Serum markers of Inflammatory Bowel Disease: A literature review

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ABSTRACT

Background: The diagnosis, prognosis, assessment of disease activity and severity, as well as the outcome of therapy of inflammatory bowel disease (IBD), Crohn’s disease (CD), and ulcerative colitis (UC), remain a challenge for physicians treating this disorder. For each of these aspects, there is no single gold standard test or examination. Endoscopy accompanied by histology examination can confirm the diagnosis of IBD. Laboratory markers have been investigated in IBD for diagnostic and differential diagnostic purposes, assessment of disease activity and risk of complications, prediction of relapse, and for monitoring the effect of therapy.

Objective: This article provides a review of the literature regarding IBD with the recommendation of prominent markers that can be used for diagnosing and monitoring the disease.

Conclusion: C-reactive protein is an acute phase reactant which is best used to assess inflammation in IBD. Fecal calprotectin and lactoferrin are reliable fecal markers to monitor disease activity. The combination of serological marker P-ANCA and ASCA can be used to diagnose CD. In clinical practice, Crohn’s Disease Activity Index (CDAI) is used as the primary tool for evaluating IBD.

Keywords: IBD, CRP, calprotectin, lactoferrin, P-ANCA, ASCA, CDAI

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INTRODUCTION

Inflammatory Bowel Disease (IBD), which includes Crohn’s disease (CD) and ulcerative colitis (UC), is a chronic condition characterized by gastrointestinal tract inflammation in recurrent episodes. Because CD involves the colonic region and has several clinical manifestations that resemble those of UC, it is often referred to as IBD although they apparently have different pathophysiologies. UC is the most common form of IBD. Unlike CD, UC is a mucosal disease which can be treated with colectomy, rarely causes complications, and in many patients, it causes minimal problems.

There is no gold standard examination or test in IBD diagnosis, prognosis, assessment of disease activity and severity, as well as therapeutic outcomes. Thus, clinicians use a combination of symptoms, clinical examination, laboratory tests, radiology, and endoscopy-histology examination. Laboratory markers for IBD have been widely researched to obtain an objective measurement of disease activity because symptoms are often objective. In addition, reliable lab markers may enable the avoidance of invasive procedures such as an endoscopy.

The ideal marker should give an easy and fast result, be inexpensive, and be reproducible between patients and laboratories. Moreover, the marker must be able to identify individuals at risk, and it should be specific. It should also be able to monitor disease activity and the effects of therapy. The marker should have a prognostic value related to relapse or the recurrence of the disease. An ideal marker for IBD will significantly assist surgeons or gastroenterologists in providing treatments. Unfortunately, there has not been any single marker that individually meets all of the requirements.

The focus of this review is to provide information on currently used markers for diagnosing IBD that can be used especially in a developing country.

EPIDEMIOLOGY

The incidence of IBD in the world is varied. The published data shows that IBD is more common in Europe and North America, but rare in Asia and Africa. The incidence in western countries is about 2-15 per 100,000 per year for UC and 0.9-11.6 per 100,000 per year for CD. The peak age for UC is 30 years and 20 years for CD. Women have 20-30% higher risk than men for CD. UC tends to occur more frequently in men. A total of 10-20% of IBD patients have one or more family members affected by IBD. In children, UC occurs less often than CD.

IBD is still rarely reported in Asian countries. However, studies show the number of cases of UC and CD has increased in the last ten years. In Asia, UC is found to be the most common form of IBD.
ETIOLOGY

The etiology of IBD is unknown. However, its possible causes are multifactorial. Some bacteria, parasites, and viruses are thought to be involved in the etiology of IBD. Commensal flora is often implicated in the development of IBD.

Smoking, the use of oral contraceptives, socioeconomic status, nutrition, diet, blood transfusion, and perinatal infection are considered as risk factors for IBD. Smoking is regarded as the most potent risk factor for the occurrence of IBD. Ex-smokers have a higher risk of UC occurrence compared to non-smokers. Smoking is also associated with the incidence of CD because of the presence of thrombogenic effects and vasculitis, and it seems to affect the patients' clinical condition and quality of life.

