Faecal calprotectin levels can differentiate between inflammatory and non-inflammatory bowel diseases

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Irritable bowel syndrome (IBS) is a common form of non-inflammatory bowel disease. IBS is painful and can result in a lowered quality of life, but does not cause permanent damage to the intestines. On the other hand, inflammatory bowel diseases (IBD) such as Crohn's Disease or Ulcerative Colitis are associated with inflammation in the intestinal tract that may require pharmaceuticals or even surgery to get it under control.

The symptoms of IBD and IBS are similar, therefore differentiating the two can be difficult, often requiring examination by endoscopy. It has been proposed that faecal calprotectin, a stable protein that accumulates in the bowels in response to inflammation, can be used to more quickly and more comfortably differentiate between IBD and IBS.

In this report SBU summarises and remarks on a systematic review from the National Institute for Health Research (NIHR) in Great Britain, published in 2013 [1]. The authors of the review systematically assessed the use of faecal calprotectin as a marker to differentiate between inflammatory and non-inflammatory bowel diseases.

Original report

Waugh N, Cummins E, Royle P, Kandala N.B, Shyangdan D, Arasaradnam R. et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. Health Technol Assess 2013: 17; xv-xix, 1–211. Accession: 24286461
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Summary

Faecal calprotectin is a useful marker for differentiating between inflammatory and non-inflammatory bowel diseases, as long as other stomach or intestinal infections have been ruled out. Adoption of this test could reduce the proportion of patients needing to undergo invasive investigations, such as colonoscopy, and could result in lowered health care costs.

Remarks from SBU

- The results from the original report are based on studies of patients younger than 60 years of age, who have suffered from abdominal or intestinal symptoms for at least six weeks, for whom blood tests had excluded gluten intolerance, and who do not have typical IBD alarm symptoms (bloody bowel movements, unintended weight loss, and fever). In Sweden, this patient population is estimated to make up as much as half of all patients who present to the primary health care system with abdominal or intestinal problems. Systematic screening of this population for faecal calprotectin levels would significantly help people get the right diagnosis and reduce the number of colonoscopies performed.

- Health economic analysis indicated that faecal calprotectin tests would lead to savings, as well as marginal improvements in the quality adjusted live years (QALY) in both the primary and specialist health care sectors. This calculation was based on the fact that the faecal calprotectin test were performed prior to colonoscopy, eliminating the need for those with a negative result to submit to such an invasive test. Therefore the savings stem primarily from the reduction in the number of colonoscopies performed. A sensitivity analysis shows that even with a limited increase in the calculated patient population, the faecal calprotectin test would likely be cost effective.

- The choice of cut-off will affect which patients will be examined using colonoscopies. The cut-off for normal is 50 micrograms calprotectin per gram of faeces using ELISA. However, a grey zone exist between 50–150 µg/g for adults, and up to 200 µg/g for children. This highlights how faecal calprotectin tests should be used as a support, in combination with the overall clinical assessment of a patient, to determine

which patients need to be examined using colonoscopy.

- Faecal calprotectin is not only elevated in IBD. Bacterial infections of the gastrointestinal tract (gastroenteritis) or ingestion of non-steroidal anti-inflammatory drugs (NSAID) can result in slightly elevated faecal calprotectin levels, resulting in false positives. Even heavy abdominal bleeding and menstruation, or bacterial respiratory infections can result in elevated faecal calprotectin levels.

- As there is a lower prevalence of IBD in primary care relative to specialist care, Swedish studies focused on primary care patients who present with abdominal pain and or persistent diarrhoea are needed. Such studies should focus on the diagnostic outcomes comparing the faecal calprotectin test compared to either endoscopy or intestinal biopsy identification.

- Long term studies of people with slightly elevated faecal calprotectin levels (50–200 µg/g) are also needed to follow up how these levels change over time. Such studies would also allow the discovery of any negative effects that might result from a delayed endoscopic examination.

Summary of original systematic review

About the studies in the original systematic review

The original systematic review includes 28 studies published between 2000 and 2012. The assembled data was collected from 5 069 individuals, of whom 4 026 were adults (18+ years old. male and female), 794 children (8 months to 20 years) as well as 249 individuals of unreported sex or age. Most of the studies originated in Europe (including a few from Sweden). Studies also originated in Egypt, China, Australia, and USA. Nearly all of the studies were done in specialist care facilities. Most of the studies examined the use of enzyme-linked immunosorbent assays (ELISA) to detect faecal calprotectin.

