

What Predicts Mucosal Inflammation in Crohn's Disease Patients?

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Abstract: A number of disease-specific instruments have been created over the last 30 years to assess disease activity in Crohn's disease (CD). These disease activity indices are constituted of clinical and laboratory parameters and their role in predicting disease activity and the course of disease has been reviewed various times. Currently, the severity of mucosal inflammation, assessed by endoscopy, is considered the gold standard for disease activity in CD. In the present review the most frequently used endoscopic disease activity indices and the correlation between mucosal inflammation and clinical disease activity indices, quality of life questionnaires, and biochemical markers is critically appraised. We conclude that no clinical disease activity index or single laboratory parameter of inflammation reliably predicts the mucosal inflammatory disease activity. A new, easy-to-use and robust activity index predicting mucosal inflammation is highly needed to assess the response to investigational drugs in trials and the effect of therapeutical interventions in clinical practice.

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Key Words: Crohn's disease, clinical disease activity, mucosal inflammation, endoscopy, laboratory markers

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract, characterized by a relapsing course. It may affect any part of the GI tract with a broad spectrum of clinical presentations. The disease seems to result from complex interactions among susceptibility genes, the environment, and the immune system, finally leading to an imbalance of the immune system. This imbalance, or disease activity, results in deregulated mucosal immune responses to antigens of enteric bacteria, and is revealed by

mucosal inflammation of the GI tract and/or extraintestinal manifestations.

At present, the severity of mucosal inflammation assessed by endoscopy is considered the gold standard for disease activity in CD. In clinical practice, however, physical examination, inspection of stools, and laboratory parameters are usually employed to assess inflammatory activity. These parameters do not reliably reflect the extent and intensity of the mucosal inflammation, since mucosal inflammation is not always accompanied by a raised C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or other laboratory parameters of inflammation. On the other hand, patients may have characteristic symptoms without clear endoscopic disease activity, which can be explained by a high frequency of irritable bowel syndrome-like symptoms in patients in remission.^{1,2} Thus, endoscopy is indispensable to determine whether or not symptoms are generated by mucosal inflammation.

Before the era of biologicals and immunosuppressive agents, the main treatment goal in CD was to achieve clinical remission. In the 1990s, azathioprine^{3,4} and antitumor necrosis factor antibodies (anti-TNF α ; infliximab)^{5,6} were found to induce mucosal healing in CD patients as a secondary outcome of clinical trials. In the Accent I trial, CD patients who were found to have complete mucosal healing following treatment with infliximab needed fewer hospitalizations, surgeries, and intensive care unit stays.^{7,8} Current guidelines for the treatment of CD restrict the use of immunosuppressive agents to patients who fail corticosteroids. However, this strategy is not effective in the long-term prognosis. An alternative is to introduce more potent immunomodulators in an earlier course of disease. Recently presented preliminary data from a controlled study comparing early administration of infliximab and azathioprine ("top-down" therapy) versus conventional "step-up" therapy showed superior mucosal healing, a more rapid remission, and higher remission rates in patients in the top-down treatment arm.⁹ Whether healing of the mucosa will lead to a more benign course of the disease in the long run remains to be proven in longitudinal studies.

From this, it is evident that a reliable and easy-to-use parameter of disease activity is highly needed in trials and in clinical practice. A number of disease-specific instruments have been created over the last 30 years to measure disease activity in CD. These various, in particular, clinical and

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laboratory disease activity indices, have been reviewed in the past, apart from their relation with mucosal inflammation.^{10–17} In the present article the most frequently used endoscopic disease activity indices, and the correlation between mucosal inflammation and clinical disease activity indices, quality of life questionnaires, and biochemical markers are reviewed.

