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Can we rely on inflammatory biomarkers for the diagnosis and monitoring Crohn's disease activity?

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ABSTRACT

Background: Small bowel capsule endoscopy (SBCE) is a very important tool in the diagnosis and monitoring of Crohn's disease (CD). The Lewis score (LS) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) are used to quantify and standardize inflammatory activity observed in the SBCE.

Aim: To evaluate the correlation between the LS and CECDAI scores and inflammation biomarkers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). A secondary goal was to define thresholds for CECDAI based on thresholds already established for LS.

Methods: This was a retrospective study of 110 patients with suspect or known CD, with involvement of small bowel. Linear regression was used to calculate thresholds of CECDAI corresponding to the thresholds already established for LS. A Pearson correlation (r) was used to calculate the correlation between the LS and CECDAI scores and biomarker levels. Only patients with exclusive involvement of the small bowel were selected (n = 78).

Results: A moderate correlation was found between the endoscopic scores ($r = 0.59$, $p < 0.001$). CECDAI scores of 5.57 and 7.53 corresponded to scores of 135 and 790 in LS, respectively. There was a statistically significant correlation between CRP and the LS ($r = 0.28$, $p = 0.014$) and CECDAI ($r = 0.29$, $p = 0.009$). There was also a significant correlation between ESR and CECDAI ($r = 0.29$, $p = 0.019$), but not with LS.

Conclusion: There is a moderate correlation between the two scores. This study allowed the calculation of thresholds for CECDAI based on those defined for LS. We found a weak correlation between SBCE endoscopic activity and inflammatory biomarkers.

Key words: Lewis score. Capsule Endoscopy Crohn's Disease Activity Index. Small bowel capsule endoscopy. Inflammatory biomarkers.

INTRODUCTION

Since its approval by the Food and Drug Administration (FDA) in 2001, small bowel capsule endoscopy (SBCE) has rapidly become the state of the art technique for small bowel imaging (1). It allows a non-invasive evaluation of the mucosa with a higher sensitivity for inflammatory lesions than other non-invasive diagnostic modalities such as MRI or CT scan (2-4), although it does not enable the assessment of small bowel wall thickness or extraluminal involvement (2,3).

Crohn's disease (CD) is an idiopathic inflammatory condition that may affect any segment of the gastrointestinal tract and affects the small bowel in up to 66% of patients with the disease (5). This disease arises from the interaction between genetic and environmental factors, with periods of remission and relapse requiring close clinical management for therapy and disease monitoring (5). The diagnosis of this condition is based on the clinical presentation (chronic diarrhea, abdominal pain, weight loss or growth failure), in addition to extra intestinal manifestations (such as fever, arthritis/arthralgia, pyoderma gangrenosum, perianal disease) and/or altered laboratory based values (anemia, inflammatory markers), gastrointestinal endoscopy and histology data and/or abnormal imaging (6).

One of the main indications for SBCE is suspected Crohn's (7) disease after a negative ileocolonoscopy (8). SBCE may also be used to assess disease extent and activity in patients with established CD and may influence patient management and prognosis (4,9-11). Mucosal healing is an emerging concept in CD management as a therapeutic goal, which has been associated with a good prognosis (12). There is no validated definition for this endpoint (2) but it has been associated with a lower relapse and hospitalization rate and a reduction in the prevalence of fistulae and surgery (13-15). Several recent studies have evaluated the ability of SBCE to detect mucosal changes in patients with known CD. The

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majority of studies concluded that SBCE was an effective and safe tool for the evaluation of mucosal healing in assessing small bowel treatment response during follow up (16-19). LS and the CECDAI are two index scores developed and validated to standardize the extent and severity of small bowel inflammation on SBCE (20,21).

Biomarkers have been thoroughly evaluated in Crohn's disease and are useful tools for diagnosis, assessment of disease activity, prediction of relapse, risk of complications and monitoring of the response to therapy (22). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are standard laboratory surrogates of the acute phase inflammatory activity (6). The aim of this study was to evaluate the correlation between SBCE scores (LS and CECDAI) and inflammatory serum biomarkers (CRP and ESR). A secondary aim was to define the thresholds for CECDAI based on the thresholds already established for LS.

