Fecal calprotectin use in inflammatory bowel disease and beyond: A mini-review

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Gastrointestinal (GI) symptoms, such as abdominal pain and diarrhea, are common presenting symptoms in the general population. Determining the underlying cause of these symptoms is often challenging. The development of noninvasive diagnostic tools is useful to differentiate organic from functional bowel diseases and may reduce the need for unnecessary invasive procedures such as colonoscopy. One of these diagnostic tools is the measurement of fecal calprotectin (CPN), a major cytoplasmic protein in neutrophils (1).

Fecal CPN has gained popularity because of its high sensitivity and specificity in the diagnosis of inflammatory bowel disease (IBD) (2). In addition, it is a relatively simple and inexpensive test. However, it should be noted that many conditions have been shown to be associated with fecal CPN elevation, and that intestinal inflammation is a common feature in those conditions. The degree of elevation varies according to the cause, which may interfere with the diagnostic value of the test. Therefore, a broad knowledge of these conditions is essential for understanding the clinical utility of fecal CPN. The present review is aimed at highlighting the different causes associated with fecal CPN elevation.

HISTORY

The first description of CPN in the literature was in 1980 by Fagerhol et al (3) when it was named 'L1 protein'. Thereafter, it has been mentioned in the literature under different names such as MRP-8/14, calgranulin and cystic fibrosis antigen. In 1992, Roseth et al (4) developed the first method for isolating and quantifying CPN in stool using ELISA and rabbit anti-CPN. Many years later, an improved, commercially available and validated ELISA was developed, which measures CPN concentration in mg/kg rather than mg/L as in the original assay (5). Over the past two decades, fecal CPN was described to be a useful marker of several GI diseases. These include gastric cancer, colorectal adenoma or cancer, Crohn disease (CD) and ulcerative colitis (UC) (6).

FECAL CPN

CPN is a 36 kDa calcium-binding heterocomplex protein consisting of two heavy chains and one light chain. It belongs to the S-100 protein family and is derived predominantly from neutrophils and monocytes. CPN and its subunits appear to have mainly regulatory functions in inflammatory processes, as well as antimicrobial and antiproliferative activities (1). Being resistant to enzymatic degradation, it can be easily measured in stools with a commercially available ELISA immunoassay. Due to its high sensitivity and specificity, relative simplicity, quick turnaround time and long stability at room temperature (up to seven days), it has been increasingly used in the diagnostic process for IBD (4). The test can be performed on 50 mg to 100 mg of random stool samples that can be sent to the laboratory by mail because the protein is remarkably stable in stool. It costs approximately USD$100 per assay. Fecal CPN concentrations in healthy individuals have been established in several studies. In the original study, the median stool CPN concentration in healthy adult was 2 mg/L, and the suggested cut-off for a positive test was 10 mg/L. In the newer assay, the suggested upper...
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<table>
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<th>Conditions associated with fecal calprotectin elevation</th>
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<td>Inflammatory</td>
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<td>Inflammatory bowel disease</td>
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<td>Pouchitis</td>
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<td>Graft rejection following intestinal transplant</td>
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<td>Collagenous colitis</td>
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<td>Ankylosing spondylitis</td>
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<td>Systemic sclerosis</td>
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<tr>
<td>Diverticular disease</td>
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<td>Celiac disease</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Infectious</td>
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<tr>
<td>HIV</td>
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<tr>
<td>Infectious diarrhea</td>
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<tr>
<td>Neoplastic</td>
</tr>
<tr>
<td>Colon cancer</td>
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<tr>
<td>Intestinal polyposis</td>
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<tr>
<td>Pancreatic cancer</td>
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<tr>
<td>Iatrogenic</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
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<tr>
<td>Proton pump inhibitors</td>
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<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Miscellaneous</td>
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<tr>
<td>Liver cirrhosis</td>
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<tr>
<td>Food allergy</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
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<tr>
<td>Cystic fibrosis</td>
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<td>Young age</td>
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limit of normal has been increased by a factor of five, to 50 µg/g (7). However, the test appears to have better diagnostic precision for IBD at a cut-off of 100 µg/g than at 50 µg/g (2).

