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TOPIC HIGHLIGHT

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Evaluation of inflammatory activity in Crohn's disease and ulcerative colitis

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Abstract

Crohn's disease and ulcerative colitis evolve with a relapsing and remitting course. Determination of inflammatory state is crucial for the assessment of disease activity and for tailoring therapy. However, no simple diagnostic test for monitoring intestinal inflammation is available. Noninvasive markers give only indirect assessments of disease activity. Histopathological or endoscopical examinations accurately assess inflammatory activity, but they are invasive, time consuming and expensive and therefore are unsuitable for routine use. Imaging procedures are not applicable for ulcerative colitis. The usefulness of ultrasound and Doppler imaging in assessing disease activity is still a matter of discussion for Crohn's disease, and an increased interest in computed tomography enterograph (CTE) has been seen, mainly because it can delineate the extent and severity of bowel wall inflammation, besides detecting extraluminal findings. Until now, the available data concerning the accuracy of magnetic resonance enterography in detecting disease activity is less than CTE. Due to this, clinical activity indices are still commonly used for both diseases.

Key words: Crohn's disease; Ulcerative colitis; Inflammatory bowel disease; Diagnostic test; Therapy; Inflammatory markers

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises two major disease entities: Crohn's disease (CD) and ulcerative colitis (UC). Its etiology is not completely understood, but it is characterized by chronic inflammation of the gastrointestinal tract. Treatment is generally effective in relieving symptoms, but is not curative. Typically, these diseases evolve with

a relapsing and remitting course. Exacerbations are characterized by diarrhea, abdominal pain and rectal bleeding.

Determination of inflammatory activity is crucial for the assessment of disease activity and for tailoring the therapy. Ideally, a disease marker must be disease specific, mirror the presence of activity, be easily applicable in clinical practice and identify patients at risk for relapse. However, no such disease markers have been described so far.

Numerous clinical activity indices and other noninvasive markers are used in IBD, but they all give only indirect assessments of disease activity and none are accurate in evaluating inflammatory activity as found by histopathological or endoscopical examination. On the other hand, endoscopic evaluation is difficult to perform, invasive, time consuming and expensive, and hence is unsuitable for routine use. In the biological era, mucosal healing in CD is associated with a longer duration of remission and fewer hospitalizations, so endoscopic evaluation becomes essential[1]. It is clear that treatment must have an impact in the natural course of the disease. In the pre-biological and pre-immunosuppressive era, more than 80% of patients with CD required some kind of surgery during their lifetimes and approximately 75% of patients displayed new lesions on endoscopy 1 year after surgery[2-4]. In UC, ultimately, up to a third of patients with extensive disease will require a colectomy at some point during the disease's course[4].

Identifying whether patients are in a relapsing or remission phase is important to offer an adequate therapy and since intestinal symptoms are a frequent cause for referrals to gastroenterologists, it is crucial to distinguish between non-inflammatory functional problems such as irritable bowel syndrome (IBS) and IBD. IBD is characterized by unpredictable flare-ups of symptoms that impair the patient's quality of life. So, markers of inflammation are important in the follow-up of patients, especially during periods of low disease activity, when it is essential to detect sub-clinical intestinal inflammation and to predict relapsing disease. This could promote a refinement of therapy to the actual needs of each case.

This article aims to make a critical review of clinical, endoscopic, laboratory and image markers of disease with respect to their ability of establishing disease activity.

CLINICAL ACTIVITY INDEX

The instrument most commonly used to quantify disease activity in CD has been the Crohn's disease activity index (CDAI). It is a scoring system derived from the sum of products from a list of 8 items that combines subjective symptoms, objective findings on examination and laboratory testing (Table 1)[5]. Index values of 150 or below are associated with non-active disease. Values between 151 and 220 indicate mild activity, and between 221 and 450 indicate moderate to severe activity. Values over 450 indicate extremely severe disease. However, reproducibility of the CDAI is limited by a great deal of inter-observer variation and, in fibrostenotic disease, it may reflect poorly on bowel inflammation as a cause of symptoms because it induces subjective measurements[6]. Other disease activity indices include van Hees index, the Cape Town index, Oxford index and Talsted index, but none result in a better approach to identify relapses[7-10].