METHODS

A retrospective cohort study was performed that included patients with suspected or known CD who underwent consecutive SBCE. All patients had an ileocolonoscopy as the first endoscopic diagnostic procedure. Patients taking aspirin or non-steroid anti-inflammatory drugs discontinued the medication at least four weeks before the SBCE examination (2). Prior to SBCE, patients were on a clear liquid diet for 24 hours and fasted for 12 hours. The SBCE videos were reviewed and the LS was calculated by one single experiment investigator (more than 100 SBCE sequence reviews) using the software application in the RAPID Reader® v.8 workstation. The LS was calculated by dividing the small bowel transit time (SBTT) into three tertiles. A subscore of inflammation was calculated for each tertile based on the characteristics of villous edema and ulceration. In those patients where the capsule did not reach the cecum, small bowel tertiles were determined based on the last small bowel image. The final score was the sum of the tertile with the highest score and the stenosis score, rated for the whole examination (20). Although there is no automatic software available, the CECDAI (Niv score) was calculated by dividing the small bowel in half on the basis of small bowel transit time of the capsule and each segment was scored individually. CECDAI consists of three parameters: inflammation score (score 0-5; erythema, hyperemia and edema, denudation, nodularity, aphthae, erosion, ulcer and bleeding), extent of disease (score 0-3; focal, patchy, and diffuse) and narrowing score (score 0-3; single-passed, multiple-passed and obstruction) (21). All three parameters were calculated separately for the proximal and distal segments of the small bowel and the total CECDAI score was calculated by adding the score of both segments (21).

The blood samples were collected within ± 7 days of the SBCE procedure (based on department protocol) and without changing the medication during this period. ESR was considered as elevated when the levels were higher than 12 mm/h and CRP, when levels were over 2.90 mg/l in accordance with the reference values used in our hospital.

Statistical analysis was performed with SPSS® version 22.0 (IBM, Armonk, New York, USA). The categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations. All reported p values are two-tailed, with a p value of 0.05 indicating statistical significance. A linear regression (model $Y = a + bX$, 95% CI) was used (the same methodology used by Koulaouzidis A et al.) to define the thresholds for CECDAI (corresponding to those defined for LS) (23). Pearson's correlation was used to calculate the correlation between the inflammation scores and inflammatory biomarkers (CRP and ESR). This analysis only included patients with isolated small bowel CD. The Evans classification (1996) was used to define the power of the correlation (0.0-0.19 very weak; 0.2-0.39 weak; 0.4-0.59 moderate; 0.6-0.79 strong; 0.8-1 very strong) (24). The Student's t-test was used to test the differences between the mean of the biomarker values according to the severity of inflammatory activity.

RESULTS

One hundred and ten consecutive patients were enrolled and all patients fulfilled the inclusion criteria. The mean age was 35.2 ± 13.1 years and 67 were females (60.9%). The patients with isolated small bowel involvement corresponded to 70.9%. There was involvement of both the small bowel and colon in 29.1% of patients and there was involvement of the upper gastrointestinal tract in 18.2% of the cases. CRP mean levels were 9.60 ± 16.8 mg/l, and ESR levels were 17.2 ± 13.7 mm. The mean LS was 1,108 ± 1,361 and CECDAI was 8.11 ± 6.16. The mean time of SBTT was 305 ± 133 min (Table 1).

A moderate correlation between the LS and the CECDAI was observed ($r = 0.59$, $p < 0.001$) (Fig. 1). In our cohort, CECDAI thresholds of 5.57 and 7.53 corresponded to LS values of 135 and 790, respectively. To calculate the association between inflammatory biomarkers and the SBCE scores, a subanalysis was performed only with patients (n = 78) with isolated small bowel CD. In this group, the mean age was 35.1 ± 12.5 years and 46 were females (59%). The mean CRP was 9.88 ± 19.4 mg/l and ERS was 16.8 ± 14.1 mm. The mean CECDAI was 7.49 ± 5.60 and LS was 898 ± 1,141 (Table 1).

There was a weak but statistically significant correlation between CRP and the LS ($r = 0.28$, $p = 0.014$) and the CECDAI ($r = 0.29$, $p = 0.009$) (Figs. 2 and 3). There was also a correlation between ESR and the CECDAI ($r = 0.29$, $p = 0.019$) (Fig. 4), and no correlation was found between ESR and the LS. Patients with a CECDAI ≥ 7.53 had significantly higher values of serum inflammatory biomarkers than patients with CECDAI < 7.53 (CRP: 4.36 *vs* 17.0 mg/l, $p = 0.004$; ESR: 13.4 *vs* 20.9 mm, $p = 0.032$). CRP values were also significantly higher (CRP: 20.7 *vs* 5.07 mg/l, $p = 0.001$) in patients with LS ≥ 790, although this was not observed for ESR (Fig. 5).

DISCUSSION

The assessment of the distribution and the degree of small bowel inflammation is a critical point in the manage-

Table 1.