Levels of fecal CPN has been found to correlate well with radiolabelled white cell scanning, as well as histopathological and endoscopic features used in assessing IBD activity (8,9) (Box 1).

**CONDITIONS ASSOCIATED WITH ELEVATION OF FECAL CPN**

Many conditions have been linked to an elevation of fecal CPN (Table 1). However, the current clinical use of fecal CPN is focused on differentiating IBD from irritable bowel syndrome (IBS), monitoring disease activity for relapse and detecting disease recurrence postoperatively. The evidence for fecal CPN elevation in most of the other conditions listed is limited to case series and small observational studies.

**IBD**

**Distinguishing between IBD and IBS:** Fecal CPN has been shown to be of diagnostic value in IBD. The major systematic reviews (10,11) and meta-analyses (2,12) are shown in Table 2. In a meta-analysis of 30 studies including 5983 patients who underwent fecal CPN testing, Von Roon et al (2) found that the mean fecal CPN levels in patients with IBD were higher by 219.2 µg/g compared with control subjects (P<0.001). The pooled sensitivity and specificity of fecal CPN for distinguishing IBD from non-IBD patients from nine studies of adult and pediatric populations at a 50 µg/g cut-off was calculated to be 89% and 81%, respectively.

**Disease activity and treatment response in IBD:** Notably, fecal CPN has been shown to be a reliable marker for assessment of disease activity in IBD patients (13-17). In a study of patients with CD who underwent 140 ileocolonoscopies (13), fecal CPN correlated well with the simple endoscopic score for CD (Spearman rank correlation coefficient r=0.75). This correlation with endoscopic assessment was superior to that of C-reactive protein, blood leukocyte levels and CD activity index. Additionally, fecal CPN discriminated among the various subgroups of endoscopic activity index (inactive, mild, moderate and high activity). The sensitivity and specificity of fecal CPN for detecting endoscopic active disease (simple endoscopic score for CD ≥4) was 89% and 72%, respectively, at a cut-off value of 70 µg/g.

Similarly, a study of 134 patients with UC showed a significant correlation with the Rachmilewitz endoscopic activity index (r=0.834) (18), which was superior to the Rachmilewitz clinical activity index, C-reactive protein and blood leukocyte for the detection of disease activity. Also, fecal CPN was able to discriminate among various groups of endoscopic activity indices. The sensitivity and specificity of fecal CPN for detection of endoscopic active disease (Rachmilewitz endoscopic activity index ≥4) was 93% and 71%, respectively, at a cut-off of 50 µg/g.

Fecal CPN has been investigated in assessing IBD patients’ clinical response to treatment. A study of 38 patients (27 UC, 11 CD) presenting with disease relapse had fecal CPN measured at presentation, and at week 4 and week 8 after treatment (19). Treatment of relapse was individualized according to standard recommendations for management of IBD. UC patients showed a significant correlation of fecal CPN with the clinical score at week 4 after treatment (r=0.424, P<0.01), while CD patients showed a significant correlation with the clinical score (Harvey-Bradshaw index) at week 8 after treatment (r=0.704, P<0.01).

**Predicting relapse in IBD:** Several studies have indicated the value of CPN in predicting relapse in IBD, and have been the subject of a meta-analysis (20) (Table 3). This included a total of 672 patients of whom 318 had UC and 354 had CD. For CPN to predict relapse there was a pooled sensitivity and specificity of 78% and 73%, respectively. The data were comparable for both UC and colon/ileocolonic CD.