The aims of the report were to examine the accuracy and cost effectiveness of using faecal calprotectin as a marker to distinguish between IBD and IBS.

The reference tests used were endoscopic inspection, including intestinal biopsies. The measured outcomes were sensitivity, specificity as well as number of QALY.

The studies were grouped as follows:

Studies to discriminate between IBD and IBS in adults (7 studies, 730 individuals).

Studies to discriminate between IBD and non-inflammatory bowel disease[1] (11 studies, 8 with 744 children, and 3 with 540 adults).

An additional ten studies investigating the ability of the faecal calprotectin test to differentiate between organic and non-organic intestinal diseases were included in the original systematic review. This comparison is less relevant, as organic intestinal diseases include a mix of patients with intestinal problems such as polyps, diverticulitis (the formation of pouches in the wall of the bowels), or gluten intolerance. We have chosen to omit the results from those studies in this summary.

Results

Of the seven studies focused on the ability of the faecal calprotectin test to discriminate between IBD and IBS in adults, five used a cut-off value of 50 µg/g. A meta-analysis [1] of these results indicated a sensitivity of 93% (83 to 97%) and a specificity of 94% (73 to 99%) (Table 1 – adults).

Six of the eight studies focused on the ability of the faecal calprotectin test to discriminate between IBD and IBS in children, also used 50 µg/g as the cut-off value. A meta-analysis [1] of these results indicated a sensitivity of 99% (95 to 100%) and a specificity of 74% (59 to 86%) (Table 1 – children).

Table 1 Sensitivity and specificity for the diagnosis of IBD with the help of the faecal calprotectin test.

Patients	Cut-off	Sensitivity	Specificity
Adult	50 µg/g	0.93 (0.83–0.97)	0.94 (0.73–0.99)
Child	50 µg/g	0.99 (0.95–1.00)	0.74 (0.59–0.86)

One study investigated six different cut-off values for the faecal calprotectin test. A summary of these results are presented in the original systematic review [1].

[1] *IBS is less common in children, therefore a comparison between IBD and non-inflammatory bowel disease (non-IBD).*

Health economy

The health economic analysis in the original systematic review was done by an external group of analysts. The group developed a cost-utility model to calculate the cost-effectiveness of the faecal calprotectin test to aid in the discrimination between IBD and IBS in primary care settings. The model was also applied to the discrimination between IBD and non-IBD in children in specialist care.

The model was based on a scenario analysis where it was assumed that all patients who are remitted to specialist care will be examined by colonoscopy. The cost analysis takes into account false negative test results, where patients with IBD are missed by the faecal calprotectin test, using the assumption that it would take 12 weeks to correct the mistake.

Primary care, adult patients: faecal calprotectin test compared with a remiss from a general practitioner with no test

In the basic analysis, a semi-quantitative quick-test (cut-off 15 µg/g) and an ELISA-test (cut-off 50 µg/g) were compared to the direct remittance to specialist care with no test (Table 2).

The calculations are based on a patient population with a 6.3% prevalence of IBD. The analysis estimates that the faecal calprotectin tests can lead to savings compared to directed remittance without test: on average GBP 83 per patient for the semi-quantitative quick-test and GBP 82 for the ELISA test (Table 2). The savings are largely due to the reduced number of colonoscopies necessary as the faecal calprotectin test reduces the number of false positive patients remitted for colonoscopy.

According to the analysis, a general practitioner is hypothesized to incorrectly identify 19.8% of the total patient population having IBD, whereas the semi-quantitative and ELISA tests lead to a lower proportion of false positives, 5.1 and 5.6%, respectively (Table 2).

The model used to calculate quality adjusted life years, QALY, was based on a 25 year old patient with a ten year time horizon. The result indicated a marginal improvement of approximately 0,001 QALY for using the faecal calprotectin test to aid diagnosis (Table 2).

Table 2 The costs and QALY associated with different tests done in primary care.

Different tests – primary care	False positives, %	Costs (GBP)	QALY[2]
No test	19.8	3 297	6,228
Semi-quantitative quick test, 15 µg/g	5.1	3 214	6,229
ELISA, 50 µg/g	5.6	3 215	6,229

[2] *6.2 QALY over a ten year time horizon means that the patient experiences 6.2 years of full health over ten years.*

Specialist care, children: direct remittance to colonoscopy compared with the faecal calprotectin test

A comparison was made between the direct remittance to colonoscopy and the faecal calprotectin test using the cut-off values of 50 µg/g or 100 µg/g for discriminating between IBD and non-IBD (Table 3).

