Noninvasive Testing for Mucosal Inflammation in Inflammatory Bowel Disease

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KEYWORDS

• Biomarker • Inflammatory bowel disease • Crohn's disease • Ulcerative colitis
• Fecal calprotectin • C-reactive protein

KEY POINTS

- Fecal and serologic biomarkers have gained increasing attention by the physicians for the diagnosis and follow-up of inflammatory bowel disease (IBD).
- Biomarkers are rapid, inexpensive and noninvasive, and can be used in different stages of the disease with high sensitivity and specificity.
- Fecal markers such as calprotectin and test for C-reactive protein are used to assess disease activity, predict relapse, and monitor the treatment response.
- New noninvasive tests are being studied and the future years look promising for IBD.

Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), is characterized by a relapsing and remitting course that cause a chronic inflammation of the gastrointestinal tract. The classic treatment goal has been focused on the control of clinical symptoms and clinical remission to guide treatment. However, it has been well-known that clinical symptoms are frequently inconsistent with endoscopic findings, especially in CD.[1] More recently, the goal of mucosal healing has emerged as the new treatment target to change the evolution of the disease.[2]

Colonoscopy is the gold standard technique for the diagnosis and assessment in IBD. Nevertheless, this procedure has several limitations. It is a technique that consumes longer time and is invasive; at the same time, it requires dietary restriction and the preparation of the colon, which is unpleasant for the patient. Currently, there are new noninvasive biomarkers to improve the detection of disease activity, prognosis prediction, and treatment adjustment. Those biomarkers can avoid IBD patients to be evaluated unnecessarily with invasive, expensive endoscopic examinations.

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This article discusses the advances in serum markers and stool markers of inflammation and how they serve as a complement for the monitoring of the disease and the eluding some endoscopies. Finally, we review recent technical advances and new kinds of biomarkers.

SEROLOGIC MARKERS AND ANTIBODIES

Several serologic tests have been used in IBD clinics. The existence of antibodies to microbial antigens highlights the abnormal immune response produced in IBD patients. The most investigated ones are perinuclear antineutrophil cytoplasmic antibodies (pANCAs) and anti-*Saccharomyces cerevisiae* antibodies (ASCAs), which have been used to improve the diagnosis of IBD to distinguish CD from UC.[3] Whereas ASCA are generally found in CD patients (39%–76% in CD vs 5%–26% in UC), pANCA are more common among UC patients (20%–85% in UC vs 2%–28% in CD).[3,4] The specificity of these 2 combined markers tends to be higher than sensitivity, and for this reason, these markers are more useful in the differentiation of the IBD subtypes than in population screening.[4] Although ASCA and pANCA may be used to identify high-risk patients with complicated disease course,[5–8] a metaanalysis has demonstrated inconsistent results owing to the heterogeneity of different studies.[9] Finally, ASCA and pANCA have also been tested for their relationship with the response to therapy.[7] In this sense, pANCA may identify a CD subgroup with a poorer response to infliximab.[10,11] The combination of pANCA+/ASCA− could be predictive of nonresponse to infliximab in patients with refractory luminal CD.[12] Nevertheless, this serotype has been associated with early clinical response to infliximab in UC patients.[13]

The presence of other antibodies to microbial antigens as antibodies to outer membrane porin (anti-OmpC), flagellin (anti-Cbir1), *Pseudomonas flourescens*–associated sequence I-2 (anti-I2), and antibodies to flagellin A4-Fla2 and Fla-X in around 50% of CD patients supporting the role of altered microbial sensing in the pathogenesis of the disease.[6,14] New antiglycan antibodies, such as antilaminaribioside carbohydrate IgG, antichitobioside carbohydrate IgA, antisynthetic manobioside antibodies has been associated with complicated disease phenotype (stricturing or penetrating complications) and risk for surgery in CD patients.[7,8,15,16] Moreover, the expression of I-2 antibodies against a bacterial antigen of *Pseudomonas fluorescens* has been associated with highly clinical response to fecal diversion in CD patients (clinical response of 94% with I-2 positive vs 18% with I-2 negative).[17]

Although in clinical practice these serologic markers are not commonly used, their role in the management of IBD patients requires further investigation and prospective studies to verify its usefulness.

BLOOD MARKERS OF ACUTE PHASE RESPONSE

C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) are the most commonly available and used blood markers. CRP is an acute phase protein with a short half-life (19 hours).[18,19] It is produced by the hepatocytes in response to an inflammatory trigger (cytokines as IL-6, tumor necrosis factor [TNF]-α and IL-1β) associated with active IBD. However, CRP is not specific marker for intestinal inflammation and the levels are also increased in infections, autoimmune disorders or malignancy.[6] The CRP levels in health is less than 1 mg/L, and during acute IBD levels can increase by 100-fold.[6,19] Considerable single heterogeneity exists in CRP generation. Elevations in CRP are more common in CD than in UC by the elevation of IL-6 and the transmural condition in CD.[20] A study showed that a 10% of active CD patients had low CRP (<10 mg/L) and those patients had a predominance of pure ileal disease, low