Table 1 Crohn's disease activity index items and weighting factors

Item (daily sum per week)	Weighting factor
Number of liquid or very soft stools	2
Abdominal pain score in one week (rating, 0-3)	5
General well-being (rating, 1-4)	7
Sum of physical findings per week	
Arthritis/arthralgia	
Mucocutaneous lesions (e.g., erythema nodosum, aphthous ulcers)	
Iritis/uveiti	
Anal disease (fissure, fistula, *etc.*)	
External fistula (enterocutaneous, vesicle, vaginal, *etc.*)	
Fever over 37.8 ℃	20
Antidiarrheal use (e.g., diphenoxylate)	30
Abdominal mass (no = 0, equivocal = 2, yes = 5)	10
47 minus hematocrit (males) or 42 minus hematocrit (females)	6
1-x (1-body weight divided by a standard weight)	1

In order to evaluate the overall state of well-being of patients, with a focus on various domains, the Inflammatory Bowel Disease Questionnaire is the most widely accepted disease-specific instrument and measures separate domains for bowel, social, systemic and emotional function[11].

In UC, the clinical activity index most commonly used to define the severity of disease was established by Truelove and Witts[12]. It defines mild and severe disease activity, with moderate activity being present when there are intermediate symptoms. In the mild form there are fewer than four stools daily, with or without blood, with no systemic repercussion and a normal erythrocyte sedimentation rate (ESR). In moderate one, the number of stools daily is greater than four but with minimal systemic repercussion. In the severe form, there are more than six stools daily with blood and with evidence of systemic repercussion, as shown by fever, tachycardia, anemia, or an ESR greater than 30. Clinical remission was defined as 1 or 2 stools per day without blood, absence of fever and tachycardia, a normal hemoglobin or its tendency towards reference values, a normal erythrocyte sedimentation rate and weight gain. It is simple and easy to use, but lacks precision, especially in the definition of more severe cases. It is not clear how many systemic features are required, and, furthermore, an attack can be followed by fever, tachycardia or anemia, which would characterize it as severe, but the patient may look well. Not unrarely, patients can present moderately severe symptoms and that the original index did not predict. Additionally, neither the Truelove and Witts Severity Index nor the definitions, as clinical remission or improvement, have been validated, and also, not being quantitative, no disease severity score is generated. Various attempts to create a numerical index have been made, such as the St. Marks Index, the Clinical Activity Index (also known as the Rachmilewitz Index), the Physi-

cian Global Assessment, and the Lichtiger Index. None have been validated and there is no evidence that any of them are better than Truelove and Witts[13-16].

Although not mentioned in the original classification of Truelove and Witts, the term fulminant is used to describe a particularly severe form and is defined by more than 10 evacuations per day, continuous presence of blood in stool, temperature above 37.5 ℃, heart rate over 90 beats/min, erythrocyte sedimentation rate above 30 mm and a need for transfusion.

NON-INVASIVE MARKERS

A great deal of research has been devoted to the search for a laboratory marker of disease activity in IBD in past decades. The reasons for this are firstly to overcome the subjectivity of symptoms by means of an objective evaluation and, secondly to avoid endoscopic and imaging procedures, which may be invasive, expensive and time-consuming[17]. With the introduction of newer biological therapies, there might be potential for laboratory markers in selecting responders along with their role in monitoring therapy[17]. Differential diagnosis with IBS and the follow-up of patients in periods of low disease activity, in order to detect sub-clinical intestinal inflammation and to predict disease relapses, are other important roles of these markers[18].

