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Challenges in Diagnostic Accuracy of Fecal Calprotectin in Pediatric Inflammatory Bowel Disease in Family Practice, Systematic Review

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Abstract: **This systematic review aimed to evaluates the use of Calprotectin as marker for inflammatory bowel diseases among children and the challenges facing family physicians using this method to accurate the diagnosis of IBD in children. Literature searches were conducted in Medline (through PubMed), the Cochrane Library, and Scopus. Using both MeSH terms and All Fields, the following search terms (synonyms and combinations) were used: ("Leukocyte L1 Antigen Complex" [Mesh] OR "calprotectin"[tw]) AND ("Inflammatory Bowel Diseases"[Mesh] OR "inflammatory bowel disease"[tw] OR "inflammatory bowel diseases"[tw] OR "IBD"[tw] OR "Crohn"[tw] OR "Colitis"[tw]). We searched publications up to October 2016. Thus faecal calprotectin is an accurate marker of IBD in both children and adult patients. In pediatric patients, the calprotectin assay had better sensitivity and specificity than in adult patients in identifying organic causes of chronic diarrhea. Children with organic diarrhea had significantly higher faecal calprotectin values than those without diarrhea.**

Keywords: **Calprotectin, Inflammatory Bowel Disease, Chronic Diarrhea.**

1. INTRODUCTION

Primary care physicians frequently manage recurrent abdominal pain or diarrhea in adults and children. These symptoms account for roughly 2% to 5% of all youth assessments [(1,2)]. The occurrence of inflammatory bowel disease is on the boost in both kids and grownups [(3,4)]. The condition consists of 2 significant types of persistent intestinal inflammation: Crohn's disease and ulcerative colitis. Suspicion is raised in patients with relentless (≥ 4 weeks) or persistent (≥ 2 episodes in 6 months) stomach pain and diarrhea. In addition, rectal bleeding, weight-loss, or anemia increase the possibility of the condition [(5,6)]. Pathognomonic indications or signs do not exist. Endoscopic examination with histopathological tasting are usually thought about important in the examination of patients with believed inflammatory bowel disease [(5,6)]. Numerous patients think about endoscopy and the needed bowel preparation to be unpleasant [(7)]. In a fairly big percentage of individuals with presumed inflammatory bowel disease the outcomes of endoscopy will be unfavorable [(8)]. Postpone in identifying IBD, and the resultant hold-up in invoice of proper treatment, might lengthen suffering and can cause issues such as anemia, irreparable development failure, and postponed sexual maturation [(9,10)].

Inning accordance with standards, medical care physicians ought to refer patients with persistent diarrhea, frequent stomach pain, or both for professional care if warnings exist [(11,12)]. The warnings are nonspecific and discriminate improperly in between natural and practical intestinal illness, [(13,14)] frequently causing recommendation and comprehensive diagnostic screening. For child with practical conditions, recommendation or comprehensive screening might postpone proper interventions and additional decline health [(15,16)].

Calprotectin is a calcium-binding protein released from neutrophils during intestinal inflammation that can be easily measured in feces [(17,18)]. In specialist care, evidence shows it to be a useful, simple, noninvasive test that can rule out IBD in patients with gastrointestinal symptoms [(19,20)].

This systematic review aimed to evaluates the use of calprotectin as marker for inflammatory bowel diseases among children and the challenges facing family physicians using this method to accurate the diagnosis of IBD in children.

2. METHODOLOGY

Systematic review study was conducted we followed the Preferred Reporting Items for Systematic Reviews (PRISMA) framework in performing this study [28].

Search strategy:

Literature searches were conducted in Medline (through PubMed), the Cochrane Library, and Scopus. Using both MeSH terms and All Fields, the following search terms (synonyms and combinations) were used: ("Leukocyte L1 Antigen Complex"[Mesh] OR "calprotectin"[tw]) AND ("Inflammatory Bowel Diseases"[Mesh] OR "inflammatory bowel disease"[tw] OR "inflammatory bowel diseases"[tw] OR "IBD"[tw] OR "Crohn"[tw] OR "Colitis"[tw]). We searched publications up to October 2016.

Study selection:

Different reviewers performed the search and screened the initial selection of titles and abstracts for relevance and to exclude duplicates. Relevant studies were retrieved in full text and assessed in relation to pre - defined inclusion and exclusion criteria. References from eligible studies were manually scanned for potentially relevant articles missed in the electronic databases. Studies were limited to humans and to English language.

