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Research Article

Correlation between Fecal Calprotectin (CP) and Magnetic Resonance Enterography (MRE) in Crohn's Disease Activity; at Al-Najah National University Hospital: A Retrospective Study

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Abstract

Background: Thanks to technical advances, imaging modalities are playing an increasingly important role both in the diagnosis and in the clinical management of chronic inflammatory bowel disease (IBD), especially with Crohn's disease. The diagnosis of inflammatory bowel disease (IBD) is based on laboratory tests and histological evidence. However, imaging methods have also become an important part of diagnosing and monitoring the progress. Fecal calprotectin (CP) is an established biomarker for evaluating inflammatory processes in the colon. It is used to detect neutrophils in inflammatory tissue and allows a differentiation between inflammatory and non-inflammatory diseases of the lower intestinal tract. Due to the high sensitivity, the analysis of the fecal CP provides reliable information about the intensity of the inflammatory lesion and adequately reflects the disease activity that can be detected endoscopically. This study aims to find the relationship between fecal CP and Magnetic Resonance Enterography (MRE), in the diagnosis and prognosis of Crohn's Disease.

Methods: In order to conduct the correlation between Fecal CP and MRE, a retrospective study was performed on 500 Crohn's-diagnosed patients from Gastroenterology and Radiology department at Al-Najah University hospital; from January 2017 to January 2020 who underwent MRE and Fecal CP (within a period of 30 days).

Results: The mean age of the study participants was 33.5 years, and 64.6% of them were males. The MRE score mean was 1.21, and the mean of Fecal CP levels was 324.44 mcg/g. Moreover, it was noticed that the mean of Fecal CP levels in the score "2" MRE group was 614.9 mcg/g, 103.68 mcg/g in the score "1" group, and 32.4 mcg/g in the score "0" group. The results of the regression model demonstrated that there was a statistically significant relationship between Fecal CP levels and MRE results (r2=0.363, P=0.000).

Conclusion: Fecal calprotectin correlates well with MRE activity, thus Fecal CP could be used as a predictor marker to select for MRE assessment.

Keywords: *Fecal Calprotectin; MRE; Chron's Disease; IBD; Magnetic Resonance Imaging*

Introduction

Crohn's disease and ulcerative colitis represent the two most important subtypes of chronic inflammatory bowel disease. Immunological, genetic and environmental factors are postulated in the pathogenesis, which leads to an immune reaction against the intestinal flora

[1]. There is no significant gender predominance. The median peak age for both entities is between 20 and 30 years, with a second peak between 60 and 70 years for Crohn's disease and 70 - 80 years for ulcerative colitis. In principle, however, the disease can occur at any age.

The diagnosis and management of chronic inflammatory bowel disease (IBD) require a comprehensive examination of clinical, endoscopic, histological and imaging studies. While endoscopy with the option of biopsy of the large intestine and the terminal ileum as well as the following histological work-up is the gold standard in the diagnosis of chronic intestinal diseases, imaging plays a role in the assessment of activity and extramural extent in monitoring the course and in assessing the therapeutic response an important role.

The imaging methods used are Magnetic Resonance Enterography (MRE) (orally administered contrast agent) or MR Enteroclysis (contrast agent administered via a small intestinal probe). Computed tomography (CT) is mainly used to clarify acute complications such as abscess formation or perforations. Early changes can be detected with capsule endoscopy; in later stages, capsule endoscopy has its limitations because of the risk of capsule retention due to strictures [2].

Crohn's disease is a chronic, relapsing inflammatory disease that can manifest itself along the entire gastrointestinal tract. The ileocecal region is affected in around 50% of cases, followed by the ileum in 30% and the colon in 20% [1]. The inflammatory process is transmural, i.e., the entire stratification of the intestinal wall is affected. Fistula formation is therefore a common complication of Crohn's disease. The infestation takes place discontinuously, which means that affected and non-infected parts of the intestine can follow one another. The latter are known as "skip lesions". The Crohn's disease can be divided into 4 subtypes:

1. Active inflammatory
2. Fistulation/ perforating
3. Fibro-stenosing
4. Reparative / regenerative [3-5].

The different subtypes can coexist and do not necessarily merge into one another sequentially. Patients with Crohn's disease are at an increased risk of colorectal cancer and hematological diseases such as lymphoma; for the latter there may also be an increased risk due to the therapy [3].