ENDOSCOPIC DISEASE ACTIVITY INDICES

Mucosal inflammation of the GI tract in CD is characterized by a number of reproducible mucosal (skip) lesions: erythema, edema, pseudopolyps, aphthoid ulcers, (longitudinal) ulcers, and stenosis.¹⁸ It has been shown that it is feasible for a cooperative multicenter group to collect reproducible endoscopic data in CD in a standardized way.¹⁹

Crohn's Disease Endoscopic Index of Severity (CDEIS)

In 1989 the French "Groupe d' Etudes Thérapeutiques des Affections Inflammatoires Digestives" (GETAID) developed an endoscopic index for assessing the severity of mucosal inflammation in CD, the CDEIS.¹⁹ This index is based on the previously mentioned endoscopic findings in 5 segments of the gut (ileum, right colon, transverse colon, left colon, and rectum), prospectively collected in 75 patients with colonic or ileocolonic CD. It correlates with the endoscopist's global evaluation of lesion severity. The elaboration of the score requires analog scale transformation.

The agreement between paired evaluations of the CDEIS as assessed by 2 endoscopists of data recorded during colonoscopy was excellent (intraclass correlation of 0.96, $P < 0.001$). The CDEIS was validated in 103 colonoscopies. Hereafter, it was used as a marker of mucosal healing in a number of therapeutic trials.^{3–7} At present, the CDEIS represents the gold standard for evaluation of mucosal inflammation in CD. The CDEIS score generally ranges from 0–30. A higher score indicates more severe mucosal inflammation. A clinically meaningful reduction in score or a specific cutoff value which defines remission has not been determined.

Simple Endoscopic Score for CD (SES-CD)

Recently, the SES-CD has been developed and validated to simplify endoscopic activity assessment.²⁰ The score does not require analog scale transformation as in the CDEIS. It is based on 4 endoscopic variables (ulcer size, ulcerated and affected surfaces, stenosis) in the same 5 ileocolonic segments considered in CDEIS. The endoscopic parameters are scored from 0–3. The SES-CD was derived from the results of 70 patients and validated in 121 CD patients. The interobserver agreement for all selected variables was excellent (kappa coefficient 0.791–1.000). It does not come as a surprise that the SES-CD is highly correlated with the CDEIS ($r = 0.920$).

Rutgeerts' Score

Rutgeerts developed an endoscopic score system to measure the presence and severity of endoscopic recurrence in the neoterminal ileum after ileocecal resection. This scoring system was derived from observations in a cross-sectional study of 114 patients after ileal resection.^{21,22} Scores range from 0 (no lesions in the distal ileum) to 4 (diffuse inflammation with larger ulcers, nodules, and/or narrowing).

CLINICAL DISEASE ACTIVITY SCORES

Crohn's Disease Activity Index (CDAI)

To date, the most used and broadly accepted clinical activity score worldwide in trials is the Crohn's disease activity index (CDAI).²³ It is recommended as the gold standard for disease activity in CD by the European Medicines Agency (EMA) for the development of new medicinal products for the treatment of CD.²⁴ The score, developed in 1976, is the product of multivariate regression analysis with data prospectively collected from 187 visits from 112 patients. The physician's overall evaluation of "how the patient was doing" ("very well," "fair to good," "poor," and "very poor") was correlated with 8 independent variables (selected out of 18 potential predictor variables), which were the number of liquid stools, the severity of abdominal pain, general well-being, the occurrence of extraintestinal manifestations, the need for antidiarrheal drugs, the presence of an abdominal mass, the hematocrit value, and body weight. The calculation of the CDAI is based on a 7-day diary. In a following study the values of the 8 coefficients of the CDAI were rederived using data from 1058 visits of patients.²⁵ The rederived coefficients were similar to the original ones. New and original index values calculated on the same data from patient visits correlated highly; therefore, continued use of the original version was suggested. A CDAI score of 150 or less indicates remission, 150 to 220 mild disease activity, a score of ≥ 220 or ≤ 450 moderate disease activity, and > 450 severe disease activity. Several reports show that the endoscopic disease activity correlates poorly with the CDAI ($r = 0.32$; $P < 0.001$; $r = 0.13$ NS).^{26,27}