Underscoring the value of regular monitoring of CPN, De Vos et al (21) determined levels every four weeks on patients with UC receiving infliximab, and found that the best predictor of a flare were two consecutive CPN levels >300 µg/kg. Those patients considered to be in deep remission (partial Mayo score <3 at all times and endoscopic Mayo score 0 at week 52) had consistently low CPN levels (<40 mg/kg).

**Cost:** With respect to cost, Waugh et al (10) conducted a comprehensive review regarding the economic value of fecal CPN in distinguishing IBD from IBS. They found that by reducing the number of unnecessary colonoscopies/gastroenterologist referrals, the use of fecal CPN test could lead to cost savings, especially in the secondary care setting. Furthermore, a recent cost-effectiveness study found that fecal CPN screening for a patient suspected to have IBD saved USD$417 per patient screened (22) (Box 2).

**Subclinical disease:** Interestingly, fecal CPN has been used to demonstrate the presence of subclinical intestinal inflammation in the first-degree relatives of CD patients (23). This particular study included 49 patients, 16 spouses and 151 first-degree relatives of CD patients. There was a statistically significant higher fecal CPN in the patients and first-degree relatives compared with the spouses and the control group (P<0.0001).
Pouchitis
Patients undergoing restorative proctocolectomy for UC have a 40% lifetime risk of developing pouchitis (24), which is an inflammatory condition of the pouch with neutrophil infiltration of the mucosa (25). The role of fecal CPN as a biomarker of this condition was assessed by a study of 54 patients who had undergone restorative proctocolectomy for UC and familial adenomatous polyposis (26). Six of 46 UC patients had pouchitis and pre-pouch ileitis, 13 had pouchitis alone and 27 were uninfamed. Of the eight familial adenomatous polyposis patients, one had pouchitis and pre-pouch ileitis, and seven had pouchitis alone. Fecal CPN >50 µg/g correlated significantly with high endoscopic inflammatory scores (scale of 0 to 6, depending on the number of acute macroscopic inflammatory features seen) (P<0.001). In addition, fecal CPN >50 µg/g correlated significantly with higher histological inflammation score (modification of the Moskowitz 12-point scoring system) (P<0.001).

Having established that fecal CPN levels are elevated in IBD, there are still a number of disorders that present with diarrhea that may impact on the interpretation of results. These are discussed below (Box 3).

Collagenous/microscopic colitis
Collagenous colitis is a disorder characterized by watery diarrhea, microscopic mucosal inflammation and deposition of collagen below the surface epithelium of colonic mucosa (27). There are generally no endoscopic abnormalities and colonic biopsy is needed to establish the diagnosis.

The value of fecal CPN as a biomarker of collagenous colitis was evaluated by a study that involved 21 patients with active collagenous colitis, 12 patients with collagenous colitis in remission and 13 healthy controls (28). The median fecal CPN level in the active disease group was 80 µg/g compared with 26 µg/g in the disease remission group (P=0.025), and 6.25 µg/g in the control group (active versus control P=0.002).

In a recent study of 78 patients with chronic nonbloody diarrhea, 15 were found to have microscopic colitis (29). However, there was no correlation between this and CPN levels, indicating the importance of colonic biopsy for making this specific diagnosis.

Graft-versus-host disease
Diarrhea is common after hematopoietic stem cell transplant. The differential diagnosis includes infectious causes, chemo- or radiotherapy-associated toxicity, and GI graft-versus-host disease (GI-GVHD). Endoscopy remains the gold standard for the diagnosis of GI-GVHD.

