Fecal calprotectin: a biomarker for intestinal inflammation

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In the clinical setting may be difficult the discrimination of patients with inflammatory bowel diseases from those with functional intestinal disorders due to the overlapping and non-specific symptoms, such as abdominal pain and altered bowel habit. Several blood markers currently help clinicians in the management of these patients, but the low specificity makes them unreliable for the detection and monitoring of the disease activity. The gold standard to establish a diagnosis of organic bowel disease is colonoscopy with multiple biopsies, but is an invasive and costly procedure. In the last decade, fecal calprotectin (FC), a cytosolic protein mainly found in neutrophil granulocytes, has been proposed as a surrogate marker of intestinal mucosa inflammation and has been associated with several gastrointestinal disorders. We recently addressed FC ability in distinguish inflammatory from functional disorders, taking into consideration different pathological intestinal conditions. In this research highlight we provide a brief review on FC role as a biomarker of intestinal inflammation discussing the clinical applications.

Keywords: Fecal calprotectin; Inflammatory bowel disease; Irritable bowel syndrome; Sensitivity; Specificity


Fecal Calprotectin (FC) is a 36.5KDa calcium and zinc binding heterocomplex protein that belongs to the S-100 protein family [1,2]. FC is mainly found in neutrophils granulocyte accounting for up to 60% of the cytosolic proteins but also in monocytes, macrophages and epithelial cells. FC has several biological properties including antimicrobial, immunomodulatory and anti-proliferative activity, and it is released during cell activation (active release) or cell death (passive release) [3,4]. Because of inflammatory stimuli, FC can be found in feces following leucocytes migration from the altered gut wall to the mucosa where it can exert its functions. Furthermore, FC is stable in stool and is resistant to bacterial proteolytic degradation [5].

Actually, FC could be easily measured by conventional ELISA methods and is considered a useful tool for the detection and monitoring of a several gastrointestinal disorders, especially inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn’s disease (CD). In fact, in clinical practice differentiating patients with organic diseases from those with functional disorders (i.e. irritable bowel syndrome [IBS]) may be difficult because of a wide spectrum of overlapping symptoms including abdominal pain, bloating, diarrhea, constipation or altered bowel habit. The gold standard for evaluation of macroscopic and microscopic colonic inflammation is colonoscopy with multiple biopsies for histological examination [6]. However, colonoscopy is an invasive and expensive procedure. Available blood biomarkers like erythrocyte sedimentation rate and C-reactive protein or serological markers like anti-neutrophil cytoplasmic antibodies and anti-Saccharomyces cerevisiae antibodies showed poor sensitivity (Se) and/or poor specificity (Sp) for intestinal inflammatory conditions [7]. Conversely, FC reflects...
alterations mainly dependent on the lower digestive tract. Reported Se and Sp values in distinguish organic from functional intestinal disorders ranges from 63% to 100% and from 79% to 98%, respectively [8-13].

Elevated levels of FC can be found not only in IBD but also in other gastrointestinal pathological conditions including infective colitis, microscopic colitis, eosinophilic colitis, adenomas, colorectal cancer [14]. A recent meta-analysis reported a comprehensive list of causes of abnormal results for FC other than gastrointestinal diseases that includes drugs (non-steroidal anti-inflammatory drugs and proton pump inhibitors), untreated food allergy, obesity, liver cirrhosis and young age (<4 years) [14], however elevations in FC levels is much lower than those found in bowel organic disease, especially IBD. This analysis grouped 670 patients from 6 different studies in which IBD was endoscopically diagnosed in 215 patients (32%) [14]. Authors reported FC pooled Se and Sp of 93% and 96%, respectively, concluding that FC screening of patients with suspected IBD would result in a 67% reduction of endoscopic approaches [14].

Several reports investigated FC ability in predicting relapse in patients with IBD [15-17]. Considering that IBD is characterized by a succession of relapse and remissions, Costa and colleagues evaluated FC predictive value for clinical relapse in 38 patients with CD and 41 patients with UC followed for 12 months [15]. Authors found that CD and UC patients in clinical remission with FC values greater of 150 µg/g had 2-fold and 14-fold increase relapse risk, respectively [15]. D’Incà and colleagues performed the same research in a cohort of 97 patients with UC and 65 patients with CD but found a significant positive correlation between FC concentration (> 130 µg/g) and probability of relapse only in UC patients [16]. Considering these conflicting results, Garcia-Sanchez and colleagues prospectively evaluated 135 IBD patients (66 CD and 69 UC) and showed that FC values greater than 120 µg/g were able to predict relapse risk with Se = 80% and Sp = 60% in both CD and UC patients [17].

In our recent study entitled “Fecal calprotectin is an effective diagnostic tool that differentiates inflammatory from functional intestinal disorders” we evaluated FC concentration and diagnostic accuracy in a cohort of patients reporting abdominal complaints with and without bowel inflammation, taking into consideration different intestinal pathological conditions [18]. All patient underwent colonoscopy and all diagnosis were histologically proven. Patients with inflammation showed median FC values of 268 µg/g (95% CI, 151-343) in comparison to patients without inflammation that showed median FC values of 49 µg/g (95% CI, 23-101) [18]. Interestingly, when we stratified patients with inflammation according to final diagnosis, median FC values were 349 µg/g (95% CI, 286-500) and 92 µg/g (95% CI, 39-256) in patients with IBD and patients with other bowel inflammatory conditions (microscopic colitis, eosinophilic colitis and non-specific colitis), respectively [18]. Actually, FC values lower than 50 µg/g are considered normal results, whereas values greater than 100 µg/g indicate positive results [19]. According to a previous study by Licata and colleagues [20], we found that the cut-off value of 150 µg/g maximized Se (66.7%) and Sp (90.5%) for distinguish patients with and without bowel inflammation, whereas cut-off values of 50 µg/g and 100 µg/g showed Se = 84.4% and Sp = 52.4%, and Se = 68.9% and Sp = 71.4%, respectively [18]. With a cut-off of 150 µg/g we were able to classify correctly 90% of IBS cases and 88% of IBD cases with an area under the curve (AUC) of 0.931, indicating an excellent diagnostic accuracy [18]. However, considering the final diagnosis, FC showed just a moderate diagnostic accuracy in distinguishing IBS and IBD from other inflammatory colitis (AUC = 0.673 and 0.793, respectively) [18].

In primary care setting, a cut-off of 50 µg/g could be recommended in order to rule out patients with IBS. Re-testing after 3 months patients with initial FC values between 50 - 150 µg/g and persisting symptoms despite IBS treatment, could be suggested prior to perform further invasive examinations [21]. Conversely, in patients referring to secondary/tertiary care a higher cut-off that enhances specificity could be recommended to improve the appropriateness of colonoscopy, thus avoiding unnecessary invasive examinations.

**Conflicting interest**

The authors declare that they have no conflicting interests.

**References**