3. RESULTS AND DISCUSSION

In a relatively large percentage of individuals with presumed inflammatory bowel disease the outcomes of endoscopy will be unfavorable [8]. A 3rd of grownups with bleeding associated signs have no irregularities on endoscopy, and this percentage increases to half with non-bleeding signs such as diarrhoea, stomach pain, and weight reduction. Recognition of low danger patients would decrease the variety of unneeded intrusive endoscopic treatments. Alternatively, physicians wish to have the ability to recognize those with an adequately high possibility of inflammatory bowel disease to validate seriousness for endoscopy.

Usage of an easy, non-invasive, and low-cost screening test to make a presumptive diagnosis of inflammatory bowel disease would assist to reach these objectives. Decision of calprotectin levels in stools might be a great screening approach. Calprotectin is a significant protein discovered in the cytosol of inflammatory cells (21). The protein is steady in stool samples for as much as 7 days at space temperature level and one sample of less than 5 g suffices for a trusted measurement [18]. These qualities enable stool sample collection in your home and prospective hold-ups in transportation to the lab.

Among our recognized research studies [19] revealed that in European secondary and tertiary care centers the measurement of calprotectin in stool is utilized as an efficient triage approach for endoscopy, which is the recommendation requirement for the diagnosis of IBD [19]. Calprotectin is a marker of inflammation that can be determined by utilizing an easy non-invasive test [21], however in other 3 [22,23,24] research studies has actually never ever been examined in kids in a medical care setting. The various patient spectrum in medical care has consequences for the pre-test probability and test characteristics. Before calprotectin testing can be recommended to distinguish functional from organic gastrointestinal disorders at the primary care level, information is required on the predictive value of fecal calprotectin at the primary care level[22,23,24].

One Dutch study [25] have showed that in all children red flag symptoms of IBD could help in diagnosis next to calprotectin at primary care by using a structured evaluation form found in (**Table 1**). Children who fulfill the inclusion criteria and have ≥1 red flag symptoms must be referred to a pediatric gastroenterologist who will decide whether the child requires endoscopic examination [25]. This decision will be based on the medical history, physical examination and blood testing. Children without red flag symptoms, or those who are not eligible for endoscopy will be followed for one year.

Table1: Red flag symptoms of IBD[25]

Red flag symptom	Measurement	Positive
Growth failure	Growth calculator	Height for age < -1 SDS
Involuntary weight loss	History	Involuntary decrease in weight
Rectal blood loss	History	Rectal blood loss with defecation

Red flag symptom	Measurement	Positive
Positive family history of inflammatory bowel disease	History	First-degree relatives
Extra-intestinal symptoms	Physical examination	Eyes (episcleritis, scleritis, uveitis), skin (erythema nodosum, pyoderma gangrenosum, psoriasis), mouth ulcers, finger clubbing, arthritis
Peri-anal lesions	Physical examination	Skin tags, hemorrhoids, fissures, fistulas, abscess
Anemia (Hb)	Hematology	4-12 years < 7.1 mmol/l,
		boy 12-18 years <8.1 mmol/l,
		girl 12-18 years <7.4 mmol/l
CRP	Chemistry	> 10 mg/l
ESR	Hematology	≥ 20 mm/h
Platelets	Hematology	> 450 x 10^9 /l

SDS = standard deviation score; Hb = hemoglobin; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

More recently, two studies [26,27] shows neutrophil-derived S100 proteins have actually been recognized as faecal markers for separating IBD and IBS. Proteins of the S100 household [S100A8/A9 (calprotectin), S100A12] are particles launched from the cytosol by triggered or harmed cells under conditions of cell tension, followed by pro-inflammatory activation of pattern acknowledgment receptors. S100 proteins are incredibly resistant to deterioration by faecal germs, making them ideal markers for gut wall inflammation [26]. Faecal S100A12 and calprotectin are particular and extremely delicate markers of intestinal inflammation and apply a strong impact upon the pathogenesis of IBD [27]. In these research studies, a few of the most appealing faecal markers, which have the potential both to differentiate IBD and to advance diagnostic practices in primary care (Figure 1) [26,27].