Literature Review

In principle, the imaging procedures relevant for IBD can be divided into two groups. On the one hand, the double-contrast examination of the small intestine and the gastrointestinal passage are available, which depict the intestinal lumen directly with the aid of an X-ray contrast medium. Due to the radiation exposure or the limited scope of the extraluminal information to be obtained, these are no longer used in clinical routine nowadays. With the help of sonography (ultrasound, US), computer (CT) and magnetic resonance tomography (MRT), both the intestinal wall and the extraintestinal structures can be assessed.

In IBD, MRI and CT enterography offer high diagnostic accuracy for the detection of the affected intestinal sections and extraintestinal complications [6]. For reasons of radiation protection, CT is not recommended for follow-up checks, but due to the short examination times it can be used for rapid diagnosis in the case of acute symptoms. In the area of the terminal ileum, the intestinal ultrasound examination has the same diagnostic value as CT or MRI [7].

The MRI of the small and large intestines is an important part of IBD diagnostics. Good bowel distension is essential during the examination, so this is best done after drinking plenty of fluids. Depending on how the liquid is administered into the gastrointestinal tract, a distinction is made between MR enterography and MR enteroclysis. In the context of MR enterography, the liquid is drunk by the person

to be examined; in the context of MR enteroclysis, the contrast agent is administered via a probe. Before the MR examination, this probe is inserted into the distal duodenum or into the area of the duodenojejunal flexure under fluoroscopic control.

The sensitivity of both methods is rated equally in the literature, but mucosal/submucosal changes can theoretically be better recorded with the aid of MR enteroclysis. One of the reasons for this is the better intestinal distension through application of the oral contrast agent with the aid of the small intestinal probe [8].

Magnetic resonance imaging (MRI) is the preferred imaging method in the evaluation of inflammatory bowel disease due to the lack of radiation exposure. In a recent meta-analysis it was reported that MR enterography, MR enteroclysis and CT enterography have comparable accuracy in the detection of Crohn's disease [9]. However, MR enterography and MR enteroclysis allow an assessment of the activity or the subtypes of the disease. The risk of incomplete filling is higher with MR enterography than with MR enteroclysis [10,11]. When evaluating patients with Crohn's disease, however, no significant differences were found between the two filling methods, although superficial pathologies could be better differentiated with the MR enteroclysis [12a complete evaluation of the gastrointestinal tract is now crucial. STANDARD RADIOLOGICAL METHODS: With the introduction of endoscopy, gastrointestinal imaging with a relatively high radiation exposure had only limited applications. The development of cross-sectional imaging allowed a much broader radiological evaluation of abdominal diseases. Due to rapid investigation techniques, excellent soft tissue contrast and the distinct advantage of eliminating exposure to radiation, magnetic resonance imaging (MRI]. In most centers, MR enterography has become established due to patient comfort. Indications for implementation are:

- Assessment of the localization of the inflammatory changes and their extent,
- Classification of subtypes,
- Follow-up in the case of a known disease,
- Exclusion of a disease in the case of corresponding symptoms,
- Susceptible relapse,
- Planning a surgical procedure [4,13].

Enteral contrast media are administered to obtain a distension of the intestinal lumen and a high contrast between the intestinal lumen and the intestinal wall. The most widespread use is biphasic enteral contrast media, which are hypointense in T1 and hyperintense in T2 [9,14,15]. The hypointense signal in the T1-weighted sequences improves the contrast between the intestinal lumen and the inflamed intestinal wall, which increasingly absorbs the contrast agent, while the hyperintense signal in the T2-weighted sequences enables the display of small ulcers that extend into the hypointense intestinal wall [16,17]. Polyethylene glycol has excellent contrast and, due to its high osmolarity, leads to intestinal distension [16,18,19]. Other contrast agents include mannitol, sorbitol, or lactulose [20].

Additionally, fecal calprotectin is a neutrophil protein and serves as a supporting marker for assessing the inflammatory activity of the intestinal mucosa. It has therefore established itself in particular for the diagnosis of chronic inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis as well as for differentiating between IBD and irritable bowel syndrome (IBS) [21and useful for the differentiation of inflammatory bowel disease (IBD]. In addition, it can also be used to support therapy control of inflammatory bowel diseases.

Calprotectin is a calcium-binding protein that is produced by neutrophils and monocytes. Fecal calprotectin (MRP 8/14) is a marker for gastrointestinal diseases of inflammatory and neoplastic origin. So far, fecal calprotectin has been used in particular to differentiate

between patients with irritable colon and those with chronic inflammatory bowel disease (IBD). The evidence from the stool correlated with the histological and endoscopic findings of the disease activity in Crohn's disease and ulcerative colitis [22]. In contrast to the previous standard markers for inflammatory processes (CRP, BSG, BB), increased calprotectin values indicate a relapse with greater certainty. If the calprotectin level in the stool is low, there is a high probability that there is no organic disease of the intestinal tract.