Total population	*Isolated SB CD*	
n	110 (100%)	78 (100%)
Gender		
Male	43 (39.1%)	32 (41%)
Female	67 (60.9%)	46 (59%)
Age, mean (SD), *yr*	35.2 ± 13.1	35.1 ± 12.5
Involvement SB	78 (70.9%)	----------
Involvement SB + colon	32 (29.1%)	----------
Involvement of superior gastrointestinal tract	20 (18.2%)	----------
Montreal classification		
Age at diagnosis:		
A1	8 (7.3%)	----------
A2	77 (70%)	----------
A3	25 (22.7%)	----------
Location:		
L1	78 (70.9%)	----------
L3	12 (10.9%)	----------
L4 + L3	20 (18.2%)	----------
Behavior:		
B1	97 (88.2%)	70 (89.7%)
B2	11 (10%)	6 (7.7%)
B3	2 (1.8%)	2 (2.6%)
Perianal disease	5 (4.5%)	2 (2.6%)
CRP, mean (SD) mg/l	9.60 ± 16.8	9.88 ± 19.4
ERS, mean (SD) mm	17.2 ± 13.7	16.8 ± 14.1
LS, mean (SD)	1,108 ± 1,361	898 ± 1,141
CECDAI, mean (SD)	8.11 ± 6.16	7.49 ± 5.6
Small bowel transit time, mean (SD) min	305 ± 133	307 ± 125
SBCE:		
Complete	94 (85.5%)	69 (88.5%)
Incomplete	16 (14.5%)	9 (11.5%)

SB: Small bowel; CD: Crohn's disease; LS: Lewis score; SD: Standard deviation; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; CECDAI: Capsule Endoscopy Crohn's Disease Activity Index; SBCE: Small bowel capsule endoscopy.

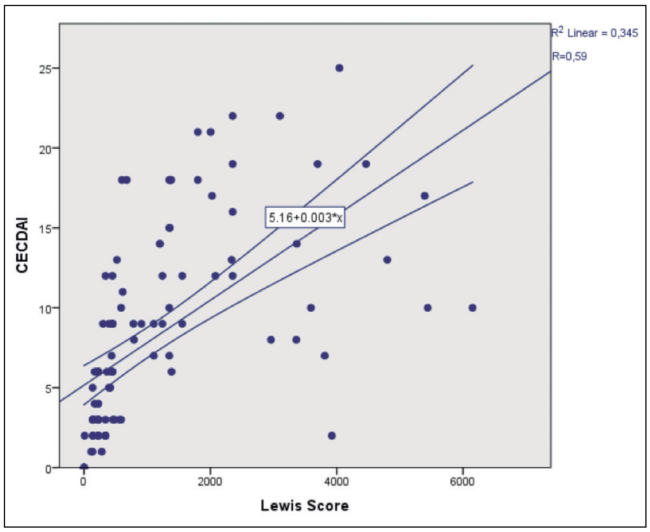

Fig. 1. Correlation between the inflammatory scores of the SBCE and the Lewis score (LS) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) values. Linear regression of CECDAI and LS, 95% confidence interval.

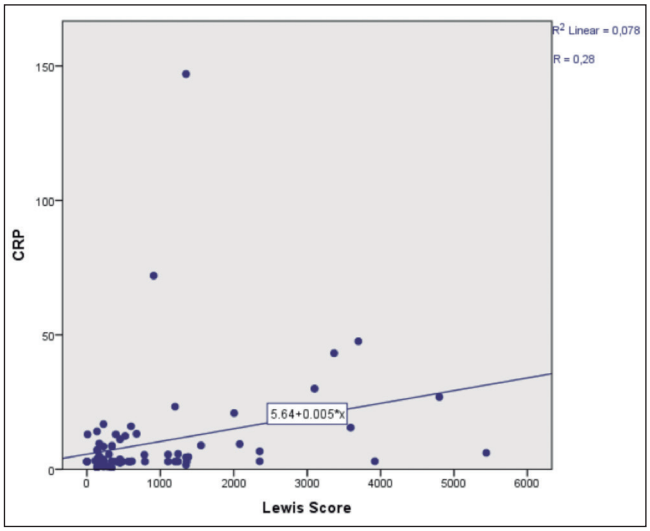

Fig. 2. Correlation between C-reactive protein (CRP) and Lewis score (LS).