Serology markers

The acute phase response indicators ESR and C-reactive protein (CRP) have long been used as markers of inflammation and, consequently, of disease activity in IBD. CRP is the most studied among them and is considered to have the best performance. Produced by hepatocytes in low rates under normal circumstances, it rises rapidly in situations of systemic inflammation, under the influence of interleukin-6, tumoral necrosis factor-α and interleukin 1β[19]. It correlates well with clinical, endoscopic, radiological and cross-sectional activity markers in IBD, especially in CD, but not in UC[17,18,20,21]. CRP has the advantage of an early rise after onset of inflammation and a rapid decrease after its resolution, due to its short half-life of 19 h. In CD, ESR is hampered by its lack of specificity, slow increase and late decrease[17]. In UC there is a good correlation between ESR and disease activity, however it is not useful in distal proctitis because of the small area of inflammation involved[22,23]. In CD, ESR may correlate with colonic CD involvement[24]. Both polymerase chain reaction and ESR relate to systemic host responses but not with intestinal inflammation and, as a consequence, have no predictive value for the course of the disease[18].

Leukocytosis, commonly found during disease activity, may be the consequence of a number of inflammatory conditions and stressful situations. It may also increase or decrease as a consequence of therapy (corticosteroids, azathioprine and 6-mercaptopurine). Thrombocytosis may occur in inflammatory states, but the range of normal values is too wide to allow for good sensitivity or specificity. Decreased levels of serum albumin may be found during activity of CD, but malnutrition, malabsorption, as well as intestinal protein loss may also lead to albumin level reductions[17].

Other classical acute phase proteins that can be detected in the serum of IBD patients are α1-acid glycoprotein (orosomucoid), fibrinogen, serum amyloid A, β2-microglobulin, α2-globulin, and α1-antitrypsin. The levels of circulating orosomucoid correlate with disease activity of IBD as assessed by standard indices. Furthermore, circulating orosomucoid levels correlate with the protein loss into the gut, but its five day half-life in serum limits its usefulness as an indicator of improvement in disease activity[25]. Most of these acute phase markers have been sparsely studied and do not show advantages over CRP in detecting and monitoring inflammation in IBD[17,26].

The search for an etiologic agent involved in the initiation of the immune-mediated bowel injury of IBD has led to the discovery of immune markers present in the sera of patients with CD and UC. The DNase-sensitive anti-neutrophil cytoplasmic antibody, with perinuclear highlighting (p-ANCA) on immunofluorescence, directed to a nuclear histone has been shown repeatedly to be present in the sera of 60% of UC and 20% of CD patients, with 5% of non-IBD patients being p-ANCA-positive. Anti-*Saccharomyces cerevisiae* (*S. cerevisiae*) IgA and IgG antibodies (ASCA), directed against a specific oligomannosidic epitope present on the cell wall of the yeast appears to represent an immune response to the antigens on the *S. cerevisiae* itself, or a cross reaction to an unidentified antigen present on the cell wall of a luminal bacteria[27-30]. ASCA is expressed in 60% of CD, 10% of UC, and 5% of non-IBD patients. Other microbial antigens recently identified to be involved in the IBD immune response [*Escherichia coli* outer membrane porin C (OmpC), the *Pseudomonas fluorescens* CD-related protein (I2), and anti-CBiR1 (anti-flagellin)] are present in 50% of CD patients and uncommon or not detected in the UC and non-IBD population. The role of these antigens in the diagnosis of IBD, in the differential diagnosis between CD and UC and in disease stratification and course are promising. The role of these emerging antigens as indicators of disease activity has not been established[26,30-33].

Recently, it was observed that elevated serum levels of antibodies specific for certain carbohydrate structures might have a relationship with CD[34]. Malickova *et al*[35] evaluated anti-chitobiose carbohydrate antibody, anti-laminaribiose, carbohydrate antibodies, and anti-mannobiose carbohydrate antibodies in Central European patients with IBD and concluded that that a panel of anti-carbohydrate antibodies might provide additional help in distinguishing IBD from non-IBD disease patterns. However, anti-carbohydrate assays are not helpful for predicting CD behavior[35]. Another study, conducted by Rieder *et al*[36], showed the clinical value of serum anti-glycan antibodies for the prediction of a more complicated disease course in adult patients with CD.