PATHOPHYSIOLOGY

Both genetic and environmental factors play an essential role in the pathogenesis of IBD. A new hypothesis also links the innate immune system and intestinal epithelium to the pathogenesis of this disease.

The role of the innate immune system

This hypothesis of the pathogenesis of IBD suggests that intestinal inflammation is immune-mediated. Chronic inflammation happens because of an excessive aggressive activity of effector lymphocytes and proinflammatory cytokines, which serve as a control mechanism. The hypothesis also suggests that IBD may occur due to primary failure of regulatory lymphocytes and cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta to control inflammation and effector pathways. The T cells resistance to apoptosis after activation is claimed to be the central pathogenic mechanism in CD.

NOD2 gene

Genetic factors play an important role in the pathogenesis of IBD, with 5% -10% of patients reported to have a family history. Research on family history and twins supports a stronger genetic influence with respect to CD as compared to UC. NOD2 gene mutations are found in one-third of individuals with CD. The NOD2 gene is an intracellular protein in bacterial products which activates the components of the innate immune system. NOD2 mutations associated with CD are still being studied.

The role of epithelial cells

Intestinal epithelium as a part of the innate immune system maintains mucosal homeostasis. In consequence, epithelial cell dysfunction can be a primary cause of IBD. Epithelial cells are a selective barrier between the body and the intraluminal microenvironment. This barrier failure can cause intestinal inflammation.

The role of the environment

Major environmental factors implicated in the pathogenesis of IBD are smoking, appendectomy, perinatal events, and socioeconomic factors. Commensal bacterial flora is an environmental factor often associated with the development of IBD. In animal experiments, intestinal inflammation did not develop when rats were placed in sterile conditions.

CLINICAL ASSESSMENT

The anatomic location and degree of inflammation determine more dominant symptoms, including rectal bleeding, diarrhea, and abdominal pain. There are several gastrointestinal clinical features of IBD. Abdominal pain is an early symptom of CD. Abdominal pain is often severe in intestinal stenosis areas. Symptoms caused by intestinal stenosis are also frequently found on the CD. Nausea and vomiting may accompany a severe stenosis.

Abdominal pain is often accompanied by either bloody or non-bloody diarrhea. The nature of diarrhea in CD depends on the part of the intestine, small intestine, or colon that is involved. Ileitis usually produces a high-volume watery stool, while colitis produces stool with less volume but more frequent occurrence. Stool consistency may vary from hard to watery. In severe cases, an
individual may defecate 20 times a day. Bloody stool is rarely found in CD compared to UC. Bowel movements which cause bloody stool are usually intermittent, and the blood can be bright red or dark red. Flatulence worsens the intestinal discomfort.  

Perianal discomfort is also prominent in CD. Itching or pain around the anus may be due to inflammation, fistula or abscess around the anal region or anal fissure. Fecal incontinence may accompany perianal CD. The esophagus and stomach are rarely involved in CD. When involved, there may be difficulty in swallowing (dysphagia), upper abdominal pain, and vomiting.

IBD is also known to cause systemic symptoms such as anemia. In children, there is a failure to grow normally. Fever rarely occurs unless there are complications such as abscesses. In older individuals, it can cause weight loss which is usually associated with the loss of appetite or malabsorption of carbohydrates and or lipids. Extraintestinal symptoms of IBD may manifest as erythema nodosum, uveitis, episcleritis, or spongyarthropathy (arthritis, enthesitis).

**DIAGNOSTIC STUDIES**

**Endoscopic diagnosis**

Colonoscopy shows mucosal inflammation starting from the anorectal margin and widening proximally, with a gradual or firm transition from the affected area to normal mucosa. In mild UC, the mucosa will appear erythematous, granular, and there might be a loss of vascular pattern. In moderate UC, there is erosion or micro-ulcers. In severe UC, there are shallow ulcers with spontaneous bleeding.