### TABLE 2
Studies evaluating the performance of fecal calprotectin (CPN) in distinguishing inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS)

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study design</th>
<th>Subjects/studies, n/n</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Cut-off value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waugh et al, 2013 (10)</td>
<td>Systematic review</td>
<td>730/7</td>
<td>93</td>
<td>94</td>
<td>50 µg/g</td>
<td>Included many studies of different GI conditions. The seven studies included in this table specifically compared IBD with IBS.</td>
</tr>
<tr>
<td>Jellema et al, 2011 (11)</td>
<td>Systematic review (primary care)</td>
<td>863/9</td>
<td>64–100</td>
<td>70–100</td>
<td>Multiple cut-offs ranging from 10 mg/L to 170 µg/g</td>
<td>When compared with other blood and fecal tests (CRP, ESR, IgG, ANCA, lactoferrin), CPN performed the best</td>
</tr>
<tr>
<td>Van Rheenen et al, 2010 (12)</td>
<td>Meta-analysis</td>
<td>670/6 (adults)</td>
<td>93</td>
<td>97</td>
<td>50 µg/g (Most studies)</td>
<td>CPN theoretically has the potential of reducing the number of patients requiring colonoscopy by 67%.</td>
</tr>
<tr>
<td>Von Roon et al, 2007 (2)</td>
<td>Meta-analysis</td>
<td>5983/30</td>
<td>95</td>
<td>91</td>
<td>50 µg/g</td>
<td>IBD patients were compared with a heterogeneous group of patients with other GI conditions and showed a statistically significant higher level of CPN</td>
</tr>
</tbody>
</table>

ANCA Antineutrophil cytoplasmic antibody; CRP C-reactive protein; ESR Erythrocyte sedimentation rate; GI Gastrointestinal; IgG Immunoglobulin G

### TABLE 3
Summary of the major studies correlating fecal calprotectin (CPN) with inflammatory bowel disease activity/relapse in adults

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Patients, n</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mooiweer et al, 2014 (17)</td>
<td>164 (83 CD, 74 UC, 7 unclassified)</td>
<td>86</td>
<td>72</td>
<td>The study used a cut-off of 140 µg/kg, and used the Mayo endoscopic activity score to assess mucosal inflammation</td>
</tr>
<tr>
<td>Faubion et al, 2013 (16)</td>
<td>264 (157 CD, 107 UC)</td>
<td>78</td>
<td>54</td>
<td>The sensitivity and specificity are for CPN at cut-off of 100 µg/g and SES-CD ≥4. The sensitivity and specificity in UC was not mentioned. However, there was a strong association with Mayo endoscopic score ≤1</td>
</tr>
<tr>
<td>Lobatón et al, 2013 (15)</td>
<td>123 UC</td>
<td>73.5</td>
<td>89.7</td>
<td>These values are for fecal CPN &gt;250 µg/g to predict Mayo endoscopic score ≤1</td>
</tr>
<tr>
<td>Schoepfer et al, 2013 (14)</td>
<td>228 UC</td>
<td>91</td>
<td>90</td>
<td>The study used a cut-off of &gt;57 µg/g to predict endoscopic active disease using modified Baron Score ≥2 points</td>
</tr>
<tr>
<td>Mao et al, 2012 (20)*</td>
<td>672 (meta-analysis of 6 studies; 318 UC, 354 CD)</td>
<td>78</td>
<td>73</td>
<td>This study had multiple CPN cut-off ranges, from 50 µg/g to 340 µg/g. Identification of relapse was based on clinical activity indices or endoscopic findings.</td>
</tr>
<tr>
<td>Schoepfer et al, 2010 (13)</td>
<td>122 CD</td>
<td>89</td>
<td>72</td>
<td>These results are for CPN ≥70 µg/g correlated with SES-CD. The study also shows superior diagnostic accuracy compared with C-reactive protein, blood leukocyte and CD activity index</td>
</tr>
</tbody>
</table>

*This meta-analysis includes several earlier studies. CD Crohn disease, SES-CD Simple endoscopic score for CD; UC Ulcerative colitis

