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Editorial

Update on Inflammatory Markers in IBD

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic gastrointestinal inflammatory condition. It is a fairly common diagnosis in the United States and can cause significant morbidity, resulting in hospitalization and surgery. It is associated with a significant impact on healthcare costs [1,2]. In some settings, it may be difficult to determine if a patient's clinical symptoms are a result of active gastrointestinal inflammation. Alternative causes of symptoms include fibrostenotic sequelae of CD, infections, adhesive disease as a result of prior surgeries, and underlying irritable bowel syndrome. The best method for determining the presence of active inflammation is direct visualization and biopsy during ileocolonoscopy [3]. Although safe to perform, endoscopic procedures may not be appropriate in all situations, are invasive, require a bowel preparation, are often performed with sedation and may not be able to access the involved area. Additionally, in this era of cost-consciousness, less expensive evaluations would be preferred. Imaging modalities including computerized axial tomography scans and magnetic resonance imaging with or without enterography can be useful in evaluating mucosal inflammation, but the former involves ionizing radiation and both incur a significant cost [4]. As such, highly sensitive and specific, low-cost, non-invasive measures of inflammation would be useful tools to evaluate symptomatic patients with IBD. Alternative markers have been studied, and hopefully some will prove worthy as clinical tools.

There are several markers currently in use in clinical practice, although all are imperfect. Serum C-reactive protein (CRP) is commonly used and often, but not always, is elevated in patients with active IBD. There is a cohort of IBD patients who do not mount a CRP response. Additionally, there are patients without active IBD who have an elevated CRP, due to its lack of specificity. The use of high-sensitivity (hs)-CRP has been examined to assess if it is of greater utility than the standard CRP measurements [5]. In 260 patients with CD, elevated hs-CRP signified more severe disease and thus a rationale for more aggressive therapy ($p = 0.024$). Additionally, patients with elevated levels were at increased risk of relapse at 3 and 12 months ($p = 0.007$ and $p = 0.001$). In contrast, other studies have not demonstrated the utility of the hs-CRP, especially in those patients unable to mount an elevation of their CRP [6]. In a study of pediatric CD patients, 39 patients underwent colonoscopy and disease activity assessment. Of the twenty-five patients who had active disease with undetectable standard CRP levels, the hs-CRP could not facilitate differentiation of those with active or inactive disease.

The use of simple measurements of routine labs has been examined to assess their utility in evaluating inflammation, as they are inexpensive and easy to perform. An example is the neutrophil-lymphocyte ratio in patients with UC. Using retrospective analysis, patients with active disease had ratios of 3.22 ± 1.29 versus 1.84 ± 0.69 in those with inactive disease and 2.01 ± 0.64 for controls [7]. Alternatively, an increase in the red cell distribution width may be a subtle tool for determining active inflammation; however, it may only be useful in patients without anemia, limiting its utility [8]. Potentially, platelet indices could be biomarkers for disease activity as well [9]. Changes in mean platelet volume and platelet distribution width and an increase in platelet-hematocrit ratio seem to correlate with disease activity. Unfortunately, although inexpensive, these routine measurements may be too insensitive to accurately assess the presence and degree of inflammation in the IBD patient.

Procalcitonin, the peptide precursor of calcitonin, has been evaluated for use as a biomarker of inflammation, with or without the simultaneous measurement of CRP, in patients with CD [10]. In isolation, a procalcitonin level greater than 0.14 ug/L correlates with disease activity, especially in patients with more severe disease (Sensitivity = 100%; Specificity = 96%; AUROC = 0.963; $p = 0.0001$). The serum procalcitonin levels seem to correlate well with other measures of activity, including endoscopic and radiologic measures. Using both CRP (CRP >5 mg/L) and serum procalcitonin (> 0.05 μg/L) measurements together may further improve the accuracy for defining severe crohns disease activity, compared to an isolated measurement of CRP level (AUROC = 0.783 vs. 0.674; $p = 0.01$). Serum procalcitonin may also be helpful in distinguishing active disease in patients with UC, but further studies are needed.