Colonoscopy can help distinguish UC from CD. The characteristics are recognized based on rectal involvement, aphthous ulcers, skip lesions or areas of inflammation interspersed with normal mucosa, cobblestone pattern, and irregular and longitudinal ulcers.

Not all endoscopic biopsy specimens can distinguish CD from UC. This often occurs in the case of proctitis. The diagnosis of indeterminate colitis is usually temporary because the disease cannot be classified as either CD or UC. This happens in less than 10% of IBD patients. Most patients can eventually be diagnosed with UC or CD.

**Histological studies**

In UC, the typical inflammation is limited to the mucosal surface. The infiltrates vary in density and composition during the active disease stage or during remission. Infiltrates are composed of lymphocytes, plasma cells, and granulocytes. Granulocytes are prominent during acute conditions and in the crypt abscess. The typical features include goblet cell depletion, crypt distortion composition, decreasing crypt density, and ulceration. The typical features in CD are the presence of epithelioid granulomas. Epithelial dysplasia indicates a risk of cancer in older patients with UC.

**LABORATORY TESTS FOR DIAGNOSIS AND MONITORING**

**Common laboratory tests**

Leukocyte count will increase as an acute phase response. However, it is not specific to IBD and may be seen in other inflammatory conditions. Leukocyte count is also influenced by some therapies used for IBD, such as glucocorticoids which increase the count, or azathioprine and 6-mercaptopurine which decrease the count. Platelet or thrombocyte count will also increase and become a sign of inflammation not specific to IBD. Albumin is a negative acute phase reactant. A decrease in the levels of albumin can be found in many inflammatory conditions.

Anemia is a significant complication of IBD. Anemia in IBD is a combination of iron deficiency anemia and inflammation or anemia of chronic disease caused by the adverse effects of the activated immune system. Furthermore, metabolic disorders and vitamin deficiency can exacerbate anemia in IBD. Some data suggest that hepcidin, a peptide produced by hepatocytes, is a major mediator of anemia because of its role in iron homeostasis and metabolism. Inflammation increases hepcidin. Hepcidin examination can provide a differential diagnosis of anemia during inflammatory conditions. A study conducted by Oustomanolakis et al. in 2011 showed that serum hepcidin concentration changed significantly in patients with IBD when compared to healthy controls.

**C-Reactive Protein (CRP)**

CRP is a pentameric protein consisting of five monomers. Under normal circumstances, CRP is produced by hepatocytes in a small amount (<1 mg/L). If there is an acute phase stimulus such as inflammation, hepatocytes influenced by interleukin-6 (IL-6) will rapidly increase CRP production and reach peak levels of 350-400 mg/L. These responses will be reinforced by IL1-β and tumor necrosis factor alpha (TNF-α). The half-life of CRP is about 19 hours. In general, 10-40 mg/L of CRP is found in mild inflammation or virus infection. Severe active inflammation or bacterial infection will increase CRP to 50-200 mg/L. In
severe conditions and burns, CRP may reach a very high level of 200-250 mg/L.\(^3\)

With the presence of acute phase stimulus, CRP is produced quickly within hours and can reach a concentration of 500-1000 times higher than the basal conditions. The short half-life ensures that the concentration declines rapidly when the stimulus disappears. It makes CRP a valuable marker in detecting and monitoring the presence of inflammation.\(^15\)

In CD, the concentration of CRP correlates well with the disease activity and with Crohn’s Disease Activity Index or CDAI. An increase in CRP (> 45 g/L) estimates the need for colectomy in patients with IBD.\(^15\) Although CRP is found in many inflammatory diseases including IBD, the responses are different between CD and UC. A strong CRP response is associated with CD, whereas UC has only a weak CRP response or even a non-existent one.\(^3\)