**BOX 3**
Inflammatory bowel disease is the only well-studied indication for fecal calprotectin test. However, because this test is a marker of gastrointestinal inflammation, it may have other potential uses.
However, the invasive nature of this procedure and the fact that this procedure may yield nonspecific findings, has led to a search for non-invasive markers. Fecal CPN may be a good marker due to the inflammatory nature of GVHD. This hypothesis was prospectively tested by Rodríguez-Otero et al (30), who recruited a total of 72 GVHD patients, of whom 51 had GI-GVHD. There were no statistically significant differences in fecal CPN levels between the GI-GVHD and non-GI-GVHD groups. The sensitivity of fecal CPN was only 30%. However, in this study, 21 of the 51 GI-GVHD patients had stage 1 GVHD, which has less inflammation than more advanced stages of GI-GVHD. Notably, higher concentrations of fecal CPN were strongly associated with steroid-resistant GVHD (P=0.0001).

A recent study of 59 patients with GVHD showed that mean fecal CPN in the patient with GI-GVHD was 500 ±492 mg/kg compared with 95 ±9 mg/kg in non GI-GVHD patients (P<0.003) (31). Sensitivity and specificity were 100% and 81.8%, respectively, at a cut-off of 160 mg/kg. However, the authors did not specify the stage of GVHD. These results were consistent with a prospective study of 23 post-stem cell transplant patients presenting with diarrhea, 11 of whom had colonoscopy-proven GI-GVHD (32). The fecal CPN level in patients with GI-GVHD was significantly higher than in patients with non-GI-GVHD diarrhea (P<0.001). The calculated sensitivity and specificity of fecal CPN were 83.3% and 90.9%, respectively, at a cut-off of 250 mg/kg. In this study, most of the patients presented with more advanced stages of GI-GVHD in the late period.

In an intriguing study, Alibrahim et al (33) measured fecal CPN levels in 24 patients with systemic sclerosis. They observed that the mean fecal CPN level was significantly higher in patients with systemic sclerosis compared with patients with other autoimmune diseases (P<0.05). Fecal CPN was found to be significantly higher in patients with systemic sclerosis compared with 83.3% and 90.9%, respectively, at a cut-off of 250 mg/kg. In this study, most of the patients presented with systemic sclerosis. These results suggest that fecal CPN may be a useful marker for systemic sclerosis.

Ankylosing spondylitis
Ankylosing spondylitis (AS) and IBD are known to share some clinicopathological features. These include chronic inflammation of unknown etiology, genetic overlap, and similar microscopic and macroscopic findings in gut inflammation (34-37). In addition, 5% to 10% of patients with AS have concurrent IBD (38).

A pilot prospective study of 39 patients with AS and 42 healthy controls showed a significant difference in the median fecal CPN in the AS group compared with the control group (P<0.001) (39). Another study showed that 68% of 210 AS patients had positive fecal CPN without associated GI symptoms (40). However, patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), which can cause fecal CPN elevation, were not excluded. In fact, fecal CPN levels were found to be higher in the latter group of patients (40).

Systemic sclerosis
GI involvement in systemic sclerosis is known to have an inflammatory component (41). Therefore, a study of 81 systemic sclerosis patients was conducted to evaluate the role of fecal CPN as a biomarker of GI involvement of this disease (42). The study showed that 62 of 81 (76%) patients had a positive fecal CPN test using a cut-off of 50 µg/g. The mean CPN level was 174 ±49 µg/g. Furthermore, mean fecal CPN was significantly higher in patients with pathological cineradiography results compared with patients with normal cineradiography (P<0.013).

Diverticular disease
Given the therapeutically beneficial effect of 5-aminosalicylic acid and the histologically inflammatory nature of diverticular disease, the potential use of fecal CPN as a marker for this disease was investigated (43). Tursi et al (44) used a semiquantitative test to assess fecal CPN elevation in 48 patients with newly diagnosed diverticular disease, 16 healthy controls and 16 patients with IBS. There was a significant fecal CPN elevation in patients with symptomatic uncomplicated diverticular disease and acute diverticulitis compared with the other groups. Fecal CPN levels normalized after treatment with mesalazine and rifaximin, in both symptomatic uncomplicated diverticular disease and acute diverticulitis.

