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“Calprotectin as a method of screening for irritable bowel syndrome”

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Abstract:

Irritable bowel Syndrome (IBS) is a very common functional digestive disorder which affects 10-15% of the population. It mainly affects young and middle-aged adults, especially in western industrial societies. The main symptoms consist of cramps, bloating and bowel motion alterations. Although it is a benign digestive disorder, investigations to rule out organic digestive disease are of utmost importance, and for that reason having a sensible maker or investigation is very important to avoid invasive, complicated or expensive procedures. Calprotectin, a protein biomarker which is present in human faeces during gastrointestinal inflammatory processes, has shown promise as a good method to rule out inflammatory digestive disease. Investigating calprotectin levels may therefore be a cheap and effective method for distinguishing inflammatory from non-inflammatory Bowel diseases. Therefore, the purpose of this scoping review is to compile the most recent evidence on the use of calprotectin levels in general practice.

Introduction:

Similarities between Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) have been well investigated in medical literature. IBS is a gastrointestinal disorder characterised by chronic abdominal pain and altered bowel habits in the absence of any organic cause. IBD however, involves a similar presentation but with evidence of inflammation in the gastrointestinal tract, and similar disease burden, as both conditions cause reduced quality of life for patients and social stigma, and so quick and accurate diagnosis is imperative for effective treatment plans.[6]

The distinction between IBD and non-inflammatory gastrointestinal conditions, such as IBS, can be challenging on clinical grounds alone. Given the frequent overlap in symptoms, particularly those of abdominal pain and altered bowel habits, it can be quite difficult for clinicians to determine the cause of the patient's symptoms. Differentiating these two conditions is important for physicians in relation to not only different treatment options, but also in cost saving measures.

The diagnosis of IBD is based on both symptoms and investigations. For patients with symptoms and diagnostic studies suggestive of active IBD, such as bloody diarrhoea, elevated CRP or faecal calprotectin, we assess the degree of intestinal inflammation with a number of tests. Beginning with endoscopy, biopsies taken during a colonoscopy can help determine the degree and extent of disease activity.(REF) Flexible sigmoidoscopy may be an alternative to colonoscopy for patients with distal colitis.(REF) Endoscopy, however, is costly, time-consuming, and associated with some level of risk and discomfort for patients.(REF) A biomarker which, when normal, yields a sufficiently low

post-test probability of IBD that colonoscopy can reasonably be avoided holds tremendous value in this scenario.

This is even more pertinent due to the prevalence rates of IBS globally. These vary between 1.1% and 45%, based on population studies from countries worldwide, with a pooled global prevalence of 11.2%[4]. There is an expected increase in the cases of IBD worldwide also, which will incur greater costs exponentially for healthcare systems around the world.[6]

Endoscopy waiting times in Ireland most recently reached a level that led to consultants calling for action from the health service executive as endoscopy waiting lists have reached 27,747 people, with 1,911 people waiting 18 months or more for their procedure[5].

Calprotectin, a cytosolic protein derived predominantly from neutrophils, is present in several bodily fluids at levels proportional to the degree of inflammation. (REF) Under normal circumstances, its concentration in faeces is six times higher than in plasma, underscoring its potential to perform as an accurate biomarker of intestinal inflammation[3].

Faecal calprotectin has been shown in multiple studies to have a very good positive predictive value for the diagnosis of inflammatory bowel disease. In one study, a faecal calprotectin above a threshold of 50mcg/g had a pooled sensitivity and specificity for IBD of 81 to 87 percent, respectively[1]. In a meta-analysis, patients with IBS symptoms and a CRP level of <0.5 or calprotectin level of <40ug/g, there was a </= 1 percent probability of IBD[2]. This shows the value in using faecal calprotectin as a useful tool to decide whether further investigation of chronic abdominal symptoms is necessary.

Discussion:

In order to distinguish between IBD and IBS, one faces many challenges given the frequent overlap in symptoms, particularly abdominal pain and altered bowel habits. As we know, Endoscopy is considered the gold standard for diagnosing IBD, and subsequently in distinguishing between IBD and IBS. Therefore having a biomarker in FCP that can help distinguish between the two, can play a huge role going forward. In a meta-analysis of 10 studies including 867 children, FCP was shown to have a sensitivity of 99% for IBD[7]. The specificity was lower at 65%, but for screening purposes, high sensitivity is of greater importance than high specificity. Of relevance to General Practice, a study showed that of 255 patients who presented to their GP with a gastrointestinal complaint, 58% were diagnosed with IBS, by the GP[8]. Thus, special guidelines and training of GPs to apply a more integral approach may help reduce the cost of healthcare and may lead to a more favourable course in patients with IBS[9]. In a recent prospective

cohort study of 789 young adults in the UK, the negative predictive value of FCP </= 100ug/g for IBD was 99% among patients without "alarm symptoms" such as rectal bleeding or abdominal pain associated with weight loss[7]. The NPV remained excellent even in the presence of said alarm symptoms[7]. With this, investigators estimated that 279 specialist referrals were avoided and that £160 per patient were saved through the use of FCP[10].

It is important to note that although the NPV and specificity were very high in the aforementioned studies, they were not 100%. Meaning that a small number of patients with reassuring FCP values were still confirmed to have IBD. In one study done in the UK, seven of 789 patients examined were ultimately confirmed to have IBD despite a "negative" FCP test[7]. Another issue facing the wide scale use of FCP, is that quantitative agreement of absolute calprotectin levels between assays is generally suboptimal, particularly at higher values[11]. Therefore, FCP measurements obtained using different assays, or even in different laboratories, should not be considered interchangeable. As such, serial FCP monitoring in any given patient should ideally be performed using the same method, including the same laboratory.

Conclusion

Faecal calprotectin is very useful for determining the cause of gastrointestinal symptoms, when it is difficult to differentiate between organic and functional causes by symptoms or clinical examination[12]. It can be used in practice to differentiate inflammatory bowel disease from irritable bowel syndrome where the signs and symptoms are very similar but the pathology is different.

As mentioned above, measurements of faecal calprotectin should be conducted in the same laboratory using the same method ideally. With this, it can be a very useful tool to help distinguish between IBD and IBS. This can both lead to better outcomes for patients and reduced need for further investigations such as referral to endoscopy. Considering how common gastrointestinal symptoms are as a presentation to general practitioners, the use of faecal calprotectin is one that should be implemented and will likely be implemented going forward more frequently. The use of FCP not only reduces waiting lists for endoscopy, but as mentioned in discussion, also reduces specialist referrals and expenditure for patients themselves.

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