The relationship between pro-inflammatory cytokine serum levels and IBD activity has been demonstrated. More recently, correlation between cytokines and endoscopically determined mucosal inflammation was demonstrated, suggesting the potential role of these markers in determining

disease activity[37-42]. IL-6 in active CD and IL-10 in recovery of CD have demonstrated a good correlation, which has been reproducible between studies[43].

Stool test

A number of reasons have led to the development of fecal markers of inflammation in IBD in addition to, or in substitution of, serum markers. As they are derived from stools, they may be of easy access. Also, they may have a higher specificity than serum markers, since they may reflect intestinal rather than systemic inflammation, a result of the close contact of stools with intestinal mucosa and of the possibility that it may wash out molecules related to inflammation or damage. Finally, they may avoid endoscopic examinations, since they are related to mucosal inflammation[17,18].

Stool markers cannot be considered specific for IBD, since they can be increased in situations of mucosal inflammation, irrespective of an infectious or non-infectious etiology. Markers expressed by phagocytes may be more specific for inflammation, while markers found in epithelial cells may be more sensitive and can increase in conditions of non-inflammatory stress[18].

Fecal occult blood (FOB) and α-1 antitrypsin are markers of mucosal damage and/or disturbed barrier function. FOB determination lacks specificity for IBD and cannot be related to disease activity[44]. α-1 antitrypsin is considered a sensitive but non-specific parameter reflecting enteric inflammation in IBD and has been replaced by other fecal markers[45].

Substances related to phagocyte influx and activation comprises another group of IBD fecal markers with pathophysiological rationale. They appear as a result of leukocyte degranulation consequent to the activation of innate immunity which, in IBD, relates to phagocyte gathering and cytokine production in areas of inflammation. One interesting and already classic application of this rationale is the use indium-111-labelled granulocyte scintigraphy[46,47]. However, this technique is expensive, involves long-term stool sampling, exposure to radiation, and may not be applicable in clinical routine. This is why leukocyte degranulation markers have been studied. Even in situations of milder inflammation, products from activated phagocytes within the mucosa may spill over into the lumen and remain stable in single random stool samples, making them a more sensitive, cheaper and easier alternative to indium-111-labelled granulocyte scintigraphy[48].

Lactoferrin, polymorphonuclear elastase, eosinophil cationic protein (ECP), eosinophilic protein X (EPX), myeloperoxidase and lysozyme are among the leukocyte degranulation markers better evaluated so far. ECP and EPX are eosinophil degranulation markers that have been described in IBD, but are considered inferior to other markers and more indicative of pathological processes that involve eosinophils[49-51]. Lactoferrin, polymorphonuclear (PMN) elastase, myeloperoxidase, and human neutrophil lipocalin are neutrophil degranulation markers detected in the stool. Lactoferrin is the most accurate among them, but it may be present in cells other than granulocytes (i.e., epithelial cells) and may have anti-inflammatory action. Also, its pathogenetic link to IBD has not yet been elucidated.

Recently, a group of molecules with pro-inflammatory activity have been described as part of the innate immune system. The innate immunity starts our primary host defense by recognizing invading microorganisms through pathogen-associated molecular patterns (PAMPs). Activated or damaged cells can secrete the damage-associated molecular pattern proteins (DAMPs). The precise mechanism by which microorganisms activate inflammation in IBD is only partially known, but it seems that PAMPs and DAMPs have an important interaction. There are probably multiple positive feedback loops between both molecules and their overlapping receptors may amplify inflammatory processes. As DAMPs are related to the initiation of cell stress and inflammation and are found in areas of intestine affected by IBD, they are considered good candidates as markers of disease activity. S100A8, S100A9 and S100A12 are recently described DAMPs that are ligands to pattern recognition receptors, such as toll-like receptors 4 and receptors for advanced glycation end products and directly related with the amplification inflammatory processes[52-54].