Celiac disease
Celiac disease is a chronic immune-mediated disorder that primarily affects the GI tract. Histologically, celiac disease is characterized by villous atrophy and crypt cell hyperplasia, with both lamina propria and epithelial infiltration by lymphocytes, macrophages and plasma cells. One adult and two pediatric studies have correlated fecal CPN level with the inflammation in celiac disease.

In a study of 28 untreated adult celiac patients and 30 healthy volunteers (45), the mean fecal CPN levels were 45 ±36 µg/g and 36 ±35 µg/g, respectively. Although this difference was not statistically significant, it revealed a trend toward higher fecal CPN in celiac patients. Capone et al (46) assessed the correlation between CPN levels above a cut-off of 75 µg/g with symptoms, histology (Marsh grade) and tissue transglutaminase in 50 patients (46). They came to the conclusion that there was no signal for subclinical inflammation in celiac disease.

Fecal CPN was found to be significantly higher in 31 children with untreated celiac disease compared with 33 treated celiac disease patients and 34 normal controls (47). The mean fecal CPN was 117.2 ±37 µg/g in celiac patients compared with 37.1 ±37 µg/g for celiac children on a gluten-free diet and 9.6 ±9.1 µg/g in the control group (P<0.001). The second study included 29 children with newly diagnosed celiac disease and 10 healthy children (48). The mean fecal CPN was 13.4 ±3.4 mg/L in celiac patients compared with 4.3 ±3.4 mg/L in the controls (P<0.004).

Although there is no convincing evidence to support the use of fecal CPN as a diagnostic marker for celiac disease in the adult population, it may be considered as one of the possible causes of fecal CPN elevation in pediatric cases.

Pancreatitis
Pancreatic enzymes play a major role in digestion and absorption, and alterations of the normal secretion of these enzymes has been shown to have significant effect on intestinal ecology including bacterial overgrowth, change of bile acid absorption and modification of intestinal permeability (49-51). These changes may be expected to be associated with intestinal inflammation.

A study of 90 patients with different pancreatic diseases aimed to determine the association between pancreatic diseases and intestinal inflammation (52). This study included 20 patients with chronic pancreatitis and 11 patients with a history of recent acute pancreatitis. It was found that 55% and 40% of those patients, respectively, had high fecal CPN compared with only 4.3% of the normal control group. In this study, a semiquantitative method was used with a cut-off of only 15 µg/g, indicating that there is unlikely to be any confusion between IBD and pancreatic disorders.

Infectious diarrhea
Stool culture is considered to be the gold standard for the diagnosis of infectious diarrhea. However, the time required to obtain results (typically 48 h) and the relatively high cost of this test has led to a search for alternative diagnostic methods. Understandably, many stool biomarkers have been tested, of which fecal CPN showed the most promising results. A large multicentre study of 2383 patients with acute diarrhea showed a sensitivity and specificity of 83% and 87%, respectively, for fecal CPN in the diagnosis of acute bacterial diarrhea (53). The mean fecal CPN level for patients with culture-proven bacterial diarrhea was 142.84 ±21.34 mg/L compared with 16.8 ±5.3 mg/L in culture-negative patients. However, this study did not test patients for viral or parasitic infections.

Three viral infections were tested in a pediatric study that assessed fecal CPN elevation in patients with bacterial and viral diarrhea (54). These infections were rotavirus (52 patients), adenovirus (eight patients) and norovirus (31 patients). The mean fecal CPN levels were 89 ±37 µg/g, 95 ±31 µg/g and 93 ±33 µg/g, respectively, compared
with 43 µg/g in the control group. The mean fecal CPN level for bacterial (Salmonella, Campylobacter) diarrhea was 754 µg/g, indicating a clear separation from viral diarrhea patients.

