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Review

Faecal immunochemical tests (FIT) in the assessment of patients presenting with lower bowel symptoms: Concepts and challenges

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ABSTRACT

Colonoscopy is a relatively scarce resource in many countries, including Scotland, and a simple investigation which would aid general practitioners in particular in decision-making as to which patients presenting with lower bowel symptoms warranted referral would be of much help. Faecal immunochemical tests for haemoglobin (FIT) have many advantageous characteristics and are now proven to be of considerable value in the timely assessment of patients with symptoms of lower bowel disease. Quantitative FIT provide numerical estimates of faecal haemoglobin concentration (f-Hb) and, at low f-Hb cut-off, FIT have high sensitivity for colorectal cancer (CRC) and could be used as a rule-in test to stimulate rapid referral, especially when symptoms are suggestive of serious bowel disease. Perhaps more importantly, a low f-Hb gives considerable reassurance that significant bowel disease (CRC + higher-risk adenoma + inflammatory bowel disease) is absent and further investigation may not be warranted: however, no test is perfect, so some cases will remain undetected using FIT alone and robust safety netting is required, possibly including watching and waiting, referral to clinics in secondary care, or a repeat FIT. Moreover, the FIT results should not be taken in isolation, but clinical impressions and the results of other investigations, probably including the full blood count, should be considered. Challenges still exist, however, and harmonisation of aspects of the available FIT analytical systems is required. Moreover, a number of seemingly valid clinical concerns remain and these require resolution through further research and reporting of studies done in real clinical practice.

Introduction

Colonoscopy is crucial to the early diagnosis of significant bowel disease (SBD), including colorectal cancer (CRC) and inflammatory bowel disease (IBD). Unfortunately, there is evidence, such as that gathered by Bowel Cancer UK, demonstrating that there is a current crisis in endoscopy throughout the UK with services being underfunded, demand outstripping supply, chronic staff shortages and growing

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waiting lists for investigations.[1] In part, the demand which has led to the increase in referrals from primary care to endoscopy, gastroenterology and surgery in secondary care has been due to the publicity surrounding the bowel screening programmes running in the four countries of the UK and the information that is given to participants with negative screening test results on the need to pay attention to any bowel symptoms and report these as soon as they become apparent. Moreover, campaigns such as Detect Cancer Early in Scotland[2] and Be Clear on Cancer in England[3] have encouraged people with symptoms to make an appointment with their general practitioner (GP) as soon as possible.

Unfortunately, although the symptoms of SBD, namely, repeated rectal bleeding or blood evident on passed faeces, a change in bowel habit that continues for more than four weeks without returning to usual, diarrhoea on its own or with constipation, abdominal pain especially after eating, unexplained loss of weight and tiredness, are very common presentations in primary care; however, these are well documented to be very poor predictors of SBD.[4] Thus, the challenge was to find and then use an investigation that assists the GP to determine which patients with lower bowel symptoms would benefit most from referral to secondary care for colonoscopy. The primary purpose of this review is to summarise the evidence that faecal immunochemical tests for haemoglobin (FIT) can assist in the triage of these patients and to discuss the challenges that still exist to ubiquitous introduction of FIT as a routine investigation in primary care.

Faecal immunochemical tests for haemoglobin (FIT)

Faecal immunochemical tests for haemoglobin (FIT) make use of antibodies, usually polyclonal, to the globin moiety of haemoglobin. Most FIT have simple to use, hygienic faecal specimen collection devices in which a probe attached to the cap of the device is used to collect faeces into dimples or grooves at the end of the probe. Then, the probe is reinserted into the device, which contains a volume of buffer, which confers some stability on any haemoglobin (Hb) present in the faeces. An important point is that these must be used for collection of faecal samples for FIT analysis since faecal haemoglobin (f-Hb) is unstable; collection of faeces into the traditional pot with later analysis can lead to false negative test results.[5] FIT have many positive attributes, including being unaffected by dietary constituents and more specific for lower gastrointestinal bleeding.

FIT are available in two formats.[6] The first is qualitative FIT, which give a dichotomous, positive/negative result, usually using lateral-flow immunochromatographic cassettes or strips, similar to the very widely used pregnancy tests which detect urinary human chorionic gonadotropin (hCG).[6] The disadvantages of qualitative FIT have been very well documented[7,8] and, since these are not used widely in the UK,[9] this review is mainly concerned with the application of quantitative FIT. Quantitative FIT, usually involving automated immunoturbidimetry on small bench-top dedicated analytical systems, provide a numerical estimate of the faecal haemoglobin concentration (f-Hb).[6]

Faecal haemoglobin concentrations (f-Hb)

Quantitative FIT have become the most widely used non-invasive investigation in both opportunistic and programmatic screening for CRC[10] and much has been learned from the results obtained in screening about f-Hb and the factors that affect f-Hb.[11]

It has been shown that f-Hb is directly related to the severity of colorectal disease.[12] In addition, it has been documented in more detail[13] that median f-Hb is higher in those with CRC than those with no pathology or with minor non-neoplastic pathology. Individuals with low-risk adenoma (LRA), and polyp CRC cancers have lower f-Hb than more advanced stage CRC. Higher f-Hb is also found in those with higher-risk adenoma (HRA: three or more polyps, any polyp >10 mm diameter) than with LRA, in large compared with small adenoma, and also in adenoma displaying high-grade dysplasia as compared to those with low-grade dysplasia. Thus, it is hardly surprising that screening the asymptomatic using FIT is very successful.

In addition, in CRC screening programmes, because of this relationship, as the f-Hb cut-off concentration applied to decide which participants are offered colonoscopy is increased, the positivity rate, CRC and adenoma detection rates, and sensitivity decrease, while positive predictive value and specificity increase.[14] Further, as the f-Hb cut-off is increased, the interval cancer proportion, that is the number of CRC found in participants who had a negative screening test result but had a diagnosis of CRC before the next screening episode was scheduled, rises.[15]

Furthermore, a number of factors affect the f-Hb found in different populations: f-Hb is higher in men than in women and increases with age[16,17] and these relationships differ in magnitude from country to country.[18] In addition, f-Hb is dependent on deprivation, f-Hb increasing as deprivation increases.[17,19] In consequence, there is much current interest in using more complex interpretation of the f-Hb of participants in CRC screening than application of one f-Hb cut-off for all to decide on referral for colonoscopy through incorporation of such variables into a risk-score.[20] In addition, it has been elegantly shown that f-Hb below the cut-off applied in CRC screening is related to the risk of future colorectal disease, particularly if detectable on two occasions.[21]

FIT in the assessment of patients presenting with lower bowel symptoms: background

Even until recently, in spite of the proven relationship between f-Hb and severity of colorectal disease and the successful use of FIT in CRC screening, there was little interest in the application of FIT in the assessment of patients presenting in primary care with lower bowel symptoms. This may have been in part due to the fact that the traditional tests for the presence of blood in faeces, namely, guaiac-based faecal occult blood tests (gFOBT), had many problems and difficulties in all stages of the performance of this apparently simple investigation.[22] Moreover, older guidelines from the National Institute for Health and Care Excellence (NICE),[23] the Scottish

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