Problem statement

Inflammation activity is the mainstay to diagnose and follow up. When patients are not in a relapse, they underestimate the burden of the disease, thus focus has shifted to more objective assessors of disease activity. Markers of systemic inflammation in general have low specificity and sensitivity, however, Fecal CP is not. Elevated levels of Fecal CP in the GI correlates well with disease activity. The known gold standard for assessing activity is MRE, which is invasive and expensive, however, Fecal CP is not. It's an affordable, simple fecal test. We found that Fecal CP correlates well in its findings with MRE, and, by this we are doing a great favor for doctors and patients of IBD for routine follow up and prognosis of the disease. With this, doctors can shift from doing a routine MRE, to a simple Fecal CP test.

Objectives

The general objective of our study was to find the correlation between fecal calprotectin and MRE in detecting the severity and activity of Crohn's disease.

Specifically, we aimed to:

- Decrease the burden and cost upon hospitals and patients.
- Depend on noninvasive marker (Fecal CP) in following up and evaluating flare ups in Crohn's instead of invasive MRE imaging.
- Engage in fecal calprotectin tests in the gastroenterology department in all medical centers.

Methodology

Study design and setting

A retrospective study was conducted among Crohn's disease patients, who underwent MRE, in the Northern west bank. The study was conducted at Al Najah National University Hospital. A tertiary hospital in Nablus with a gastroenterology and radiology units that covers the North West bank of Palestine.

Study population

Patients with Crohn's disease who underwent an MRE assessment during follow ups at Al Najah National University Hospital and fulfill the following inclusion criteria was considered as a sample of the study (65 patients).

Inclusion criteria

We included patients who:

- Age > 18 years.
- Had established diagnosis of Crohn disease with small bowel involvement.

- Agreed to participate in the study.
- Underwent MRE assessment to monitor disease activity during follow ups and stool sampling to measure fecal CP (within a maximum of 1 month before MRE).

Exclusion criteria

We excluded patients who

- Had intolerance or contraindication to undergo MRE
- Had any change in clinical symptoms that led to change in the therapeutic regimen between laboratory test and MRE examination
- Had exclusive colonic involvement
- More than one month interval between fecal calprotectin and MRE.

Variables

Radiological variables

The MRE score was done blindly by two radiologist experts at An-Najah National University Hospital, where the MRE results were divided into 3 categories: score 0 indicates normal findings, score 1 indicates mild to moderate findings and score 2 indicates severe findings.

Fecal calprotectin

Will be measured by quantitative enzyme linked immunoassay. The intensity of color is proportional to the amount of calprotectin in the fecal sample with concentration of calprotectin being calculated using values recommended by the laboratory. Results are expressed in microgram per gram of feces Values below 50 μg/g will be considered normal.

Data collection and analysis

Data was collected retrospectively. Fecal calprotectin level and MRE records were obtained from Al-Najah laboratory department and Radiology department, respectively.

Statistical analysis will be performed using SPSS version 23. A P value less than or equal. 05 will be considered statistically significant. Data will be presented as mean ± SD or median (1st quartile, 3rd quartile) as appropriate, for continuous variables and as frequencies (proportions) for categorical variables. To assess the correlation between fecal calprotectin and MRE, simple linear regression model was used0.

Results

Socio-demographic information

The mean age of the study participants was 33.5 years, and 42 (64.6%) of them were males (Table 1).

Socio-demographic Variables		N	%
Gender	Male	42	64.6%
	Female	23	35.4%
Age	13-20 Years	4	6.1%
	21-40 Years	44	67.7%
	41-62 Years	12	18.5%
	>62 Years	5	7.7%

Table 1: *Socio-demographic characteristics of participants (N = 65).*

Frequencies and descriptive statistics of fecal CP and MRE scores

From (Table 2), the MRE results were found as: 48.4% of the participants had MRE score "2", 27.4% had score "1" and 24.2% had score "0". Moreover, regarding the fecal CP levels; 46% of the participants had a Fecal CP level less than 100 mcg/g, 36.5% had Fecal CP more than 250 mcg/g and 17.5% had Fecal CP levels from 101-250 mcg/g.

Frequencies and descriptive statistics of Fecal CP and MRE Scores		N	% (valid)	Mean	Std	Valid	Missing
MRE Score	**0**	15	24.2%	1.21	.82527	62	3
	1	17	27.4%				
	2	30	48.4%				
Fecal CP Levels (mcg/g)	**>100**	29	46%	324.44	426.51	63	2
	101-250	11	17.5%				
	>250	23	36.5%				

Table 2: *Frequencies and descriptive statistics of Fecal CP and MRE Scores.*

Descriptive association between fecal CP levels and MRE results

It was noticed that the mean of Fecal CP levels in the score "2" MRE group was 614.9, 103.68 in the score "1" group, and 32.4 in the score "0" group (Table 3).