The complex S100A8/S100A9 was named calprotectin, and a strong correlation between it and indium-111-labelled granulocyte scintigraphy, the gold standard method for detecting inflammatory activity in IBD, has been demonstrated[47]. Calprotectin is commercially available and an assay for S100A12 is under development[55]. Calprotectin can be used in disease monitoring, showing a closer correlation to endoscopic and histological evidence of inflammation than clinical indices, and detecting inflammatory activity before the appearance of clinical signs[56-58]. However, calprotectin seems more predictive of relapse in UC than in CD[58,59]. Rapid, qualitative or semi-quantitative tests were developed and seem promising for discrimination of IBD from IBS. A recent meta-analysis involving 13 studies with 670 adults and 371 children and teenagers showed that fecal calprotectin is a useful screening tool for identifying patients who are most likely to need endoscopy for suspected inflammatory bowel disease[60].

The performance of the fecal markers lactoferrin, PMN elastase and calprotectin, along with CRP and clinical indices, compared to endoscopic measures of inflammation has been evaluated. The three fecal markers are able to define disease activity both in UC and CD, and distinguish both IBDs from IBS in some situations depending on the marker, even in the absence of activity. None of the three markers seem superior in their ability to reflect endoscopic inflammation, but all three are superior to CRP in their diagnostic accuracy[19].

Abnormalities in intestinal permeability using urinary concentration of sugar probes can be used as a predictor of imminent relapse of clinically inactive CD. Large sugar molecules (i.e., lactulose) and small molecules (i.e., mannitol), both with near 100% elimination in urine, are mixed in a drink and measured in urine as an index of tight junction function. Tight junctions are dynamic structures that respond to many stimuli and are particularly sensitive to cytokines in situations of inflammatory stress. Studies have shown that, in patients with CD in clinical remission, an increased intestinal permeability can predict the risk of

Table 2 Simple endoscopic score for Crohn's disease

Variable	Values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1 to 0.5 cm)	Large ulcers (0.5 to 2.0 cm)	Very large ulcers (> 2 cm)
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected surface	< 50%	50%-75%	> 75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

relapse[61-63]. In all studies, the frequency of relapses was significantly different between those with normal and abnormal intestinal permeability tests.

ENDOSCOPY

Endoscopy is usually useful to diagnose CD involving terminal ileum and colon and to distinguish it from UC. It is also important to determine the extent and severity of the disease, to assess response to treatment and to screen for dysplasia. Additionally, endoscopy allows for direct visualization of the mucosa and acquisition of biopsies, becoming the primary diagnostic tool.

An endoscopic scoring system has been developed and validated for monitoring activity in CD, and to assess severity of ileal and colonic disease. However, it is time consuming and complicated, due to the analysis of multiple aspects of lesions. It is named Crohn's disease endoscopic index of severity (CDEIS) and it is based upon the presence of four types of lesions: superficial ulcers, deep ulcers, ulcerated stenosis or non-ulcerated stenosis, all of which should be recorded in five different segments: terminal ileum, ascending colon, transverse colon, descending and sigmoid colon, and rectum[64]. The combination of values allows the calculation of a severity score, which ranges from between 0 and 30. Unfortunately, in a subsequent study, the same authors demonstrated that the use of endoscopy and the CDEIS to guide therapeutic decisions with regard to corticosteroid therapy was not helpful clinically[65].

Years later, Dapermo *et al*[66] proposed a simplified model based on ulcer size, ulcerated surface, affected surface and narrowing of lumen present in the ileum, right colon, transverse colon, left colon and rectum, with a score ranging from 0 to 3 (Table 2). Reproducibility of these parameters was confirmed and it was highly correlated with both CDEIS and CDAI.