ment of CD patients. The LS is based on the number and extent of segments of villous edema, aphthae and ulcers or the presence of stenosis (20). Inflammatory activity is classified into three degrees of severity: a) a score of < 135 is compatible with no change or clinically insignificant mucosal changes; b) a score of ≥ 135 to 790 is defined as mild mucosal disease; and c) a score of ≥ 790 is defined as moderate to severe disease (20). CECDAI is based on the assessment of three parameters: inflammation, disease extent and luminal narrowing (21). No clear threshold of inflammation has been consistently defined for CECDAI so far (25). However, cut-off values of 3.8 and 5.8 correspond to the LS thresholds of 135 and 790, respectively, which have been previously described (23). In our study we found the cut-off values of 5.57 and 7.53 corresponding to LS values of 135 and 790, respectively. This difference may be explained by the larger number of patients included in our study and by the fact that our cohort had higher LS mean values, probably due to a higher inflammatory activity. It is also important to highlight that CECDAI takes into account erythema, hyperemia, denudation and nodularity, and these aspects are not included in LS, which may explain the higher final CECDAI score.

A statistically significant correlation was demonstrated between the two endoscopic scores, which is in line with a previous published study (23). These scores provide a

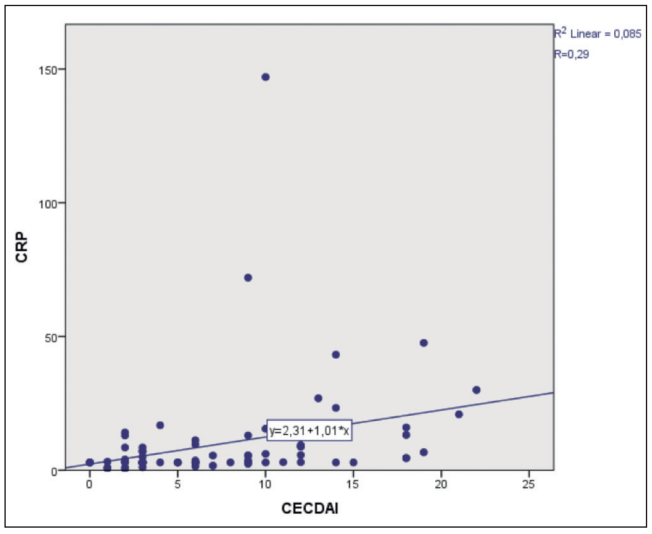

Fig. 3. Correlation between C-reactive protein (CRP) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI).

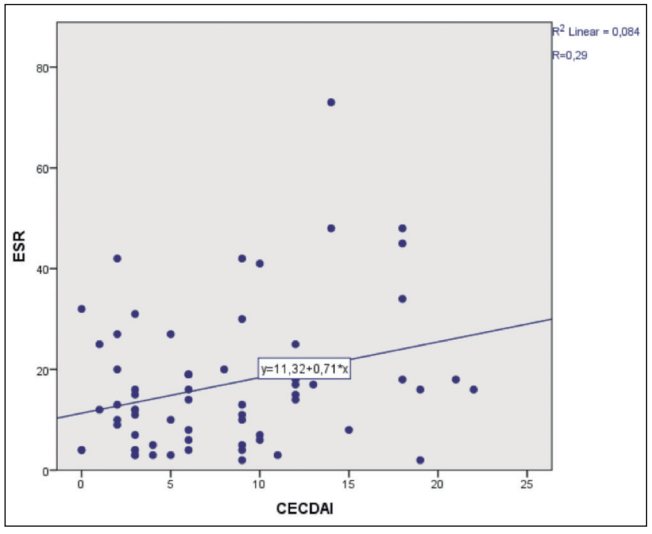

Fig. 4. Correlation between erythrocyte sedimentation rate (ESR) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI).

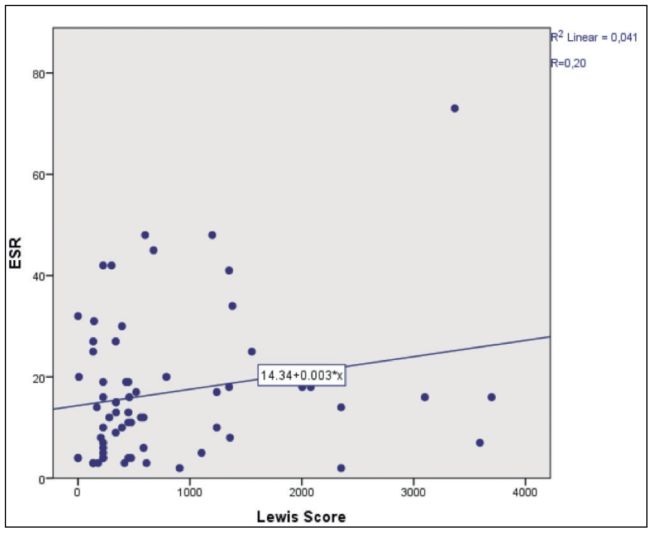

Fig. 5. Correlation between erythrocyte sedimentation rate (ESR) and Lewis score (LS).

reproducible methodology for the interpretation and estimation of endoscopic activity of inflammatory disease. Although both the LS and the CECDAI have been validated in the setting of Crohn's disease, due to the non-specific characteristics of small bowel inflammatory lesions, the inflammatory activity is graded regardless of its etiology (20,21).