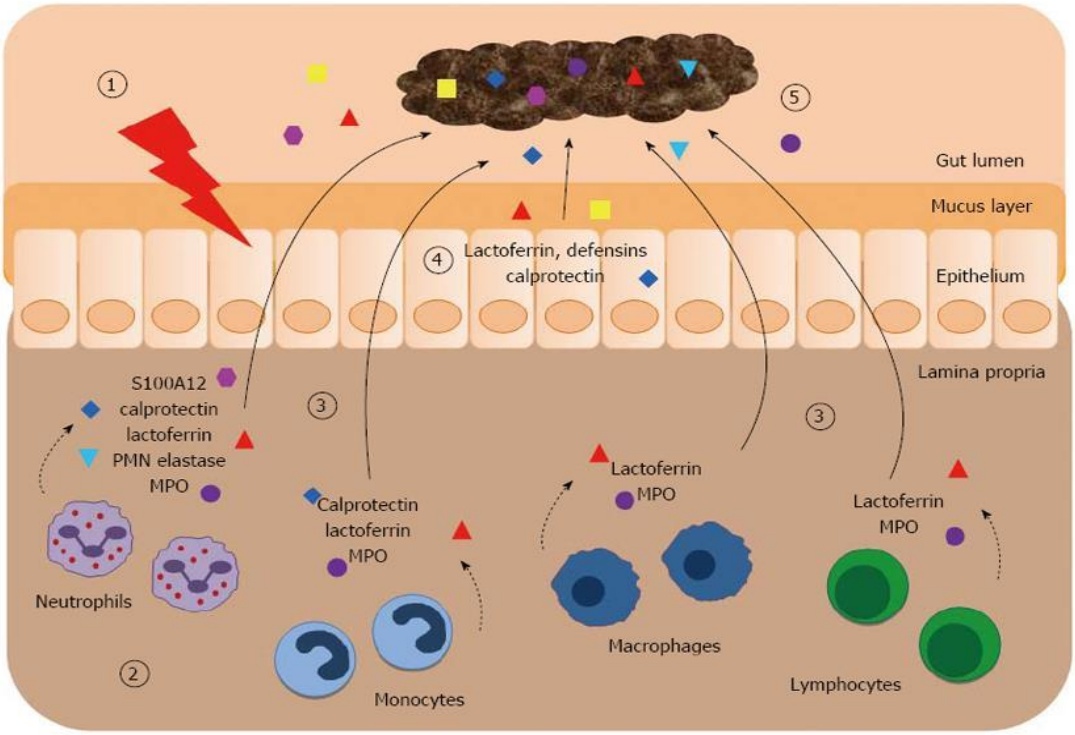

Figure1: Faecal markers of intestinal inflammation. [26]

(1) Initially, unidentified triggers affect the epithelium and lead to an activation of the intestinal immune system; (2) The initiated immune response involves the influx of different innate immune cells (*e.g.*, granulocytes, monocytes, macrophages) and cells of the adaptive immune system (*e.g.*, T cells) into the affected mucosa. These cells actively secret inflammatory mediators or release granule proteins by cell degranulation. The contents of neutrophil granules [lactoferrin, polymorphonuclear (PMN) elastase, myeloperoxidase (MPO)] have antimicrobial properties. The cytosol is the source of

the damage associated molecular pattern proteins S100A8/A9 (calprotectin) and S100A12); (3) During early stages of intestinal inflammation these released proteins spill over from the mucosa into the gut lumen; (4) Some of these factors (including defensins) are also released from the epithelium and the mucus layer; (5) In direct contact with the intestinal mucosa, the faecal stream contains the specific proteins of mucosal disease. The detection of these markers in faeces indicates the presence and degree of intestinal inflammation.

Elevated faecal calprotectin levels have been reported in multiple organic GI diseases when compared with functional GI diseases. In a large-scale study, Tibble et al [29] determined that at a cutoff value of 10 mg/L, faecal calprotectin had a sensitivity of 89% and a specificity of 79% for detecting organic disease, which performed better than the respective values for a positive RomeIcriteria diagnosis (85% and 71% respectively). Following this, Costa et al [30] discussed the value of setting a cutoff point determined by the collective results of complete GI investigations on all patients with chronic abdominal pain and diarrhea. For example, by using a cutoff of 60 μg/g they were able to produce their optimal diagnostic accuracy, with a sensitivity of 81% and a specificity of 88% [30]. In another study, for patients presenting with lower GI symptoms, D'Incà et al [31] reported a sensitivity, specificity and diagnostic accuracy of 78%, 83% and 80% respectively for diagnosing inflammatory disease, irrespective of diagnosis. Similar results have also been obtained in the paediatric population [32,33,34]. Carroccio et al [33] reported specificities which were in line with previous studies, but the sensitivities were far lower. This was attributed to a combination of a higher potential number of referrals for possible coeliac patients (due to their hospital being a tertiary centre for food intolerance), and the reported high frequency of negative calprotectin results for patients with coeliac disease. Furthermore, they highlighted the association between false-positive results for faecal calprotectin and both nonsteroidal anti-inflammatory drug use and liver cirrhosis, believed to be due to the mucosal abnormalities associated with each [35].

4. CONCLUSION

We assume that this sensitivity is a representative estimate for sensitivity measured in children with IBD symptoms in primary care. Thus faecal calprotectin is an accurate marker of IBD in both children and adult patients. In pediatric patients, the calprotectin assay had better sensitivity and specificity than in adult patients in identifying organic causes of chronic diarrhea. Children with organic diarrhea had significantly higher faecal calprotectin values than those without diarrhea

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