The enzyme adenosine deaminase (ADA), is involved in purine metabolism and its main isoenyzme is ADA2. Levels for both appear to correlate with disease activity in patients with either types of IBD [11,12]. ADA may be a marker for T-cell activation, although its specific role in IBD is not clear. CD patients with active inflammation had higher total ADA levels than those in remission or healthy controls (22.9 ± 4.9 U/L, 14.0

± 3.4 U/L, 13.24 ±2.4 U/L, p < 0.001). ADA2 levels were also elevated in patient with active disease, compared to those with inactive disease or controls (19.7 ± 1.9 U/L, 12.3 ± 1.2 U/L, 12.2 ± 0.9 U/L). Similarly, patients with active UC were more likely to have elevated serum ADA levels compared to those in remission and controls (11.12 U/L ± 2.03, 7.99 ± 2.04 U/L, 8.55 ± 2.26 U/L, P < 0.05), with a sensitivity of 83.3% and specificity of 84.2%. ADA levels did not correlate well with ESR (r = 0.231, p = 0.14) or CRP (r = 0.506, p = 0.001). Additionally, although it is difficult to compare the two studies, levels for active UC patients were lower than in controls and patients with inactive CD in the comparative study, perhaps implicating significant overlap.

Stools studies for markers of inflammation have also been examined in their utility for evaluating degree of inflammation. Fecal calprotectin (FC) has been used as a non-invasive measure of disease activity in both CD and UC patients. Calprotectin is a cytosolic protein in granulocytes [13]. It is stable at room temperature and can be measured up to one week after collected. Either enzyme-linked immunosorbent assays (ELISA) or a new rapid quantitative-point-of-care test can be used (FC-QPOCT) [14].

In a study of 126 patients with UC or CD and 32 patients with IBS, fecal calprotectin levels were compared to the patient's clinical status, blood biomarkers and colonoscopic scores [15]. FC levels correlated with the endoscopic appearance in both IBD groups of patients. Levels of FC > 250 μg/g were associated with large ulcers and levels < 250 μg/g were indicative of remission. In a study of 60 UC patients (30 with active and 30 with inactive disease) and 20 controls, FC levels correlated with clinical and endoscopic evidence of activity. Levels of FC were: 232.5 mg/L (0.75 – 625, active UC) versus 11.7 (0.2 – 625, inactive UC) mg/L, and 7.5 (0.5- 512, controls) mg/L, p < 0.001) [16]. In a meta-analysis of 6 studies of 318 UC and 354 CD patients, FC was useful in predicting relapses and appeared to be equal reliable in patients with either disease [17]. FC could be used to predict relapse with a pooled sensitivity of 78% (95% CI: 72-83) and 73% (95% CI: 68-77).

However, FC may not be completely reliable. Symptom scores in CD patients did not correlate well with FC levels in a study by D'Haens, et al. Additional studies in the CD pediatric population did not find FC to correlate with other clinical markers of disease [18]. There has also been significant overlap in levels of FC amongst the groups studied.

Fecal lactoferrin, measurable by ELISA, is a protein found in neutrophils, is resistant to degradation, and appears to be an additional marker for disease activity. In a study examining 148 patients with CD (79), UC (62) and controls (22), lactoferrin was elevated in patients with active disease [19]. Levels were substantially elevated in patients with UC (1880 ± 565 ug/mL) and CD (1701 ± 382 ug/mL), compared to normal controls, (1.17 ± 0.47 ug/mL, P < 0.001). Very high levels may also be helpful in predicting a future flare of disease. Patients who flared were more likely to have elevated levels than those who stayed in remission (845 ± 452 ug/mL vs 190 ± 90 ug/mL, p = 0.003).

Other stool markers have been examined and their utility needs to be verified. A quantitative fecal immunochemical test (FIT) was evaluated in stool collections from 310 colonoscopies in 152 patients with UC and compared to Mayo endoscopic scores [20]. FIT values over 100 ng/ml predicted a Mayo score of 2 or 3 (sensitivity 0.87 and specificity 0.60). Of patients with a Mayo score of 0, 92% had FIT scores less than 100 ng/ml.

Fecal myeloperoxidase (FMPO) has been examined in patients with UC [21]. Fifty-five patients with UC were compared with 54 controls. Patients with active disease had elevated median levels of FMPO compared to controls, with the highest levels in those with more endoscopically severe disease. However, it was not useful in predicting extent of disease or histologic grade. Additional markers, including fecal MMP-9, Fecal M2-PK and chitinase 3-like-1 may be other useful markers for determining disease activity in patients with IBD [22-24].