There is an important need for accurate biomarkers to accurately assess disease activity and potentially predict relapses. The ideal marker should be specific and sensitive, reproducible, rapid, easy to perform, readily available and cost effective (22). CRP and ESR are widely used as surrogate markers in CD for diagnosis and therapeutic monitoring (26). CRP is a pentameric protein consisting of five monomers and is one of the most important acute phase proteins in humans (22,27). It is produced by hepatocytes in low quantities and its production increases under the influence of IL-6, TNF-α and IL-1β with an inflammation stimulus (22,27). This surrogate has a short half-life and is often up-regulated within hours after the onset of inflammation, and rapidly decreases after resolution of the stimulus (22,27). ESR is an indirect measure of inflammation, corresponding to the rate at which erythrocytes migrate through the plasma. An increase in plasma viscosity occurs due to the production of acute phase response proteins (22,27).

A correlation was found between CRP and the two endoscopic scores. With regard to ERS, there was a correlation with the CECDAI but not with the LS. Higher values of CRP and ERS were found in patients with a CECDAI score ≥ 7.53 compared with patients with CECDAI scores < 7.53 (CRP: 4.36 *vs* 17.0 mg/l, p = 0.004; ERS: 13.4 *vs* 20.9 mm, p = 0.032). CRP values were higher in patients with LS ≥ 790 (CRP: 20.7 *vs* 5.07 mg/l, p = 0.001) as compared to those with an LS score < 790. These biomarkers together with inflammatory scores of SBCE are currently used for diagnosis, treatment decisions and therapy stratification.

The new therapeutic endpoint of CD is achieving mucosal healing. Several studies have established a poor correlation of clinical symptoms with endoscopic inflammation (28). A recent study by Kopylov U et al. of 55 patients showed that 92.9% were in clinical remission and 40.4% were in clinical-biomarker remission; likewise, a moderate to severe small bowel inflammation by SBCE was present in 21.1% and 4.7% of patients, respectively. Only 13.5% of patients were in deep remission, which was defined by the absence of symptoms, CDAI < 150, mucosal healing as the restoration of normal mucosal appearance and a

decrease of inflammatory biomarkers (17). This goal was associated with an improved health related quality of life and a decrease of complications that required surgery and hospitalization (17). A prospective study by Boal Carvalho P et al. showed that within a population of 12 patients in sustained corticosteroid-free remission, 75% of patients had significant inflammatory activity in SBCE (29). These studies reinforce the importance of the evaluation of small bowel inflammatory activity by SBCE for the management and prognosis of patients with CD.

This study verified the fact that although higher levels of CRP and ESR were associated with higher values of the inflammatory scores, the strength of the correlation was very low, thus highlighting the need to evaluate the status of the small bowel mucosa and the treatment response by SBCE. Due to its non-invasive nature and detailed imaging, SBCE is an important technique not only for diagnosis but also for the follow-up and assessment of mucosal healing.

Fecal calprotectin is another biomarker that has shown a good accuracy in the detection of endoscopic active disease (30,31). Although it has demonstrated a good correlation with the inflammation of the colon, its value for the assessment of small bowel inflammation in IBD remains to be elucidated. In fact, a recent study found that even in the presence of large ulcers, patients with ileal CD did not have markedly elevated fecal calprotectin levels (32). In addition, calprotectin data was not available in this cohort as it is a recently described inflammatory biomarker and the study was retrospective.

To conclude, the role of SBCE and inflammatory biomarkers in the diagnosis and management of CD is still evolving. Although both endoscopic scores (LS and CECDAI) have been validated, no threshold of inflammatory activity for the CECDAI has been widely adopted. This study has determined the CECDAI cut-off values based on the thresholds defined for LS. Ideally, the small bowel should be assessed with a non-invasive endoscopic method such as SBCE, which has validated scores that measure inflammatory activity. This is of greater importance as there is a poor correlation between SBCE endoscopic activity and inflammatory biomarkers.

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