Harvey Bradshaw Index

The Harvey Bradshaw index or "simple index"²⁸ is a simplified version of the CDAI. In all, 112 consecutive patients were assessed with the CDAI and the Harvey Bradshaw index. This last index consists of 5 of the 8 items of the CDAI, based on data of the day before the visit. The Harvey Bradshaw index is independent of (but complementary to) laboratory criteria of inflammatory activity, such as measurement of ESR, plasma viscosity, or CRP.²⁸ As can be expected, the correlation with the CDAI is excellent ($r = 0.88$; $P < 0.01$).²⁹ In 1986, Gomes et al²⁹ reported a significant correlation between their endoscopic score and the Harvey

Bradshaw index in 22 CD patients with colonic disease ($r = 0.68$; $P < 0.05$).

van Hees or Dutch Index

This index is a combined clinical and laboratory index based on data of 63 CD patients who had been submitted to a total of 85 clinical examinations. The index has been prospectively validated.³⁰ On the basis of 18 predictor variables, 3 physicians gave an overall evaluation of the severity of inflammatory activity in each patient. The index correlates poorly with the CDAI,³⁰ probably due to its use of laboratory-based items (albumin, ESR) when compared to the CDAI. Simonis et al³¹ found a low predictive value of the van Hees index for endoscopic disease activity.

Several other clinical disease activity indexes have been developed in the past, including the Organisation Mondiale de Gastroenterologie (OMGE) index,³² the Cape Town index,³³ the Bristol score,³⁴ and the St. Mark's index.³⁴ These validated indices all correlate well with the CDAI, because a large part of the score in all these indices is contributed by the symptoms of well-being, frequency of liquid stools, and abdominal pain. The relation between these indices and endoscopic disease activity has not been studied, but a poor correlation can be expected because of the large overlap of these indices with the CDAI.

QUALITY OF LIFE

Quality of life of CD patients is usually assessed by employing the Inflammatory Bowel Disease Questionnaire (IBDQ). The IBDQ is a disease-specific, health-related, quality-of-life questionnaire, containing 32 items, with a graded response range of 1 (worst) to 7 (best) and a total score of 32 to 224.³⁵ The 32 items can be divided in 4 dimensional scores, including bowel symptoms (e.g., stool frequency and abdominal pain or cramps; 10 items), systemic symptoms (e.g., fatigue and energy loss; 5 items), emotional well-being (e.g., depressed feelings; 12 items), and social function (e.g., limited sexual activity; 5 items). A substantial portion of the total CDAI score is derived from the "the general well-being" and "the intensity of abdominal pain" items. In this respect there is an overlap between the CDAI and both the bowel symptoms domain and the systemic domain of the IBDQ. In 2004 Casellas et al³⁶ found a significant correlation between clinical activity (Harvey Bradshaw index) and quality of life (using an extended version, the IBDQ-36 and a reduced version, the IBDQ-9), in 68 CD patients. Since the Harvey Bradshaw index is a simplified version of the CDAI, it is not surprisingly that quality of life did not correlate with mucosal inflammation.

LABORATORY ACTIVITY MARKERS

The subjective nature of clinical CD indices led investigators to search for laboratory markers that would indepen-

dently measure mucosal disease activity. Overall, these markers are not specific for CD, but reflect a general degree of systemic inflammation.

In 2000 Nielsen et al³⁷ published a comprehensive review of classical disease markers (including ESR, acute phase proteins, white cell and platelet counts, albumin, neopterin, and β_2 microglobulin) together with the emerging disease markers such as antibodies of the ANCA/ASCA type, cytokines, and various adhesion molecules in CD and their relation with (clinical) disease activity. It was concluded that none of the laboratory markers of disease activity in CD is specific or sensitive enough to replace basic clinical observations such as the number of daily bowel movements, general well-being, and other parameters in parallel. In this review we only focus on parameters for which the correlation with endoscopic inflammation has been studied.

Serum Activity Markers

One of the first publications in which the relation between mucosal inflammation and serum activity markers was studied dates from 1986.²⁹ Mucosal inflammation confirmed by colonoscopy in 22 CD patients was defined as no, mild, severe, or more severe inflammation. The severity of mucosal inflammation and CRP, ESR, white blood count, platelet count, or albumin were not found to be correlated.

Modigliani et al²⁷ assessed whether or not the CDEIS, hemoglobin, ESR, and serum albumin were correlated in 42 CD patients. A significant correlation existed between serum albumin levels and the CDEIS ($r = -0.31$, $P < 0.001$). Hemoglobin and ESR were not related to mucosal inflammation.