HIV
Immune activation is an important mechanism of CD4+ lymphocyte depletion in HIV infection, and is hypothesized to be due to gut flora translocation (55). A possible cause of gut flora translocation is damage of the mucosal barrier by intestinal inflammation and alteration of intestinal flora. To verify this, a study of 58 HIV-positive asymptomatic antiretroviral-naïve individuals measured fecal CPN and the alteration of gut microbiota (56). The study showed that approximately one-half of the subjects (27 of 58) had a positive fecal CPN test at a cut-off 50 µg/g. Moreover, 34% (18 of 53) of the patients had levels >100 µg/g. It will be of interest to see how fecal CPN is affected by diarrhea from various causes in this patient population.

NEOPLASTIC CONDITIONS
Colorectal cancer and adenomatous polyps
One of the earliest areas of interest regarding fecal CPN was colorectal malignancy. A pilot study in 1993 by Roseth et al (57) found that fecal CPN was increased in stools in 50 of 53 patients with colorectal cancer (CRC) and in 32 of 40 patients with colorectal polyps.

However, data from the Norwegian Colorectal Cancer Prevention trial including 2321 patients (58) suggested a poorer sensitivity and specificity of fecal CPN compared with fecal occult blood test. Similarly, in a meta-analysis, Von Roon et al (2) found that the mean fecal CPN was higher by 132 µg/g in patients with CRC compared with those without CRC (P<0.01). They concluded that fecal CPN cannot be recommended as a screening test for CRC in the general population because of low-pooled sensitivity and specificity (36% and 71%, respectively) (Box 4).

Although fecal CPN is not recommended as a screening tool for CRC due to the availability of better screening tests, colorectal neoplasms should be considered as one of the causes of fecal CPN elevation.

Pancreatic cancer
The same mechanism of pancreatic enzyme insufficiency inducing intestinal inflammation may apply to pancreatic cancer. In the aforementioned study on pancreatitis (52), eight of 15 (53.3%) patients with pancreatic cancer had a positive fecal CPN level using a semi-quantitative method; 15 µg/g was used as the cut-off, making it of very limited value in this condition.

IATROGENIC
NSAIDs
NSAIDs have been shown to induce enteropathy at different levels of the GI tract. Some studies that assessed the inflammatory process associated with NSAIDs used fecal CPN to demonstrate this effect. In a study involving 312 patients taking different types of NSAIDs, 44% had a positive fecal CPN at a cut-off of 8.9 mg/L (59). The median CPN level was 7.3 mg/L compared with 2 mg/L in the control group (P<0.001). There were no significant differences between the different NSAIDs in the amplitude of CPN elevation. Another study demonstrated that the effect of NSAIDs on fecal CPN might be seen as early as a few days after the initiation of these medications (60).

Proton pump inhibitors
Although the exact mechanism is not clear, an incidental finding from a study involving 230 subjects to assess the normal range of fecal CPN in a late middle-aged population suggested that the use of proton pump inhibitors (PPIs) was associated with a higher level of fecal CPN (61). The mean fecal CPN level for those on PPIs was 78.16 µg/g compared with 30.9 µg/g for those who were not on PPIs (P<0.001); this finding appeared to be independent of the presence of reported dyspepsia.

Hepatitis
The gut flora and bacterial translocation also play a role in hepatic encephalopathy (65). The role of fecal CPN as a marker of complications of liver cirrhosis was evaluated in a study of 61 patients with liver cirrhosis and 42 controls (66). The mean fecal CPN in the former group was 65.7 µg/g compared with a mean of 17.5 µg/g in the control group (P<0.001). Furthermore, this study showed that the degree of fecal CPN elevation is directly proportional to the severity of liver disease as assessed by the Child–Pugh score and the Model for End-stage Liver Disease scores, as well as hepatic encephalopathy and spontaneous bacterial peritonitis.