### Other acute phase reactants

Other acute phase reactants include sialic acid, alpha-1-acid glycoprotein or orosomucoid, fibrinogen, lactoferrin, beta-2-microglobulin, serum amyloid A, alpha-2-globulin, and alpha-1-antitrypsin. These markers have not been proven superior to CRP in IBD, mainly because the half-life of these proteins is longer.\(^3\)

Beta-2-microglobulin is a protein with low molecular weight and is released by activated T and B lymphocytes. The half-life is estimated to be about two hours. Beta-2-microglobulin is filtered through the glomerulus and the level increases with age and as kidney function declines.\(^3\) Orosomucoid correlates with disease activity but is less useful in clinical practice because the half-life is five days.\(^3\)

There is no explanation for the increase in IL-6, IL-1β, or TNF-α in UC. A study by Gross et al. found the IL-6 serum concentration significantly elevated in CD patients as compared to UC patients and healthy subjects as the control. The IL-6 serum concentration was over 4 U/mL in 68.5% of CD patients, 21.7% of UC patients, and 0% of healthy patients. The authors asserted that the difference might occur because in UC the inflammation only involves mucosa, while in CD it is transmural.\(^3\)

Erythrocyte sedimentation rate (ESR) is the rate at which erythrocyte migrates through the plasma. ESR depends on the plasma concentration and the erythrocyte number and size. Conditions such as anemia, polycythemia, and thalassemia will affect ESR.\(^3\) ESR measurements can help determine the severity of inflammation.\(^2\)

Compared to CRP, ESR reaches its peak less quickly, and it needs a few days to decline even though the clinical condition of the patient has improved or the inflammation has been reduced. Moreover, ESR increases with age.\(^3\)

### Fecal Marker

Fecal markers can be used because the stool can be easily obtained in patients with IBD. When there is no gastrointestinal infection, stool markers have a high specificity.\(^3\)

#### Labeled with Indium\(^{111}\)

Leukocyte labeled with Indium\(^{111}\) (\(^{111}\)In) is regarded as the gold standard of fecal markers in inflammation. The sensitivity is 97% in diagnosing IBD. However, radioactive labeling is not recommended for routine use because it is expensive, exposes the patient and the environment to radiation, and it takes 4 days for fecal collection.\(^16\)

#### Alpha-1-Antitrypsin

Alpha-1-antitrypsin is a protease inhibitor produced by the liver, macrophages, and intestinal epithelium. A 72-hours alpha-1-antitrypsin fecal clearance is a method of quantifying the intestinal protein loss to measure the activity of CD. Although fecal alpha-1-antitrypsin is useful in IBD, this marker is not routinely used and not cost-effective.\(^16\) The excretion of another fecal anti-protease, alpha-2-macroglobulin, also increases in patients with IBD. Alpha-2-macroglobulin in the stool has a positive correlation with the index of activity in CD, but not in UC.\(^16\)

#### Fecal Calprotectin

There are several proteins derived from neutrophil existing in stools: fecal lactoferrin, lysozyme, elastase, myeloperoxidase, calprotectin, and PMN-elastase.\(^3,16\) Calprotectin is a protein bound to calcium and zinc, with a molecular weight of 36 kDa.\(^3,16\) This substance has several synonyms: complex S100A8 and S100A9, and L1H L1L protein, macrophage inhibitory factor-related protein MRP8/14, calgranulin.\(^1\)

In contrast to other neutrophil markers, calprotectin represents 60% of the protein in the cytosol of granulocytes.\(^3,16\) The presence of calprotectin in stools is directly proportional to the migration of neutrophil into the gastrointestinal tract.\(^1,3,16\) Fecal calprotectin is a very stable marker. It is stable for over one week at room temperature and resistant to degradation.\(^1,3,16\)

Previous studies on the use of fecal calprotectin in IBD showed a strong correlation with the excretion of leukocytes labeled with...
In and intestinal permeability. Increased fecal calprotectin levels have been reported with the use of nonsteroidal anti-inflammatory drugs and also with age. The concentration of fecal calprotectin in healthy individuals is several times higher than in serum/plasma. Fecal calprotectin is strongly associated with colorectal inflammation, and it indicates the presence of organic diseases. Fecal calprotectin can indicate whether the activity of the disease is mild, moderate or severe, so this can be a useful marker for monitoring disease. This marker can also be used to distinguish between CD and IBS.