However, it must be asked if it is really necessary to establish an endoscopic scoring system, as objective as it is to evidentiate healing of mucosal lesions, which has become an important end point in clinical trials of CD treatment[67-69]. It remains to be defined if standardization of endoscopic evaluation can be useful in guiding therapy. Still of concern are possible pitfalls of the SES-CD index of activity including the presence of fistulas, for which endoscopy is not the best diagnostic test, and underestimation of stenosis and overestimation of non-specific lesions because of inexperience with endoscopy in patients with IBD.

In UC, endoscopy is necessary for diagnosis and for determining disease extent. In order to evaluate the clinical disease activity, various endoscopic indices have been elaborated, such as Baron Score, Rachmilewitz Endoscopic Index, Mayo Score and Sutherland Mucosal Appearance Assessment[13,70-72]. All were based in granulation scattering, vascular pattern, vulnerability of mucosa and mucosal damage (mucus, fibrin, exudates, erosions and ulcer). However, no standardized model has been established. In an attempt to determine whether or not any endoscopic indices could be established as a standard, Hirai *et al*[73] compared the Baron score with the Rachmilewitz Endoscopic Index and demonstrated that both were almost equally useful for evaluating disease activity. In another study, inter- and intraobserver agreement were evaluated, using Matt's, Mayo Score, Baron, and Blackstone indices[74]. Two hundred and seventy nine endoscopic pictures of inflammatory lesions from 93 UC patients were displayed twice to 4 expert and 4 trainee endoscopists, with a one month interval. The Matt's and Mayo indices showed a good degree of concordance for expert endoscopists in terms of inter- and intraobserver agreements, but this was not so evident with the Baron and Blackstone indices. For trainee endoscopists, all weighted kappa values for inter- and intraobserver scores using established indices were lower than for the experts. In 2007, D'Haens *et al*[75] published a study that reviewed activity indices and efficacy end points for clinical trials of medical therapy in adults with UC and recommended that absence of friability, blood, erosions, and ulcers in all visualized segments are required components of genuine endoscopic healing.

IMAGING TECHNIQUES

Abdominal and doppler ultrasound

Transabdominal ultrasound is a very well established tool to examine the liver, hepatobiliary-pancreatic tree and urogenital tract; however, its use for imaging the intestinal tract has been considered more difficult. In the past two decades, improvements in technology, specially new high frequency probes, highly sensitive color and power Doppler units and development of new contrast agents, along with an increasing experience with sonographic findings in intestinal diseases, have all contributed to establishing the role of ultrasound as a clinically important, non-invasive, radiation free and widely available imaging modality for evaluation of these patients[76,77].

Ultrasound has been successfully used as the imaging method of choice in screening patients with clinically suspected CD; it may be the first diagnostic tool employed

for young patients and can be used in the preliminary diagnostic work-up prior to further invasive tests. Another important application of bowel ultrasound is in the follow-up of patients already diagnosed with CD, in whom it may be useful to assess the site and extent of the lesions and to ensure early detection of intra-abdominal complications[78].

Although it has an important role in the evaluation of CD patients, the usefulness of ultrasound and Doppler imaging in assessing disease activity is still a matter of discussion. Several studies attempted to correlate ultrasound and Doppler findings with clinical and biochemical activity, but the published results are controversial[78].

Bowel wall thickening, bowel wall stratification and length of bowel wall involvement were all tested as sign of disease activity. Of these, only the degree of bowel wall thickening showed a significant, but weak, correlation with clinical CDAI and biochemical (erythrocyte sedimentation rate, C-reactive protein) parameters, and can be viewed as an indirect sign of disease activity[79]. Although a sensitivity of 80% has been reported for the cut-off value of 4 mm for the maximum thickness of bowel wall, the specificity of this finding alone is low due to the difficulty in differentiating inflammation from fibrosis[80,81].