Food allergy
Food allergy is defined as an immune-mediated adverse reaction following the ingestion of an allergen; therefore, fecal CPN might be used as a marker of mucosal inflammation. A pediatric study of 281 children referred with GI symptoms other than diarrhea or abdominal pain included 49 patients with allergic colitis (67). This study showed that these patients had significantly higher fecal CPN compared with controls and patients with functional bowel disorders (P<0.001). Additionally, a reducing pattern toward normal fecal CPN level occurred after at least four weeks of exclusion diet (P<0.001).

Another study (68), conducted to determine the diagnostic accuracy of fecal CPN in the diagnosis of organic causes of diarrhea, suggested that food allergies have an association with high fecal CPN level. This study included 20 children diagnosed with chronic diarrhea attributed to cow’s milk allergy or multiple food allergies, 17 (85%) of whom had elevated CPN levels.

Gastroesophageal reflux disease
Fecal CPN may also be a marker of mucosal inflammation of the upper GI tract. The aforementioned pediatric study of 281 children presented with different GI disorders (67) included 17 patients diagnosed with gastroesophageal reflux disease. The median fecal CPN value was 138 µg/g in the gastroesophageal reflux disease group compared with a median of 28 µg/g in the healthy control group (P<0.001).

Cystic fibrosis
There is some evidence of intestinal inflammation in cystic fibrosis (CF) supported by studies using gut lavage and endoscopic biopsy techniques (69,70). A study of 30 children with CF, 30 healthy controls and 15 IBD patients attempted to establish the incidence of intestinal inflammation in CF patients using fecal CPN and rectal nitric oxide production (71). All the CF patients were on pancreatic enzyme replacement before the study. The mean fecal CPN in CF patients was 219 µg/g versus 46 µg/g in the control group (P<0.01). The mean fecal CPN in the CF group was significantly lower than the mean value of the IBD group (309 µg/g) (P<0.001).

Fecal calprotectin in intestinal disorders
Graft rejection following intestinal transplant

Graft surveillance after intestinal transplant is difficult because of the need of serial invasive procedures and biopsies for the diagnosis of graft rejection. The ability to diagnose rejection noninvasively and early will be a major advantage in the care of intestinal transplant patients. To find a better method of graft surveillance, a study collected serial stool samples for CPN level from 72 postintestinal transplant patients (64 children, 10 adults, two children underwent transplant twice) (72). The patients were divided into groups based on the biopsy results (normal, rejection, viral enteritis, bacterial enteritis, non-specific enteritis, indeterminate rejection and total mucosal loss). Fecal CPN level was significantly higher in the rejection, indeterminate rejection and total mucosal loss groups (P<0.05). However, the three stool samples taken at days 4, 7 and 14 before the index biopsies showing rejection showed no statistically significant difference compared with the mucosal loss groups (72). The study concluded that the exact role of fecal CPN in monitoring of graft rejection was unclear, and more frequent prospective sampling could perhaps demonstrate an advantage as an earlier indication of rejection.

Young age (<5 years)

A tendency toward a higher fecal CPN levels in infants and young children has been demonstrated. One study analyzed fecal CPN level of 115 seemingly healthy children visiting local community centers for a routine examination (73). The children were divided into six age groups. The study showed abnormal mean fecal CPN levels for infants and young children up to five years of age (considering 50 µg/g as the upper limit of normal). The groups younger than one year of age had the highest mean fecal CPN levels (Box 5).

CONCLUSION

Although there are many conditions that may contribute to the elevation of fecal CPN level, the best available evidence currently only supports the use of fecal CPN as a screening and monitoring tool for IBD. We believe there may be an under-appreciated potential of other uses for fecal CPN as a diagnostic and follow-up tool for other GI conditions, where the individual patient acts as his/her own control. The simplicity and cost effectiveness of this test might help in decreasing the use of more invasive procedures and better planning for further investigation. However, more studies are clearly still needed to validate the utilization of fecal CPN use in different medical and surgical conditions.

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