Several factors affect the concentration of fecal calprotectin. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the concentration because the drugs may induce enteropathy in non-IBD patients. Bleeding of more than 100 mL, including menstrual bleeding, can increase the levels of fecal calprotectin. Although calprotectin is a highly sensitive marker for detecting inflammation in the gastrointestinal tract, its concentration is also elevated in neoplasia, IBD, infection, and polyps, which makes it nonspecific.

**Fecal Lactoferrin**

Lactoferrin is a glycoprotein which contains iron secreted by most mucosal membranes. This marker is a major component of the secondary granules of polymorphonuclear cells, where these cells are primary cells in the acute inflammatory response. Other hematopoietic cells, monocytes, and lymphocytes do not contain lactoferrin. When there is intestinal inflammation, leukocytes invade the mucosa, increasing the fecal excretion of lactoferrin.

Lactoferrin has antibacterial activity and resistance to proteolysis in the stools. This substance can be stable in feces for 4 days. Lactoferrin can be detected using ELISA, a simple and inexpensive technique.

Vieira (2009) showed that lactoferrin is a very sensitive and specific marker for detecting intestinal inflammation. The sensitivity is 90%, and the specificity is 92% when compared with histological evaluation.

**Fecal Pyruvate Kinase Marker**

Fecal Pyruvate Kinase marker or tumor M2PK which previously was a marker for colorectal cancer can also be used as a marker for gastrointestinal inflammation. This marker is used to differentiate organic diseases of functional bowel disease. However, the sensitivity, the specificity, and the predictive value are lower than calprotectin.

**Rectal Nitric Oxide**

Nitric oxide (NO) is a gas produced endogenously through a variety of physiological processes. Leukocytes and epithelial cells express inducible nitric oxide synthase (NOS) in response to acute proinflammatory cytokines. It leads to the production and accumulation of large amounts of NO. Rectal NO is correlated with disease activity in IBD patients. The concentration decreases in response to anti-inflammatory therapy. Therefore, NO rectal marker may be useful to monitor the response to therapy in IBD.

**Fecal Myeloperoxidase**

Myeloperoxidase, an enzyme that works to kill microorganisms, is released from primary granules of neutrophils during acute inflammation. Myeloperoxidase concentrations are proportional to the number of neutrophils in the inflamed tissue. In fact, myeloperoxidase has potential as a marker for assessing treatment success outcomes in IBD patients.

**Fecal Eosinophil Protein X**

Activated eosinophil granulocytes release eosinophil protein X (EPX). Fecal EPX levels are studied as an indicator of therapy outcomes in IBD relapse. Fecal EPX also complements endoscopic and histological evaluation in the daily care of UC patients.

**Specific Marker**

Antibodies against antigens of microbes, including yeast oligomannan (anti-Saccharomyces cerevisiae or ASCA), bacterial outer membrane Porin C (OmpC), Pseudomonas fluorescent bacterial sequence 12 (anti-12) and bacterial flagellin (Cbir1), are major IBD serological biomarkers. All these antibodies are mainly found in CD but not in UC, except ASCA which is found in 5% of UC patients.

Human autoantibodies against neutrophil called perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are thought to be an autoantibody. p-ANCA is found in 70% of patients with UC and 20% of patients with CD.