Tromm et al³⁸ evaluated various laboratory tests in relation to the endoscopic disease activity. Seventy-five CD patients were divided into 2 groups based on endoscopy: a group with severe inflammation and a group with low-grade or no inflammation. Except for the hematocrit, significant differences were found between both patient groups for the mean values of the ESR, albumin, α_1 protease inhibitor, cholinesterase, and CRP.

In 1994 the GETAID group²⁶ described in 121 consecutive CD patients rather weak, but significant correlations between the CDEIS and serum albumin ($r = -0.30$), α_2 -globulin ($r = 0.48$), α_1 -antitrypsin ($r = 0.39$), ESR ($r = 0.40$), platelets ($r = 0.28$), hematocrit ($r = 0.16$), and CRP ($r = 0.20$), while no relations with orosomucoid and white cell counts were found.

Moran et al³⁹ found an impressive high correlation for serum albumin ($r = 0.8$; $P < 0.001$) in 28 patients with mucosal disease activity in either CD colitis or ulcerative colitis employing multiple regression analysis using all endoscopic grades of disease activity,

Simonis et al³¹ investigated the suitability of objective parameters (serum α_1 -antitrypsin, acid α_1 -glycoprotein (oro-

somucoid), CRP, sialic acid, prealbumin, albumin) accessible for routine management to act as surrogate indicators for endoscopic alterations. Endoscopic findings were classified on the basis of the pattern of alterations found and were globally labeled as to whether they were remission-related or exacerbation-related. A validated index for endoscopic disease activity, e.g., the CDEIS, was not used. Thirty-six patients were included, 18 with clinically exacerbated disease and 18 after acute phase conservative therapy. Orosomucoid and prealbumin were found to be good predictors for endoscopically active disease. The model was validated in 44 patients; 29 with active disease and 15 controls.

Finally, Solem et al⁴⁰ reported a significant association between disease activity at colonoscopy and the CRP in 104 CD patients in 2005.

Fecal Activity Markers

Fecal markers comprise a heterogeneous group of substances that either leak from or are generated by the inflamed intestinal mucosa.

α 1-Antitrypsin

Fecal α 1-antitrypsin clearance reflects protein loss through the bowel wall. It is a protease inhibitor produced by the liver, macrophages, and the intestinal epithelium. A small but significant correlation between this parameter and the CDEIS was reported by the GETAID group ($r = 0.37$; $P < 0.001$).²⁶ Moran et al³⁹ found a high correlation coefficient ($r = 0.82$; $P < 0.001$) but their study population comprised CD patients as well as colitis ulcerosa patients. Fecal α 1-antitrypsin has been generally accepted as a useful marker of IBD; however, the method is not routinely available. Moreover, other fecal markers have been found to be more accurate or cost-effective than α 1-antitrypsin in CD patients.⁴¹

Calprotectin

Calprotectin is a calcium- and zinc-binding protein and accounts for 60% of the total soluble proteins in the cytosol fraction of neutrophil granulocytes. It is a marker of neutrophil turnover, since it is released from neutrophils shed from the colonic mucosa by activation of leukocytes. Calprotectin is stable during intestinal transit, resistant to colonic bacterial degeneration, and can be easily assessed in stools by means of ELISA tests. A small raise of calprotectin has been found in patients with colorectal cancer, but patients with mucosal inflammation have highly elevated fecal calprotectin levels, which appeared to be related to the degree of mucosal inflammation in IBD. D'Inca et al⁴² reported a significant correlation between endoscopic disease activity and calprotectin levels ($r = 0.480$; $P = 0.008$) in 23 CD patients. A validated index for endoscopic disease activity, e.g., the CDEIS, was not used. Roseth et al⁴³ described normalization of fecal calprotectin levels along with mucosal healing in CD.