The prevalence of IBD in the specialist care patient population was hypothesized to be 47.9%. Despite the higher prevalence of IBD in specialist care, the most savings came from a reduced number of colonoscopies when patients were tested for faecal calprotectin levels. When the faecal calprotectin test was not used, 52.1% of non-IBD patients were examined by colonoscopy. This compares to 13.5% when the faecal calprotectin test was administered with a cut-off of 50 µg/g, and 9.4% when the cut-off 100 µg/g was used. The average savings per patient is estimated to be GBP 205 per patient when the 50 µg/g cut-off is used and GBP 240 when the 100 µg/g cut-off is used (Table 3).

Again, only a marginal improvement was seen in QALY: approximately 0,001 (Table 3).

Table 3 The cost and QALY results for different tests in specialized care.

Different tests – specialist care	False positives, %	Costs (GBP)	QALY
No test	52.1	8 553	6.696
ELISA, 50 µg/g	13.5	8 348	6.697
ELISA, 100 µg/g	9.4	8 313	6.697

Conclusions according to the original systematic review

– Faecal calprotectin is a useful marker for inflammation in the intestines and can be used to help discern between IBD and IBS in difficult to diagnose adults. The test is even useful for discriminating between IBD and non-IBD in children.

– The use of the faecal calprotectin test in primary care could lead to a reduction in the number of referrals to specialist care. Faecal calprotectin may be a useful marker for confirming the clinical diagnosis of IBS. In specials care the use of the faecal calprotectin test could lead to a reduction in the number of colonoscopies for both children and adults.

– The faecal calprotectin test can lead to savings, particularly within specialist care, by reducing the number of colonoscopies.

The need for continued research according to the original report

More studies are needed that investigate whether the faecal calprotectin test is useful for patients who present to primary caregivers with abdominal complaints.

The systematic reviews authors point out that many people have faecal calprotectin levels in the grey zone between 50 and 150 µg/g. They therefore stress the importance of follow up studies to adjust the optimal cut-off values for the test. They also voice the need for more studies to determine why some people with IBS have elevated faecal calprotectin levels.

SBU examines the original systematic review

In order to assess the quality of the original systematic review, SBU has used the AMSTAR checklist for systematic reviews [2]. The original systematic review meets most of the defined quality requirements, however the systematic review did not asses the likelihood of publication bias for the included studies, and failed to declare any potential conflict of interests. The included studies were often small, and most often used only one cut-off value of calprotectin concentrations.

Irritable Bowel Syndrome, IBS

Many suffer from IBS, a chronic intestinal complaint that includes symptoms such as abdominal pain, diarrhoea and bloating. IBS is thought to affect 10–15% of the population [3], and occurs more often in women. The causes of IBS are unknown, however both hereditary and environmental factors play a role. Other factors such as diet, intestinal infections, and disrupted intestinal flora, as well as psychosocial factors such as depression and anxiety, are important for the development of IBS.

The most common symptoms of IBS are chronic or recurrent abdominal pain, altered bowel function, and bloating. The diagnosis is made based on the symptoms being chronic or recurrent for more than six months, with no organic cause. The symptoms for IBS are defined with the help of the Rome III process [4,5], and are divided into three main groups: IBS with diarrhoea; IBS with constipation; or IBS with both diarrhoea and constipation.

Treatment usually focuses on helping the patient reduce and manage symptoms and can include recommendations to alter diet or exercise habits; psychological treatments; probiotic diet; or pharmaceutical treatments including pain reducing, anti-depressive or anticholinergic medications. Medications are available to help reduce constipation, diarrhoea, and bloating which may also be of help.

Inflammatory Bowel Disease, IBD

Crohn's disease and ulcerative colitis are the two most common forms of IBD, affecting approximately 3 000 people every year in Sweden. Approximately 61 000 people were diagnosed with IBD in Sweden in 2010, giving it a prevalence of 0.65%. It is estimated that between 10 and 20% have a more severe form of the disease. The disease can affect people of all ages but the most common onset is between fifteen and thirty years of age. Crohn's disease is somewhat more common in women than men, whereas ulcerative colitis affects men and women to the same extent.

The causes of IBD are unknown, however a combination of genetic predisposition, immunological dysfunction, and the intestinal environment (for example the intestinal flora), can play an important role in the disease's development and progression.