<table>
<thead>
<tr>
<th>Table 1 Fecal calprotectin reference value in healthy children and children with IBD</th>
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</thead>
<tbody>
<tr>
<td><strong>Calprotectin Level</strong></td>
</tr>
<tr>
<td>≤50 µg Calprotectin/g in stool</td>
</tr>
<tr>
<td>50-100 µg Calprotectin/g in stool</td>
</tr>
<tr>
<td>&gt;100 µg Calprotectin/g in stool</td>
</tr>
<tr>
<td>&gt;250 µg Calprotectin/g in stool</td>
</tr>
<tr>
<td>&gt;500µg Calprotectin/g in stool</td>
</tr>
</tbody>
</table>

IBD: Inflammatory Bowel Disease, GI: Gastro Intestinal
Human autoantibodies against neutrophil

Antineutrophil cytoplasmic antibody (ANCA) is associated with primary diseases of small blood vessels, such as Wegener’s granulomatosis, polyangiitis, and Churg-Strauss syndrome. Classical examination of ANCAs is screened using indirect immunofluorescence using ethanol-fixed neutrophils. Indirect immunofluorescence shows two main staining patterns: a cytoplasmic granular pattern (c-ANCAs) and a perinuclear pattern (p-ANCAs). The staining pattern of c-ANCA shows granular cytoplasmic fluorescence which is often located among nuclear lobes. C-ANCAs mainly present in the serum of patients with Wegener’s granulomatosis and especially recognize proteinase-3. P-ANCA staining shows perinuclear cytoplasm with a homogeneous edge or surrounding the nucleus, and a nuclear widening may exist. P-ANCAs are found in patients with microscopic polyangiitis and recognize myeloperoxidase. P-ANCA staining is also seen in antibodies against other neutrophil enzymes and anti-nuclear antibodies specific to neutrophils.16

The presence of ANCAs has also been reported in patients with chronic inflammatory diseases, such as UC (60-80%), primary sclerosing cholangitis (88%), autoimmune hepatitis (81%) and CD (5% -25%).14 In these diseases, staining patterns of atypical p-ANCA are typically found. The antigens are not myeloperoxidase. Atypical p-ANCA is characterized by fine-rimmed peripheral nuclear staining.14

The prevalence of ANCAs varies between 18% and 68% with a value of $\kappa <0.2$, indicating a poor agreement. The sensitivity of ANCA in 150 patients with UC varied between 0% and 63% at five different laboratories (Prometheus, Oxford, Wuerzburg, Mayo, and Smith Kline Beecham).18 Atypical p-ANCAs are mainly found in UC (50-67%), and also in CD (6-15%). Atypical p-ANCAs are also found in autoimmune hepatitis and primary sclerosing cholangitis.15

Serologic evaluation of ANCAs and ASCAs can help patients with indeterminate colitis.18 In multicenter prospective studies, the combination of ASCA+/ANCA can indicate CD in 80% of patients with indeterminate colitis (sensitivity 67%, specificity 78%, positive likelihood ratio 3). ASCA/ANCA- can indicate UC in 64% of patients (sensitivity 78%, specificity 67%, positive likelihood ratio 2.3).18

Anti-Saccharomyces Cerevisiae Antibodies

An increase in the concentrations of ASCA antibodies is found in patients with CD. Both IgG and IgA antibodies are formed. These antibodies are found in 60-70% of patients with CD, 10-15% of patients with UC, and 0-5% of individual controls.18

Comparative research shows a wide range of sensitivity and specificity among 4 examinations which most likely is due to the selected cutoff value. The value agreement among these examinations is good.18

In contrast with p-ANCAs, ASCAs are not regarded as autoantibodies, but rather as antibodies against bacteria or fungi. The presence of ASCAs in patients with IBD is possibly because of the response to antigens S. cerevisiae or to unidentified antigens which cross-react with S. cerevisiae.18

The prevalence of ASCAs is higher in CD patients (40-60%) than in UC patients (5-14%). The prevalence in healthy controls is <5%,18

The combination of atypical p-ANCAs and ASCAs may be useful in differentiating UC from CD in patients with IBD. ASCA+/P-ANCA- is associated with CD, while ASCA-/P-ANCA+ is associated with UC. The combination of ANCAs and ASCAs has a higher specificity in distinguishing CD from UC, showing >90% in most studies, and >80% in all studies.16

