old in ileocolonic type which complicated with stricture but, in (ulcerative colitis Montreal E3) was 1006+513,this concordant with Aomatsu T and his colleague that mentioned that FC concentrations correlate with endoscopic findings [12]. Kristinsson and his colleague mentioned that the measurement of fecal calprotectin is a valuable marker for colorectal cancer, we noticed that higher initial level of fecal calprotectin associated with early dysplasia [13]. This study has several limitations. First, the number of participants is relatively small. Second, the follow-up duration was three years only.

Conclusion

Serological markers (FC and ESR, Platelet, Total protein, HB level and Albumin) which can be used instead of endoscopy as a marker of activity. Fecal calprotectin can reflect severity of the disease. The initial level of FC as a predictor of dysplasia in ulcerative patients.

Conflict of Interest

The authors have no conflicts of interest with respect to the contents of this review.

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