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EDITORIAL

Correlation of Two Capsule Endoscopy Scoring Systems with Fecal Calprotectin: Does It Really Matter?

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In the absence of a gold standard test, the diagnosis of isolated small bowel Crohn's disease (CD) is often challenging. Clinical symptoms and signs are often non-specific and may not correlate well with disease activity. We now know that barium small bowel imaging has limited value in evaluating mucosal lesions. Newer imaging modalities such as computed tomographic enterography (CTE) and magnetic resonance enterography (MRE) have higher sensitivity for detecting transmural inflammation [1], but they have limited value in evaluating isolated mucosal inflammation. Capsule endoscopy (CE), on the other hand, is an excellent, relatively non-invasive modality for direct mucosal visualization and thus can detect more subtle inflammatory change. As a result, CE is a useful tool for evaluating ulcerating diseases of the small bowel and may potentially aid in assessing disease activity and extent, as well as monitoring mucosal healing [2, 3]. However, one of the limitations has been the lack of an accurate and reproducible standardized scoring system that objectively assesses the severity of small bowel inflammation.

In 2008, Gal et al. [4] published a simple, validated Capsule Endoscopy Crohn's Disease Activity Index (CECDAI). This scoring index evaluates three parameters of small bowel pathology in CD: inflammation, extent of disease and presence of a stricture. All three parameters are calculated separately for the proximal and distal segments of the small bowel. This index has a high overall correlation (range 0.8–0.93; $p < 0.001$) and agreement (0.867). Later, Gralnek et al. [5] developed the Lewis score (LS), which is based on villous edema, ulceration and stenosis detected on CE. An excellent inter-observer agreement for the global assessment of mucosal disease severity (84–86%) was noted, although the LS has not been prospectively validated.

Both of these scoring indices potentially can be used for objectively measuring the degree of inflammatory activity. They may also be of benefit in assessing the degree of mucosal healing, which appears to be an important goal in the management of CD. Though these scoring indices are a step forward, there are important limitations. These indices were developed initially to standardize capsule reporting, but their use as a clinical tool is not yet clear and more prospective validation studies are needed. Simply stated, we do not know how accurately they measure the degree of mucosal inflammation. In addition, they have no discriminatory ability in differentiating CD from NSAID enteropathy, celiac disease, and/or ischemia.

Other non-invasive methods have been studied to assess and quantify small bowel inflammation. One promising method is measurement of fecal calprotectin (FC). FC is a human protein, released into feces from activated granulocytes and inflamed epithelia [6]. The amount of FC in feces is proportional to the granulocyte migration to the gastrointestinal mucosa. Unlike the CE scoring indices, several studies have shown an excellent correlation of FC with the severity of mucosal inflammation [7, 8]. There are many studies that confirm that FC can differentiate inflammatory from non-inflammatory gastrointestinal disorders, including small bowel inflammation [8, 9]. Therefore, many consider FC a "gold standard," reliable and highly specific marker of inflammation. So one might wonder if there is a correlation between FC and the current CE scoring indices and how it matters in measuring inflammation.

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In the retrospective study of Koulaouzidis et al. in this issue [10], they attempt to answer that question by searching for a correlation of the CECDAI and LS scoring indices with FC levels in patients with suspected isolated small bowel disease. In an earlier study [11], the same authors concluded that FC <100 μg/g was a good predictor of a negative capsule study and FC >200 μg/g was associated with a higher yield for CE (65%), and in fact, confirmed CD in 50% of cases. In the present study, 49 of 74 patients who had FC measurements and normal colonoscopy were selected for the study. Interestingly, the LS, but not the CECDAI, correlated with FC levels <100 μg/g (group A), the group with the lowest likelihood of having significant disease, based on the author's earlier study. There was no correlation between the LC or CECDAI and higher FC levels (groups B and C), the patients most likely to have significant small bowel inflammation. The fact that indices did not correlate in groups B and C is disappointing, but not necessarily surprising.

The results suggest that in patients with low FC levels, and thus a low likelihood of inflammation, the capsule is likely to be normal, reflected in a low LS. This is certainly consistent with the high negative predictive value of CE. On the other hand, it suggests that in those individuals with higher FC levels, the scoring indices do not correlate. This discordance again is not surprising and may be related to several factors some of which were already outlined by authors in the present study [10]. To begin with, the study included a very heterogenous group of patients with only 12/49 diagnosed with CD. The findings and the diagnosis in the other 37 patients were not discussed. Though previous studies have shown a good correlation between FC and the degree of inflammation in patients with inflammatory bowel disease [7–9], it's correlation in this heterogenous group is unknown. The authors allowed a 30-day gap between the capsule study and FC measurement, and while relatively short, it may influence results. This gap may in fact be significant due to subtle, spontaneous changes in the degree of inflammation one might see in active small bowel inflammation. We also do not know about any surreptitious medications that may have been used or the effect of the bowel preparation on FC measurements.

Still other factors may have contributed to the discordance. In this study, there is a single reader who performed the scoring indices and this certainly may introduce bias. Furthermore, the scoring indices are hampered by the uncontrolled movement of the capsule and varying transit times, potentially limiting the assessment of true disease activity. Additionally, the scoring systems use different findings and parameters for measuring disease activity, including stenosis, which may or may not correlate with inflammation and FC levels. The stenoses in particular, if predominantly fibrotic, may result in higher scores, but may not be associated with FC release. With all of these confounding variables, it is not surprising that there is a lack of correlation between the CE scoring indices and FC.

This brings us back to the question: Does a correlation between the CE scoring indices and FC really matter? At this time, we do not think so. The true benefit of an elevated FC level is to alert the clinician to the fact that an inflammatory process may be present or that a relapse may occur [12–14]. The true benefit to performing CE is to rule in or out significant inflammation in the small bowel. At the very least, these modalities can aid in the diagnosis and management of our patients, but more importantly, we should consider FC and CE as complementary. To have them also correlate with each other may be asking too much of this technology.

The authors should be congratulated on trying to forge new territory by attempting to correlate FC levels with the CE scoring indices. However, it is difficult to draw many conclusions from this study [10]. It does support the fact that small bowel inflammation can be difficult to diagnose and that for now, the assessment of small bowel inflammation can not be based on one single marker. It also supports the fact that non-invasive tests like FC and CE, along with cross-sectional imaging, should be considered complementary. We are confident that future prospective studies and advanced technology will improve our ability to non-invasively diagnose and assess small bowel inflammation.

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