Anti-glycan Antibodies

Glycan is a major component of the cell wall surface in most saprophytic and pathogenic fungi, yeast, and bacteria. Some anti-glycan antibodies are anti-Saccharomyces cerevisiae antibodies (ASCA), anti-chitobioside carbohydrate antibody (ACCA), anti-laminaribioside IgG (ALCA), anti-manobioside IgG (AMCA), $\Sigma$Man3, $\Sigma$Man4, Anti-L (anti-laminarin), and Anti-C (anti-chitin).13,15 These biomarkers have been tested for CD, and have a high specificity but low sensitivity.16

ASCA marker has the highest diagnostic value among anti-glycan markers. Whereas ACCA has an association with complications.19

Two immunoglobulins A (IgA) cell wall polysaccharide antibodies, anti-L and anti-C, can distinguish between CD and UC.19

D-lactate

D-lactate is a new indicator that is used to indicate the presence of damage to the intestinal mucosa and permeability changes in IBD.20 D-lactate, the gastrointestinal bacterial metabolic end product, can be produced by some bacteria. Because mammals do not have enzymes for decomposition, D-lactate will enter the blood when the intestinal barrier is damaged. Because mammals do not have D-lactate dehydrogenase, an increase in D-lactate levels can detect an increase in intestinal mucosal permeability.
Thus peripheral blood tests can indicate the degree of damage and changes in the permeability of intestinal mucosa. Many clinical trials and tests on animals have shown the usefulness of D-lactate in diagnosing IBD. However, this marker should be interpreted with caution, and further research is still needed to determine its clinical role in diagnosing IBD.

Diamine oxidase (DAO) is an active intracellular enzyme in the cytoplasm of intestinal mucosal cells. In cases where the epithelial cells of intestinal mucosa and barrier function are damaged, the release of DAO will increase. DAO will enter extracellular space, lymphatic blood vessels and blood flow, thus increasing DAO plasma concentration. Because DAO activity is stable, the concentration in the blood can indicate the damage and restoration of the intestinal cavity. This marker may be a new marker in the diagnosis of IBD. Similar to D-lactate, there is still much controversy about the usefulness of this marker, and further research is still needed.

Serum Soluble Intercellular Adhesion Molecule-1 (sICAM-1)

Intracellular Adhesion Molecules (ICAMs) are a type of glycoprotein synthesized by cells, assembled on the surface of cells or secreted to the cell epimatrix, and able to improve the adhesion between cells or between cells and the epimatrix. In normal tissues, this molecule is usually expressed in low amounts in vascular endothelial cells and the intestinal lamina propria mononuclear macrophages in mucosa and lymph. In an IBD patient's intestinal tissue, the expression and distribution of ICAM-1 significantly increases and is closely related to the degree of tissue inflammation. Adhesion molecules in vascular endothelial cells, leukocytes, and other cells can get into the cell, or go into the blood circulation, and become soluble intercellular adhesion molecule-1 (sICAM-1). In fact, an increase in sICAM-1 in serum is a marker of damage or activation of endotheliosis. Therefore, the level of serum sICAM-1 is a significant index in detecting some diseases.

Table 2  CDAI Scoring

<table>
<thead>
<tr>
<th>Variable No.</th>
<th>Variable Description</th>
<th>Multiplier</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No. of liquid or soft stools (each day for 7 days)</td>
<td>× 2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Abdominal pain, sum of seven daily ratings (0=none, 1=mild, 2=moderate, 3=severe)</td>
<td>× 5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>General well-being, sum of seven daily ratings (0=generally well, 1=slight under par, 2=poor, 3=very poor, 4=terrible)</td>
<td>× 7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Number of listed complications (arthritis or arthralgia; iritis or uveitis; erythema nodosum; pyoderma gangrenosum, or aphthous stomatitis; anal fissure, fistula, or abscess; other fistulas; fever over 37.8°C)</td>
<td>× 20</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Use of diphenoxylate or loperamide for diarrhea (0=no, 1=yes)</td>
<td>× 30</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Abdominal mass (0=no, 2=questionable, 5=definite)</td>
<td>× 10</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Hematocrit (males: 47-Hct (%), females : 42-Hct (%))</td>
<td>× 6</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Body weight (1-weight/ standard weight) x 100 (add or subtract according to sign)</td>
<td>× 1</td>
<td></td>
</tr>
</tbody>
</table>