As neovascularization and hyperemia of the bowel wall are well established findings in active CD, much effort was also made trying to correlate Doppler sonography of the superior mesenteric artery and power Doppler study of the bowel wall with other markers of activity.

Regarding Doppler sonography of superior mesenteric artery, some authors state that the available results concerning this association are conflicting, but the disagreement seems to be due to crucial differences in methodology, especially in the adopted Doppler parameters[79,82]. Van Ostayen *et al*[83-86] showed that superior mesenteric artery flow was the most reliable parameter to characterize disease activity and that the cut-off value of 500 mL/min had a sensibility between 80% and 83% and a specificity of 87% for this diagnosis. The association between increased superior mesenteric artery flow and disease activity was also supported by others[87-89].

Intestinal wall vascularity has been studied for more than a decade and the results were consistent with a correlation between blood vessel density assessed by power Doppler sonography and the degree of local inflammation assed by endoscopy or clinical and biochemical evaluation[90,91]. In this field, newer techniques such as harmonic imaging and the administration of echo-enhancing contrast agents have further improved the sensitivity and accuracy of power Doppler evaluation of the bowel wall in detecting inflammatory activity by showing increased perfusion in the affected bowel[92-96]. It has also been demonstrated that the assessment of intramural blood flow by means of power Doppler and intravenous contrast agents may discriminate inflammatory stenosis which are hypervascularized, of those cicatricially transformed, and characterized by fibrosis and hypovascularized scar tissue[97].

Although sometimes helpful in evaluating the extent of the disease, the role of transabdominal ultrasound in UC is much less important than in CD, mostly due to the fact that the disease affects only the mucosa, resulting in very subtle echographic findings, which are difficult to evaluate[76]. The mesenteric blood flow in inferior mesenteric artery, although seemingly related to clinical end endoscopic disease activity, is technically much more difficult to measure by Doppler than it is in the superior mesenteric artery due to its smaller diameter[98].

Computed tomography and magnetic resonance enterography

Computed tomography (CT) in its conventional form has played a significant role in the evaluation of complications and extraenteric manifestations of CD, such as fistulas and abscesses, but it has a limited role for depicting bowel wall and luminal abnormalities. CT enterography (CTE) is a modification of the conventional CT technique, optimized for the evaluation of small bowel. This technique utilizes multidetector CT scanners with high spatial and temporal resolutions, thin sections, multiplanar reconstructions and large volumes of ingested neutral enteric contrast material, combined with the use of intravenously administrated iodinated contrast, in order to permit visualization of the small bowel wall, mucosa and lumen[99]. Then, apart from detecting extraluminal findings, CTE can delineate the extent and severity of bowel wall inflammation[100].

CTE findings of bowel wall thickening, mural stratification, mural hyperenhancement, increased attenuation in the perienteric fat and engorged vasa recta correlate with mucosal and mural inflammation and so, with active CD[99,101].

Mural thickening refers to wall thickness of greater than 3 mm in a well distended bowel loop. It is the most frequently observed CT finding in CD, present in up to 82% of patients[102].

Mural stratification is a distinction of the bowel wall layers on CT after intravenous contrast injection; mucosa and muscular/serosa layers show contrast enhancement and interposed submucosa has a decreased attenuation, giving the wall a trilaminar appearance[103].

Mural hyperenhancement describes a segmental hyperattenuation of a distended bowel loop when compared to adjacent normal loops. This finding correlates significantly with histologic findings of active CD, being the most sensitive CTE finding of disease activity[103]. It has also been observed that the degree of bowel wall enhancement correlates with the severity of inflammation[104,105].

Increased attenuation of mesenteric fat can be due to edema or engorged vasa recta, vessels that penetrate the bowel wall perpendicular to the bowel lumen; these two findings combined are the most specific sign of disease activity and correlate with the levels of C reactive protein[105].