Nitric oxide (NO) is a small molecule radical that serves in a variety of roles in normal human physiology. Endothelium lining blood vessels use NO to cause smooth muscle relaxation and vasodilation. In another mechanism, NO is secreted via inducible nitric oxide synthetase (iNOS) by immune cells as a free radical and is toxic to certain bacteria and parasites. Thus, nitric oxide may be a useful marker for inflammation, including active inflammation in patients with IBD. In one of the first studies in this area in 1995, Oudkerk , et al. demonstrated that while median serum nitrate concentrations did not differ between patients with UC, CD, and health controls, those patients with active disease had statistically higher levels than those patients with inactive disease. Additionally, there was a significant correlation between nitrate concentration and ESR, leukocyte count, and platelet count [25]. In a related study, Kimura, et al. showed a similar relationship between serum NO levels and active disease, in addition to iNOS activity in the colon. This may suggest that the NOS activity in the affected area of bowel may be a driving factor in disease [26].

The genetics of this protein have been studied, and data is conflicting. In one study, polymorphisms in the iNOS gene (NOS2A) were not associated with a difference in frequency of UC or CD [27]. On the other hand, a similar study suggested that having certain promoter-region polymorphisms increased the risk of having UC (OR=1.64, 95% CI=1.20-2.23) or CD (OR=1.74, 95% CI=1.13-2.67) [28].

Nitric oxide can be measured or estimated in a variety of ways. Urinary nitrates were increased in 87.5% of patients with active IBD compared to only 14.3% of patients with inactive disease, while none of the healthy controls had measureable urinary nitrate [29]. In one study, salivary levels of NO in UC patients were statistically different than healthy controls, but the level could not distinguish between those patients with mild, moderate, and severe disease [30]. Ljung, et al. showed that levels of rectal NO in gaseous form were markedly elevated in patients with active IBD compared to healthy controls. Furthermore, they concluded that low rectal NO levels in patients with active disease were associated with poor clinical response to steroids and increase need for colectomy [31]. Measuring fractional exhaled nitric oxide (FeNO) is an intriguing and minimally invasive methods of estimated NO levels. Many studies in the pulmonary literature have examined this technique as a marker for severity of asthma, and while this is not completely accepted as a mainstream

management tool, the evidence is building that it is a useful adjunct [32-34].There are several reports of the successful use of hand-held devices to measure FeNO which confirms its ability to be a minimally invasive procedure [35-37]. In the initial, small study of IBD patients, Koek, et al. reported that FeNO levels were higher for CD patients compared to healthy controls (13.5 ppb vs. 10.2 ppb) and for UC patients compared to controls (15.8 ppb vs 10.2 ppb). In addition, they reported a disease activity-related increase in the FeNO of IBD patients [38]. Later, studies reported that FeNO was useful to identify patients who had pulmonary involvement of their IBD [39,40]. Recently, two additional groups reported data that further strengthens the possible usefulness of FeNO measurements in IBD patients. Quenon, et al. measured FeNO with a hand-held device in the office setting. They found that FeNO levels were higher in patients with clinically active disease vs. those with clinical remission (22 ppb vs. 11 ppb, $p<0.001$). FeNO also had a strong correlation with the CDAI, but only a fair correlation with other systemic inflammatory markers, suggesting that FeNO might be useful as an adjunct to the already existing panel of available inflammatory markers [41]. Ikonomi, et al. reported in an analysis of nationwide data that patients with clinically active IBD were more likely to have FeNO levels above 25 ppb compared to healthy controls (OR=1.09 for CD, OR=2.25 for UC) [42].

Nitric oxide is a marker of inflammation that seems to be associated with active IBD. It is likely too soon to strongly recommend measuring NO in some form as a marker of IBD; however, further studies should be conducted to establish the utility of this easily measured marker.

The development of noninvasive, inexpensive, and reliable testing for the evaluation of disease activity in patient with IBD is a critical step in the management of these patients. Although there have been advances in the field, there remains no single diagnostic test that fulfills these criteria. At best, we are still relying on blood and stool markers as an adjunct to our imaging and endoscopic modalities. The crystal ball for assessing active inflammation remains elusive.

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