Table 3  MAYO Scores

<table>
<thead>
<tr>
<th>Variable description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool Frequency</td>
<td></td>
</tr>
<tr>
<td>Normal number of stools for this patient</td>
<td>0</td>
</tr>
<tr>
<td>1 to 2 stools more than normal</td>
<td>1</td>
</tr>
<tr>
<td>3 to 4 stools more than normal</td>
<td>2</td>
</tr>
<tr>
<td>5 or more stools more than normal</td>
<td>3</td>
</tr>
<tr>
<td>Rectal Bleeding</td>
<td></td>
</tr>
<tr>
<td>No blood was seen</td>
<td>0</td>
</tr>
<tr>
<td>Streaks of blood with stool less than half of time</td>
<td>1</td>
</tr>
<tr>
<td>Obvious blood with stool most of the time</td>
<td>2</td>
</tr>
<tr>
<td>Blood alone passed</td>
<td>3</td>
</tr>
<tr>
<td>Endoscopic Findings</td>
<td></td>
</tr>
<tr>
<td>Normal or inactive disease</td>
<td>0</td>
</tr>
<tr>
<td>Mild disease (erythema, decreased vascular pattern, mild friability)</td>
<td>1</td>
</tr>
<tr>
<td>Moderate disease (marked erythema, absent vascular pattern, friability, erosions)</td>
<td>2</td>
</tr>
<tr>
<td>Severe disease (spontaneous bleeding, ulceration)</td>
<td>3</td>
</tr>
<tr>
<td>Physician's Global Assessment</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Mild disease</td>
<td>1</td>
</tr>
<tr>
<td>Moderate disease</td>
<td>2</td>
</tr>
<tr>
<td>Severe disease</td>
<td>3</td>
</tr>
</tbody>
</table>

Thus peripheral blood tests can indicate the degree of damage and changes in the permeability of intestinal mucosa. Many clinical trials and tests on animals have shown the usefulness of D-lactate in diagnosing IBD. However, this marker should be interpreted with caution, and further research is still needed to determine its clinical role in diagnosing IBD.
DISEASE ACTIVITY SCORING SYSTEM

Crohn’s Disease Activity Index (CDAI)

Crohn’s Disease Activity Index (CDAI) is the primary index for evaluating disease activity and to assess the success of therapy.22 CDAI score classifies the disease activity as a remission if the score is <150, responsive if the drop is more than 70 points, mild disease activity if the score is 150-220, moderate if the score is 220-450, severe if the score is more than 450.23

MAYO Scores

Patients with a Mayo score of ≥ 6 have moderate-severe disease activity and are difficult to control. The components of Mayo scores include frequency of stool + rectal bleeding + endoscopic picture + overall assessment by clinicians.24 Mayo scores are between 0 to 12. The degrees of severity indicated by MAYO scores are remission ≤ 2, mild 3-5, moderate 6-10, severe 11-12. The overall assessment by clinicians also involves other criteria, such as abdominal discomfort, general condition of health, the physical and performance status of patients.24

CONCLUSION

There are many IBD markers, but there is not yet any single and ideal marker. C-reactive protein is an acute phase reactant that can be used to assess inflammation in IBD. Fecal markers calprotectin and lactoferrin are better to assess disease activity in IBD. The combination of serological markers P-ANCA and ASCA can be used for the diagnosis of Crohn’s disease in patients with IBD. In clinical practice, CDAI score can be used to evaluate disease activity.

REFERENCES


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