	MRE Score		
	0	**1**	**2**
Fecal CP Mean	32.4	103.68	614.9

Table 3: *Descriptive association between Fecal CP levels and MRE results.*

Correlation and relationship between Fecal CP and MRE (Simple Linear Regression Model)

In order to find out the relationship between the MRE results and Fecal CP levels, a simple linear regression model was used. As Fecal CP levels was considered as an explanatory variable, and MRE results as dependent variable.

The results of the regression model demonstrated that there was a statistically significant relationship between Fecal CP levels and MRE results (P = 0.000).

The Fecal CP explains 36.3% of variations in MRE results (as $r^2 = 0.363$), showing that the strength of the relationship between Fecal CP levels and MRE results was moderate. To verify the existence of the mentioned relationship, a multicollinearity test was carried out. The result revealed the VIF factors of the model were (< 3), indicating the non-existence of multicollinearity problem (Table 4).

	MRE Results			
	Pearson Correlation	P Value	R^2	VIF Factor
Fecal CP Levels	0.603	**0.000***	**0.363**	1

Table 4: *Correlation and relationship between Fecal CP and MRE (Simple Linear Regression Model).*

Disccusion

The present study provides data obtained in a retrospective cohort of patients which indicate that fecal calprotectin levels strongly reflect the disease activity thus guides the use of MRE.

Our results show that Fecal CP also correlates with the disease's activity in patients with Crohn's disease, when evaluated according to simple MRE scoring put by two radiological experts to objectively measure commonly assessed parameters of interest. So, the study was not designed to validate a new scoring system for ileal Crohn's disease, rather it was to assess the utility of Fecal CP in highlighting patients at high risk of poor outcomes.

By analyzing our data, we found that all patients with Fecal CP less than 100 had no disease activity so there is no role for the use of MRE for such patients. On the other hand, all patients with Fecal CP more than 250 had severe complicated active disease so they had the necessity to perform MRE. Regarding patients with Fecal CP 100-250, we found a cutoff point value which equals to 135 determines the going for MRE or not, as all values of Fecal CP below it had no complication in the small bowel thus no role for MRE.

We found many studies supporting our research results. One of them, which was conducted in Spain by multiple hospitals and universities, with 120 patients' sample, correlates between Fecal CP levels and MRIA scoring systems. A significant positive correlation was found between MRE score and Fecal CP levels with a moderate overall correlation. The study concluded that Fecal CP correlates with the degree of MRE inflammatory activity and with surgical pathology damage in ileal CD. They found Fecal CP cutoff value of 166.5.Thus, Fecal CP could be a surrogate marker of disease control used to select patients for MRE assessment and therapeutic adjustment [23].

Another study, with 119 samples, done by European Crohn's and Colitis Organization (ECCO) in multiple countries among Europe. It was Published in 2019 and found that Fecal CP correlates well with MRE assessment of ileal CD with MRE parameters associated with long-term biologic- and surgery-free remission [24].

The study has multiple strengths. It was purely conducted on Crohn's patients only. Also, values of Fecal CP were taken within 30 days interval from MRE imaging's. All data was collected from the same hospital and within the same laboratory department and radiology department. It is the first time for such study to be conducted in Palestine. Another strength, the MRE images were analyzed blindly by two expert radiologists.

Our study is limited, however, by the retrospective nature of the study, so we could not use a valid scoring system such as the MRIA scoring system, instead we use a simple scoring system applied by two radiological experts in the radiology department. Another limitation, which affected the sample size, was the absence of a backup system at An-Najah hospital before 2019 which has limited us from finding patients imaging before that. Also, the Fecal CP test was newly available at Najah National University Hospital (2017) so MRE images couldn't be matched with Fecal CP before 2017, thus, sample size was affected.

Our Recommendation, Fecal CP test should be readily available and used in all Gastroenterology departments. Use Fecal CP as a guide for doctors to decide whether the patient needs MRE or not, if Fecal CP less than 100 the patient doesn't need MRE, if Fecal CP more than 250 the patient needs MRE.

Ethical Considerations

All aspects of the study protocol were authorized by the Institutional Review Boards (IRB) and the local health authorities before initiation of this study. Written consents were obtained from patients prior to the interviews. We explained that the collected data will be used only for clinical research and their confidentiality will be preserved.

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