The most common symptom is diarrhoea. Bloody diarrhoea is common in ulcerative colitis, whereas Crohn's disease is more often associated with stomach aches. Ulcerative colitis is limited to the large intestines, but regions of inflammation can be located throughout the digestive tract in Crohn's disease.

IBD can also be associated with intestinal pain, involuntary weight loss and fever. Even other internal organs can be affected in what is called extra intestinal manifestations. IBD, especially Crohn's disease, can cause poor growth and delayed puberty in children.

It is important to diagnose IBD as early as possible so that the patients receive appropriate treatment. A diagnosis is usually set based on the patient's medical history and confirmed by endoscopic examination of the intestines. In acute cases, intensive remission inducing treatment may be necessary. Once the symptoms have subsided, the treatment will focus on keeping the disease in remission.

As ulcerative colitis and Crohn's disease in the large intestines is associated with an increased risk for colorectal cancer, part of the routine follow up for these patients includes screening for cancer.

The prognosis for people with Crohn's disease is often worse than for those with ulcerative colitis. Nearly half of patients with Crohn's disease will need surgery within ten years of their diagnosis, compared to only 10–30% of those who suffer from ulcerative colitis [6,7].

Colonoscopy

An endoscopic examination of the intestines is necessary to confirm a diagnosis of IBD. To administer a colonoscopy, the physician inserts a flexible instrument, a colonoscope, through the anus into the intestines. Using a colonoscope, the physician can examine the epithelial lining of the large and lower small intestines, taking biopsies where needed. Colonoscopy is a very useful method for discovering irregularities in the lining of the intestines such as: inflammation, ulceration, lesions, polyps or tumours. As the instrument is equipped with a high resolution camera, even the small changes associated with early disease can be detected.

Faecal calprotectin

Calprotectin is a protein principally produced by a type of white blood cell known as neutrophil granulocytes, or neutrophils. Neutrophils are part of our innate immune response and are recruited at an early stage to some sites of inflammation.

When the intestines become inflamed, neutrophils are recruited. The calprotectin contained in those neutrophils can form a stable complex with calcium that is not broken down by the digestive system, persisting through the system until it is passes out in the faeces, making it a useful marker for inflammatory illnesses such as IBD. Calprotectin is stable for up to seven days in faecal matter.

In Sweden, calprotectin is measured most often using the ELISA method in a chemical laboratory, but a quick test may occasionally be used on site at a clinic. There are several manufacturers marketing methods to analyse faecal calprotectin. EQUALIS (External quality assurance for laboratory medicine in Sweden) in collaboration with some clinical chemistry laboratories in Sweden is currently assessing these calprotectin tests.

Definitions

Cost-effectiveness
A relative term that describes a cost with respect to the benefit (or effect) an intervention causes in comparison to an alternative intervention. The use of different interventions is calculated using one outcome (for example: life-years gained, quality-adjusted life-years gained, survival rates, or cure rates).

Organic illness
A medical condition with observable morphological changes that can be measured during the progression of the illness, often with the help of biomarkers such as inflammation or tissue damage.

Functional illness (non-organic illness)
A medical condition where normal functioning is disrupted without morphological changes, such that the progression of the illness cannot be followed or measured using standardized diagnostic tests.

Sensitivity
The likelihood that a test will return a positive result for those that have the illness.

Specificity
The likelihood that a test will return a negative result for those that do not have the illness.

False negatives
The number of people with the illness that receive a negative test result.

False positives
The number of people that do not have the illness that receive a positive test result.

Meta-analysis
A statistical method for combining the results from two or more studies to get an estimate of an interventions effects.

Quality-adjusted life-years (QALY)
An expression used to describe the effects of an illness or injury in a population through calculating the number of years of full health. The measurement is constructed so that one year of life is adjusted by the quality of that life.

Continues

Definitions continued

To calculate QALY then number of years of life are multiplied by a quality of life weight between 0 and 1, where 0 represents death and 1 represents full health. For example, if one lives 5 years at full health, that would be 5 QALYs. However, if one lives 5 years with a quality of life at 50% that would be 2.5 QALY.

In this way QALY takes into account both the length of time a person lives, and the quality of their life during that time, in such a way that it becomes a general measurement that allows comparison between treatments or areas of therapy.

Suggested reading

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Translation

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Competing interests

The external expert and reviewers have filed declarations of potential competing interests with SBU. These documents are available for review at the main office of SBU. SBU has reviewed the declarations and has found no conflict of interests that would interfere with the objectivity or impartiality of these collaborators.

SBU evaluates medical methods

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