Overall, studies focused on the correlation between mucosal inflammation and laboratory activity markers are not conclusive. This can be due to the different endoscopic scorings systems used, the different study designs, but also to the small sample size in most of the studies. The levels of CRP and albumin seem to be the most useful in predicting mucosal inflammation,^{26,38,40} whereas white blood cell count and ESR are less suitable for this purpose. The fecal marker calprotectin seems to be highly useful as well.

DISCUSSION

Mucosal healing is presently considered the ultimate goal of treatment in CD, but this has only been within grasp since the introduction of azathioprine^{3,4} and, most notably, infliximab.^{5,6,44} The clinical relevance of this treatment goal is underscored by the finding that induction of mucosal healing is associated with a reduction of hospitalizations and surgical procedures.^{7,8} Therefore, in our opinion, the CDAI cannot longer remain the primary endpoint in clinical trials, since it relates poorly with the inflammatory status of the intestinal mucosa.^{26,27} The poor association is probably due to several factors. Most important, in the development of the CDAI, mucosal inflammation has not been taken into consideration; instead, the physician's overall evaluation of "how the patient was doing" was used as the gold standard. Furthermore, as pointed out previously, most laboratory markers presently used in the clinical disease activity indices (ESR, albumin, and Ht) have not been found to be reliable predictors for mucosal inflammation. Another factor, potentially explaining the poor performance of the CDAI in predicting mucosal inflammation, is the fact that the location of the disease is not incorporated in the CDAI. While patients with distal inflammatory activity will usually present with diarrhea and macroscopic blood loss, a proximal location of disease will mostly be accompanied by abdominal discomfort, pain, or systemic complaints such as anorexia, weight loss, fatigue, or fever. The heterogeneous behavior of the disease leading to different phenotypes (stenosing, perforating, and luminal disease) will further complicate the interpretation of complaints, from which most clinical activity scores are derived. At last, a substantial part of the total CDAI score is derived from subjective items (the extent of abdominal pain, general well-being) and reflects the patients' perception and interpretation of the disease and its symptoms. This is unarguably important for the quality of life of patients, and needs to be measured in clinical trials. However, the items of the CDAI show a considerable overlap with both the bowel symptoms domain and the systemic symptoms domain of the IBDQ, and it can be argued that the CDAI is redundant and the IBDQ can sufficiently meet these aspects of the patients' perception of disease. An additional practical impediment when employing the CDAI in daily practice and in clinical trials is the fact that the calculation of the CDAI is based on a 7-day diary, which

can be cumbersome for the patient and the investigator. A substantial variability exists when different observers review the same case histories and calculate the CDAI score.⁴⁵

The discrepancy between CDAI and endoscopic disease activity might explain the high placebo rates of clinical response and remission in clinical trials. Su et al⁴⁶ reported in their meta-analysis even remission rates of up to 50% in CD patients treated with placebo. Solem et al⁴⁰ stated that in post-hoc analyses of some clinical trials the subgroup of CD patients with elevated CRP concentrations had lower rates of placebo response compared with patients with normal CRP concentrations, reflecting probably a lower endoscopic disease activity in the latter group.

Using endoscopic disease indices to assess the mucosal condition poses other problems. Endoscopy is invasive, time consuming, and expensive and, hence, unsuitable for frequent use in daily practice as well as in clinical trials. Furthermore, no clinically useful and validated cutoff levels for response or remission following medical therapy have been defined.

The ideal activity index should consist of parameters reflecting the extent of mucosal involvement, a parameter of systemic inflammation to assess transmural disease and/or infiltration outside the gut, a clinical parameter (such as diarrhea), and a correction for phenotypical disease behavior. Furthermore, a disease activity index should be simple and preferably consist of cheap, widely available, and easy-to-collect parameters. Presently, such an index is not available, but we feel that to reach new and ambitious goals in the treatment of CD, clinically as well as in studies, a new disease index predicting mucosal inflammation and reducing placebo response is highly needed.

CONCLUSIONS

Currently, endoscopy is still indispensable to determine whether or not symptoms are due to active mucosal inflammation and to monitor the effect of different therapeutic interventions in patients with CD. A new clinical activity index predicting mucosal disease activity reliably without the need for endoscopic procedures would simplify and probably improve the management of CD patients in trials as well as in clinical practice.

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