CTE can also depict signs of chronic manifestations of CD, such as submucosal fat deposition, sacculations and fibrofatty proliferation[101]. The presence of intramural fat indicates past or chronic inflammation. Sacculations result from the chronic inflammatory process, leading to fibrosis and asymmetric shortening of the mesenteric border of the wall (Table 3)[106].

Many authors addressed the positive correlation between CTE findings and clinical and biochemical markers

Table 3 Computed tomography enterography findings of Crohn's disease activity and chronic disease

Disease activity	Chronic disease
Bowel wall thickening	Submucosal fat deposition
Mural stratification	Sacculations
Mural hyperenhancement	Fibrofatty proliferation
Increased attenuation in the perienteric fat	
Engorged vasa recta	

of disease activity, such as CDAI and C-reactive protein and erythrocyte sedimentation rate, respectively, but the clinical relevance of these images is still a matter of discussion[105,107]. Higgins *et al*[108] reviewed the CTE scans and clinical data of 67 patients with CD presenting abdominal pain and a clinical suspicion of either small bowel inflammation or stricture. The authors showed that CTE can detect strictures not clinically suspected, rule out strictures that were radiologically insignificant and change the perceived likelihood of steroid benefit in up to 61% of cases. The CTE ability to detect small bowel strictures can be particularly helpful when considering using endoscopic capsules, which may themselves precipitate small bowel obstruction.

CTE has a major disadvantage: the use of ionizing radiation. The increased spatial resolution of CT with new multidetector CT scanners carries along with it a greater dose of ionizing radiation. In fact, effective doses of radiation are up to five times higher with CTE when compared with small bowel follow through[109]. Considering that many patients will undergo various examinations through their lifetime, efforts should be made to minimize the number of CT examinations, decrease CT dose or considering another diagnostic imaging modality, such as magnetic resonance enterography (MRE).

MR imaging also experienced the same technical advances seen in CT in the last ten years. In a similar way, the improvement in spatial and temporal resolution of images, combined with the use of large volumes of oral contrast agents to provide bowel distention, allows the evaluation of bowel wall contrast enhancement, wall thickening and edema; findings useful for the assessment of CD activity[110].

The preference of MRE *vs* CTE has been geographical and based on expertise and public policy. With increasing awareness of radiation exposure risks, there has been a more global interest in implementing techniques that reduce or eliminate radiation exposure. Owing to this excellent soft tissue contrast, direct multiplanar imaging capabilities and lack of ionizing radiation, MRE is well suited to play an important role in the evaluation of small bowel disorders[111].

Until now, the available data concerning accuracy of MRE in detecting disease activity is less than CTE, but early results are encouraging, showing a similar sensitivity and diagnostic effectiveness[112-114], although image quality is still better with CT. Motion artifacts from small bowel motility are more severe with MRE[112], but halting peristalsis by administering 1 mg of glucagon intramuscularly before contrast-enhanced imaging reduces blurring and artifacts related to bowel motility[115].

As they are imaging methods designed to assess small bowel, both CTE and MRE are not suited for evaluating UC.

In conclusion, in the last few years, a great deal of research and the development of diagnostic tools have been devoted to the task of diagnosing IBD, predicting its course and determining activity. Many of these tools show promising results, but a lack of specificity remains a problem that precludes routine use in clinical practice. Advances in molecular medicine towards a better understanding of genetic and other etiologic factors in IBD may result in better performance of markers of disease. Endoscopy displays direct evidence of mucosal injury. However, it is time consuming, invasive, expensive and, a good deal of endoscopic evaluation criteria lack validation, making it difficult to adopt endoscopic methods for routinely monitoring the course of IBD. Imaging techniques are useful as markers in CD, but they lack applicability in UC. Considering disease markers pitfalls, clinical activity indices still have their place in IBD monitoring. In conclusion, there is not yet an ideal marker, and determination of activity depends on clinical ability to manage information given by the available complementary exams.

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