Noninvasive Assessment of Intestinal Inflammation: Inflammatory Bowel Disease vs. Irritable Bowel Syndrome

by David W. Quig, PhD and Meghan Higley, ND

Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are two chronic conditions associated with diarrhea and abdominal pain, and these symptoms are among the most common reasons that patients seek medical advice. Differential diagnosis between IBD and IBS is very important because IBD and IBS have very different underlying pathophysiology and IBD can become life-threatening, requiring extensive lifelong treatment and/or surgery. In contrast, IBS can often be treated with dietary restrictions, stress reduction and nutritive/nutritional supplements or medication.

IBD encompasses Ulcerative Colitis (UC) and Crohn's Disease (CD), which are incurable, idiopathic inflammatory diseases of the gastrointestinal (GI) tract. UC is isolated almost exclusively in the colon, but CD occurs in various segments of the GI tract; the anatomical location and degree of inflammation determine the predominant symptoms, which may include rectal bleeding. IBS does not involve inflammation or rectal bleeding, and is considered a functional disorder caused by abnormal GI motility, altered pain perception, food sensitivity, or dysbiosis. In the absence of rectal bleeding, clinical differentiation between IBD and IBS has been difficult without invasive endoscopy. A highly sensitive and specific immunoassay has recently been developed to measure the fecal concentration of the inflammatory protein lactoferrin, which facilitates noninvasive differentiation between IBD and IBS.

Lactoferrin

Fecal lactoferrin, an iron binding glycoprotein derived from polymorphonuclear neutrophils, is elevated with IBD but not IBS. During intestinal inflammation, leukocytes infiltrate the mucosa, which results in increased lactoferrin in the feces. Leukocyte-derived lactoferrin is resistant to proteolysis and freeze thaw cycles.

Clinical studies have shown that fecal lactoferrin levels of healthy persons (1.6 μg/ml) are similar to IBS patients (1.3 μg/ml), but markedly increased in patients with active IBD (Table 1). Patients with IBD oscillate between active and inactive disease states, and fecal lactoferrin increases 2-3 weeks prior to onset of clinical symptoms. During remission and effective treatment, fecal lactoferrin decreases significantly (Table 1). Therefore, disease activity and efficacy of treatment can be monitored by following fecal lactoferrin levels. The test can be ordered separately, after the initial Comprehensive Stool Analysis, to track disease activity and the efficacy of therapy in patients with IBD.

Moderately elevated levels of fecal lactoferrin may be found with red cells and leukocytes, in association with inflammatory diarrhea caused by enteroinvasive pathogens. Such levels are typically lower than those associated with even the inactive phase of IBD, and likely the result of acute damage/inflammation of the intestinal mucosa. With moderately elevated levels of fecal lactoferrin, one should check for the presence of enteroinvasive pathogens (e.g. Shigella, Campylobacter, C. difficile).

Table 1. Fecal Lactoferrin Concentrations Associated with Active and Inactive IBD

<table>
<thead>
<tr>
<th>Group</th>
<th># of Specimens</th>
<th>Fecal Lactoferrin mean mcg/ml +/- SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive UC</td>
<td>41</td>
<td>67 +/- 24</td>
</tr>
<tr>
<td>Active UC</td>
<td>31</td>
<td>815 +/- 789</td>
</tr>
<tr>
<td>Inactive CD</td>
<td>26</td>
<td>239 +/- 83</td>
</tr>
<tr>
<td>Active CD</td>
<td>51</td>
<td>672 +/- 242</td>
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Lysozyme

Lysozyme is another biomarker of intestinal inflammation. Lysozyme is an enzyme that catalyzes the hydrolysis of specific glycosidic bonds in mucopolysaccharides of the cell wall of gram-positive bacteria. Lysozyme contributes to antibacterial defense in the GI tract and is secreted by granulocytes, macrophages, Paneth cells, and Brunner’s glands, as well as normal colonic crypt cells. The main source of fecal lysozyme is intestinal granulocytes. Along with secretory immunoglobulin A (sIgA) secretion by the intestinal mucosa, lysozyme and phagocytic activity are the primary defense mechanisms against enteric infection. It is much more common to see elevated fecal sIgA and lysozyme than elevated lactoferrin associated with dysbiosis.

Markedly elevated levels of fecal lysozyme have been identified in colonic IBD compared to healthy controls. In Crohn’s Disease, excess lysozyme may be a result of active secretions of macrophages in the lamina propria, and monocytic cells in the granulomas. Additionally, Paneth cell metaplasia, a phenomenon that occurs with various inflammatory conditions of the large intestine, may be a minor contributor to fecal lysozyme.

Lysozyme is helpful in the determination of colonic inflammatory activity rather than small bowel disease. Moderately elevated levels of lysozyme may be treated with anti-inflammatory agents and/or by removing the antagonists, such as allergens or enteropathogens. Immune response to enteropathogens can be assessed by fecal sIgA levels. High levels of fecal lysozyme (>2,000) may be suggestive of IBD. To rule out IBD, check fecal lactoferrin levels.

Secretory IgA

Secretory immunoglobulin A (sIgA), a glycoprotein antibody, is the predominant immunoglobulin in intestinal mucous secretions, as well as breastmilk, tears, and oral, nasal, bronchial, and urogenital secretions. Secretory IgA antibodies in the intestine bind to antigenic epitopes on invading microorganisms, limiting their mobility and adhesion. The sIgA response at the intestinal mucosa plays a primary role in regulating the intestinal milieu, and prevents assimilation of pathogens.

The levels of sIgA in fecal specimens can be measured to assess humoral immunological activity in the gastrointestinal tract. Secretory IgA production is increased in the presence of potentially harmful antigens such as pathogenic bacteria, parasites, yeast, viruses, abnormal cell antigens, and allergenic proteins. However, sIgA production may be suppressed in cases of mental or physical stress, or inadequate nutrition. Dietary restrictions, excessive alcohol intake, body mass loss, negative mood, and anxiety have been associated with lowered sIgA production.

Elevated fecal sIgA is an appropriate response to an antigenic presence. Microbial and microscopic studies of the stool are useful in identifying if bacteria, yeast, or parasites are present. sIgA should renormalize with eradication of the pathogenic microorganisms.

Depressed fecal sIgA has been treated by probiotic supplementation of Saccharomyces boulardii, a nonpathogenic yeast. Significantly elevated levels of intestinal sIgA and subsequent enhanced host immune response have been found following S. boulardii administration in mice and rats. Depressed fecal sIgA due to inadequate diet may respond especially well to an increase of dietary L-glutamine, as the synthesis and expression of sIgA requires adequate intake of this amino acid. Animal studies have demonstrated that a glutamine-restricted diet can result in a 50% decrease in intestinal sIgA levels.

Summary

IBS is not an inflammatory condition. Although IBD and IBS share some common symptoms, IBD is a serious disease that requires proper diagnosis and chronic therapy. Fecal lactoferrin is a sensitive and specific, noninvasive biomarker for IBD, and is not elevated with IBS. Two findings of elevated levels of lactoferrin should be followed up with colonoscopy for confirmation. Fecal lysozyme is often moderately elevated with acute GI inflammation associated with severe dysbiosis, and much higher with IBD. Secretory IgA is an excellent biomarker of immunological status in the gastrointestinal tract and should be elevated as a healthy response to significant dysbiosis. The levels of these three proteins provide great insight into the degree and nature of patients’ GI inflammatory status and immunological status.

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References


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