Title: Diagnostic accuracy of faecal calprotectin estimation in prediction of abnormal small bowel radiology

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1. Clinical Question: Does a test measuring fecal calprotectin levels rather than erythrocyte sedimentation rate and C-reactive protein help to better confirm (or rule out) a diagnosis of irritable bowel syndrome?

2. PICO Parts:
P: patients with irritable bowel syndrome (abdominal pain, diarrhea, weight loss)
I: fecal calprotectin measurement
C: erythrocyte sedimentation rate and C-reactive protein levels
O: proper diagnosis of irritable bowel syndrome


I- Database Searched: Ovid Medline
II- Keyword Search Terms used: small bowel
III- MeSH Search Terms used: Irritable bowel syndrome/diagnosis

3. Methods Description (setting, population, sample size, study design):

Seventy-three patients who were undergoing barium follow through (BaFT) for symptoms of diarrhea and abdominal pain with and without weight loss were studied. The patients were from out-patient gastroenterology, general surgical clinics, and the University Hospital of Wales in Wales, Cardiff, UK. The control group consisted of 25 patients with known active Crohn’s disease (positive controls), 26 normal and healthy patients (negative controls), and 25 patients with irritable bowel syndrome (IBS) diagnosed by Rome II criteria. Patients with known malignancies, those on NSAIDs, celiac disease, on steroids for any indications, and those with cardiopulmonary, renal, or hepatic impairment, psychiatric disease or alcohol and drug dependency were excluded from the study. During recruitment, a symptom questionnaire was administered, drug history taken, and blood sample taken for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Patients were also asked to supply a single stool sample 7 days before the BaFT or 7-10 days after the BaFT and fecal calprotectin levels were then subsequently assayed.

4. Methods Interpretation (Validity):

a. Was there an independent “blind” comparison with a reference standard?
Small bowel radiology or barium follow through is often included in the work up of patients with diarrhea or abdominal pain to exclude Chron’s disease. The investigators sought to test the efficacy of a surrogate test for BaFT, the reference standard, by measuring fecal calprotectin levels in patient stool samples. The subjects and investigator were not “blinded” in this particular study, however the biochemical analyst was blinded to all clinical details when testing stool samples for calprotectin levels utilizing ELISA based methods. The gastrointestinal radiologists conducting the BaFT studies were blinded to the biochemical data of patients and reported specific parameters seen on the radiographs.

b. Did the sample include an appropriate spectrum of patients to whom the diagnostic/screening test will be applied in clinical practice?

Yes, the sample did include an appropriate spectrum of patients, as the study compared the biochemical and radiography results from patients diagnosed with Chron’s disease (positive control) to those results obtained from healthy individuals (negative control) and those with IBS diagnosed by Rome II criteria. Each of the comparison groups comprised of 25-26 individuals, and patients were recruited to participate in the study from various clinical settings.

c. Did the results of the diagnostic/screening test being evaluated influence the decision to perform the reference standard?

Selection bias was eliminated, as there were no significant differences in the baseline demographics between the three patient groups involved in the study (Table 1). Across all three comparison groups, there was no significant difference in age of participants (median age in the mid-30s) or in the female to male ratio (high female to male ratio per group).

d. Were the methods for performing the diagnostic/screening test described in sufficient detail to permit replication?

There were sufficient details regarding patient selection, as the investigators described patient criteria that were to be met for participation. These characteristics included patients undergoing BaFT for abdominal pain and/or diarrhea as well as those patients diagnosed with either active Chron’s disease or IBS based on Rome II criteria. Patients that presented with positive stool cultures or abnormal rigid sigmoidoscopy were excluded along with those with known malignancies, Coeliac disease, severe cardiopulmonary, renal, or hepatic impairment and other specific clinical manifestations. Also, analysts were blinded to patient data to avoid bias.

The methods and procedures were outlined in sufficient detail, lending it to be replicable. The distribution of calprotectin within stool samples were determined by comparing results of two
separate stool samples at 10 different sites. Analysis of stool sample was done in batches. Batch precision was determined by analyzing the same stool sample 10 different times in a single assay (within batch precision) and 10 times in separate assays (between batch precision). All samples were tested using an ELISA-based method and Biolise software to determine calprotectin concentration. Investigational assumptions and interpretations from the study match the results of the analyses.

5. Results:

The investigators sought to compare the reference standard of using BaFT to fecal calprotectin measurements in patient stool samples as a non-invasive screening biomarker in the differential diagnosis of gastrointestinal inflammation/disorders. They reported that calprotectin screening was highly effective as a screening tool discriminating between Irritable Bowel Syndrome (IBS) and Chron’s disease. Median calprotctin values were recorded for each patient group: the active Chron’s disease group measured at 227 μg/g of stool, the IBS group measured at 19 μg/g, and the normal, healthy individuals measured at 10 μg/g (p< 0.0001). The investigators reported that a cut-off fecal calprotectin value at 60 μg/g of stool, determined by ROC analysis, was the best discriminator between IBS and Chron’s disease, claiming a sensitivity of 84%, specificity of 96%, positive predictive value of 95%, and a negative predictive value of 85%. Also, comparisons were made to other screening biomarkers typically used in the clinical setting, inclusive of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). An ESR at 10 mm/hr or higher had a low sensitivity at 67% and a specificity at 95%, where as a CRP value of 6 mg/L or higher had a sensitivity of 92% and a specificity of 43% (p<0.0001). The negative predictive value (NPV) of a single sample of fecal calprotectin below 60 μg/g was 100%, where as ESR (91% at ESR> 10mm/hr) and CRP (91% at CRP levels> 6 mg/L) values were lower. A combination of ESR/CRP tests yielded a NPV of 84% in predicting absence of IBS or other organic intestinal disorders.

The investigators concluded that fecal calprotectin screening was more effective than ESR or CRP measurements in discriminating among specific gastrointestinal disorders. Fecal calprotectin values below 60 μg/g of stool ruled out Chron’s disease or other non-functional gastrointestinal disorders, but also necessitated BaFT in the patient. Values higher than the cut-off of 60 μg/g of stool were highly suggestive of moderate to severe inflammation within the gastrointestinal tract.

The results highly favor the use of fecal calprotectin testing in the clinical setting, as screening is non-invasive and excludes the need for more invasive standard protocol procedures, such as BaFT, based on specific fecal calprotectin measurements. The investigators also appropriately compared other clinically relevant screening tests, ESR and CRP. How the cut-off value of fecal calprotectin levels at 60 μg/g of stool was determined was not clearly explained in the study. The
authors did not over-interpret the results obtained from the study as the statistical analysis demonstrated the effectiveness of a majority of clinical screening tests typically used to determine presence of gastrointestinal inflammation.

6. Translational Applications (How does this study apply to your patients?):

Adequate with statistically significant results. A single stool calprotectin value of <60g/g effectively excludes Crohn’s disease. This information will exclude these patients from undergoing further testing and possible radiation exposure. This reduces patient time and cost required, and reduces health risks associated with more involved procedures such as barium swallows.

7. Reference: