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Evaluation of the diagnostic performance of estimated fecal calprotectin and serum intelectin-1 and C-reactive protein solo or in combination for differentiation between patients with query ulcerative colitis, Crohn's disease and irritable bowel syndrome

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***Abstract*---**Background: Gut-brain contact has been linked recently to functional gastrointestinal problems. This interaction begins with immune cells invading the mucosa, which then causes intestinal cells to release nociceptive mediators either directly or indirectly. These mediators can cause visceral hypersensitivity by activating sensitized neurons. Reduced serum levels of intelectin-1 may distinguish among studied cases with UC & healthy controls as well as among IBS studied cases & studied cases with UC. This is as UC studied case samples had significantly lower levels of ITLN1 than do control & IBS studied case samples, & IBS studied case samples & healthy controls did not differ significantly. Aim: in this review; Our objective was to assess the diagnostic efficacy of serum intelectin-1, C-reactive protein, & estimated faecal calprotectin alone or in combination for distinguishing individuals with ulcerative colitis from those with irritable bowel syndrome, Summary: High FCP & low serum ITLN1 together can be able to distinguish UC from IBS, predict colonoscopic & microscopic results of UC, & avoid the need for colonoscopy & biopsy, particularly in IBS studied cases. Raised FCP & lowered serum ITLN1 may distinguish UC from IBS by precisely predicting the microscopic & colonoscopic diagnostic results of UC.

***Keywords*---**fecal calprotectin, intelectin-1, C-reactive protein, ulcerative colitis, irritable bowel syndrome.

Introduction

The immune system, the gut nerve supply, the intestinal epithelium, &, in the case of the colon, the gut microbiome, which dynamically modulates the local immune function, work together to maintain gastrointestinal immunological homeostasis. The main contributors to various pathophysiological illnesses, particularly inflammatory bowel disease, irritable bowel syndrome, & chronic liver diseases, are disruptions of the intestinal epithelial barrier & gut microbiota leakage (1).

One characteristic that sets apart inflammatory bowel diseases —which contain Crohn's disease, ulcerative colitis, & indeterminate colitis—is the idiopathic, long-lasting inflammation of the digestive tract. Regretfully, their prevalence & incidence are rising globally & they are incurable. In contrast, IBS is a highly common functional gastrointestinal disorder that causes uncomfortable abdominal symptoms even in lack of structural abnormalities. It is characterized by gastrointestinal dysmotility & visceral hyperalgesia (2).

Gut-brain contact has been linked recently to functional gastrointestinal problems. This interaction begins with immune cells invading the mucosa, which then causes intestinal cells to release nociceptive mediators either directly or indirectly. These mediators can cause visceral hypersensitivity by activating the sensitized neurons. Immune activation & compromised gut barrier function most likely work in tandem, with changed microbiota, psychological stress, & dietary habits contributing to the pathophysiology. Colonoscopy examination remains the gold standard for differentiating between IBS & IBD patients; nevertheless, a new report of IBS diarrhoea due to low inflammation in individuals with quiescent CD has compounded the problem (3).

Because of the significantly lower levels in UC & Crohn's disease patient samples than in controls & IBS patient samples, reduced serum levels of intelectin-1 may be used to distinguish among studied cases with UC & healthy controls, as well as among IBS studied cases & healthy controls due to the nonsignificant variation in IBS patient & control samples (4).

These results confirmed previous research that found serum ITLN1 was substantially lower in individuals with active Crohn's disease compared to remission, IBS studied cases, & healthy controls. Serum ITLN1 was shown to be considerably lower in studied cases with CD & UC compared to healthy controls, as well as in individuals with active vs inactive illnesses. An inverse relationship exists among serum levels of ITLN1 & the existence & severity of inflammation; the applied correlation analysis supported this assumption by demonstrating a negative significant relationship among serum ITLN11evels & Mayo's endoscopic score, which is widely used in clinical trials & practice & has recently been documented as the most recommended endoscopic index in guidelines. It also has a positive correlation with the microscopic diagnosis of UC. 1of the anti-inflammatory adipocytokines, along with chemerin, vaspin, omentin, & visfatin, is intellectin-1 (omentin-1). A recent study examined the relationship among these adipocytokines & the presence & severity of IBD, finding a correlation among serum chemerin & the inflammation caused by the disease, as well as the utility

of estimated serum visfatin levels as a marker for UC activity & disease progression (5).

ITLN1 could play a role in the development of inflammatory & metabolic complications in intensive care studied cases & is linked to poor results & mortality, according to evidence supporting the relationship among serum ITLN1 & inflammation. Serum ITLN1levels had been significantly higher in non-sepsis studied cases than in sepsis & septic shock studied cases, & samples of COVID-19 studied cases had significantly lower serum levels of ITLN1 & chemerin compared to healthy volunteers (6).

Using an animal model of UC inflammation, researchers investigated the mechanisms underlying the relationship among serum ITLN1 & UC disease. They discovered that overexpression of ITLN1 inhibited endoplasmic reticulum stress-related proteins, colonic damage, inflammation, barrier damage, & cell apoptosis. Clinical research revealed a relationship among low blood ITLN1 levels & obesity, as well as an inverse significant relationship among serum ITLN1levels & cholesterol, monounsaturated fatty acid consumption, & total fat intakes. The current investigation found a negative relationship among studied cases' BMI & serum ITLN1 to corroborate this. There is a comparable inverse relationship among serum ITLN1 levels & total body fat mass (7).

Conversely, although the levels in UC studied cases had been significantly higher than in IBS studied cases, estimated serum CRP levels had been significantly higher inUC & IBS studied cases than in controls. Like this, UC & CD studied cases had considerably greater levels of inflammatory markers, such as CRP, in their serum compared to controls, & there had been a significant difference among the two groups in terms of serum total leucocytic count & serum CRPlevels. Additionally, the present investigation demonstrated a statistically significant negative correlation among blood levels of CRP & ITLN1, indicating that ITLN1 has anti-inflammatory properties. The inflammatory cascade inhibited either the manufacture of ITLN1 or its consumption. Likewise, negative correlations had been found among serum CRP & lymphocytes, namely the monocyte ratio & interleukin-22, both of which are critical for IBD-related mucosal healing (8).

There was a substantial increase in the number of studied cases with FCP levels > 150μg/ml in UC studied cases compared to IBS studied cases, & estimated levels of FCP had been greater in studied cases than in controls. Additionally, there had been a negative correlation with serum ITLN1 levels & a positive correlation with FCP & endoscopic & microscopic UC diagnostic findings as well as serum CRP. These results are consistent with recent research that used FCP for various diagnostic or patient monitoring reasons in UC studied cases (9).

Although they performed differently—high FCP had been specific & low serum ITLN1 had been a sensitive biomarker for the existence of UC—FCP & serum ITLN1 levels had been highly predictive for the UC disease & had related to disease activity as determined by colonoscopic & microscopic results forUC. Furthermore, with an accuracy rate of roughly seventy six percent & ninety percent, respectively, predicted levels of FCP & serum ITLN1 may be used to

predict the colonoscopic & microscopic results. Because of their complementary functions, these indicators may be used to distinguish between UC & IBS without the need for a colonoscopy, which has negative psychological & financial effects (10).

According to this supposition, the composite use of intestinal ultrasonography & FCP to lessen the necessity for colonoscopy in routine care for UC studied cases goes hand in hand with employing complimentary investigation to replace colonoscopy. Furthermore, the utility of a biomarker combination based on FCP & symptom-based monitoring over a symptom-based monitoring strategy, as well as the reduction of endoscopic use for disease activity evaluation to inform treatment choices. Additionally, using blood neutrophil-expressed biomarkers as an addition to fundamental IBD diagnostics may alter how treatments are chosen (11).

Calprotectin is a member of the S100family of calcium-binding proteins that is mostly present in monocytes/macrophages & neutrophils. This protein is found in the human body's blood, urine, faeces, saliva, & cerebrospinal fluid. It is involved in several biological processes, including immunoregulation & inflammation. Calprotectin acts as a warning sign in inflammation, primarily suggesting neutrophil-induced inflammatory activity. When calcprotectin binds to its cell surface receptors, it initiates signal transductions, which in turn causes leukocyte movement & the synthesis of cytokines in inflammatory areas. Remarkably, a recent study employing calprotectinknockout mice shown that calprotectin stimulates the contact between inflammatory leukocytes and renal cells, an essential step in the formation of nephritis (12).

Calprotectin could have a role in the aetiology of IBD. A higher amount of calprotectin in the serum is observed in numerous inflammatory disorders. Faecal calprotectin is currently acknowledged as a valuable test for assessing IBD disease activity. However, Calprotectin's function in systemic circulation has yet to be completely understood. Compared to normal controls, serum calprotectin levels had been greater in CD & UC (13).

Serum calprotectin levels & laboratory indicators as well as clinical disease activity had been strongly associated in CD studied cases. d serum calprotectin in forty healthy controls & 115CD studied cases. According to their research, the profile of serum calprotectin is comparable to that of CRP & clinical disease activity (measured by the Crohn's disease activity index). There is a noteworthy association among serum calprotectin & CRP in UC studied cases, but not with other laboratory values or clinical disease activity. Serum calprotectin may be a useful monitoring tool for certain individuals, as evidenced by the research's observation of a serial change in clinical disease activity, CRP, & serum calprotectin ofUC & CDstudied cases. Further research is required to ascertain their link, especially in UC. CRP is a hepatic-origin serum acute-phase reactant protein with a half-life of roughly twenty hours (14).

Its content in the serum is determined by how strong the pathogenic process is that is causing it to be produced. Given the short half-life of calprotectin in the blood (about five hours) & the association among serum calprotectin & CRPin both CD & UCseen in this research, serum calprotectin is a good indicator of the

systemic inflammatory response linked to illness. But there wasn't much of a correlation among serum calprotectin & CRP, which might be because these proteins have different sources (15).

CPN is a 36kDa protein heterocomplex that binds calcium & is made up of 1light chain & 2heavy chains. It comes mostly from neutrophils & monocytes & is a member of the S-100protein family. In addition to antibacterial & antiproliferative properties, CPN & its subunits seem to primarily regulate inflammatory processes. Because it is resistant to enzymatic degradation, an ELISA immunoassay that is readily accessible for purchase may be used to measure it in faeces. Its use in the diagnostic procedure for inflammatory bowel disease has grown because of its high sensitivity & specificity, relative simplicity, rapid turnaround time, & lengthy stability at room temperature (up to 7days). Because the protein is very stable in stool, the test may be run on 50mg to 100mg of random stool samples that may be mailed to the laboratory. An assay typically costs $100USD (16).

Numerous investigations have established faecal CPN concentrations in healthy subjects. The original research's indicated cut-off point for a positive test result had been 10mg/L, whereas the median stool CPN concentration in healthy adults was 2mg/L. The recommended upper limit of normal in the updated assay is now 50µg/g, a five-fold increase. At a cut-off of 100µg/g, nevertheless, the test seems to offer more diagnostic precision for IBD than at 50µg/g (17).

Both CD & UC have unique pathogenic characteristics. IBD may nevertheless present clinically inconsistently, exhibiting symptoms that are like those of other conditions, depending on the location & severity of the disease. When studied cases exhibit persistent or frequent episodes of diarrhoea & abdominal pain, suspicions must be raised. When alarm symptoms such rectal bleeding, fever, anorexia, or anaemia have been recorded, the likelihood of having IBD rises. It is currently not possible to diagnose UC or CD using a single parameter or laboratory value; instead, a combination of biochemical, radiological, endoscopic, & histological analyses, as well as clinical evaluation, are used to confirm the diagnosis. Of UC studied cases, ten percent have a change in diagnosis toCD, & five percent of CD studied cases have a change in diagnosis to UC (6).

When it comes to diagnosing inflammatory bowel disease, faecal calprotectin is far more accurate than serum markers like CRP, ESR, anti-neutrophil cytoplasmatic antibody, & anti-Saccharomyces cerevisiae antibody. It also seems to be fairly like lactoferrin, another neutrophilic marker measured in faeces. Numerous studies that assessed CRP & ESR in the diagnosis ofIBD found that they have high specificity (seventy-eight–one hundred percent) & low sensitivity (thirty-five to forty percent & eighteen–fifty two percent, respectively) when compared to faecal indicators. Examined the relationship between 136patients' stool calprotectin levels & measurements of CRP & IBD antibodies (ANCA, ASCA). The non-invasive separation of studied cases with IBD & IBS. CRP demonstrated a modest overall diagnostic ability (sixty four percent) & a lower sensitivity (fifty two percent) for UC compared to seventy-three percent for CD. The diagnostic potential of ANCA & ASCA had been restricted by their low sensitivity, despite their excellent specificity for the existence of IBD. The overall accuracy in differentiating among

studied cases with IBD & those with IBS improved very slightly, even when faecal calprotectin & IBD antibody testing had been combined (10).

It is well known that there is a relationship among the levels of faecal calprotectin & the activity of the endoscopic & histological stages of IBD disease. When evaluating mucosal inflammation, calprotectin consistently outperformed clinical indicators & blood markers. At present, endoscopy combined with mucosal biopsy is thought to be the best method for determining the degree & character of disease activity. On the other hand, endoscopy is a costly, invasive, & taxing operation for the studied case. A non-invasive method of monitoring disease activity is made possible by faecal calprotectin, which is particularly useful when considering the dynamics of repeated tests. Considering recent challenges to symptom-based clinical activity indices for identifying IBDremission, MH is suggested as a more accurate way for recognizing controlled disease activity in individuals with CD & UC. Long-term clinical remission, lower hospitalization & surgical resection rates, & mental health disorders have all been linked to mental health. Normal levels of faecal calprotectin in endoscopically remitted patients. However, the available information is insufficiently clear to recommend faecal calprotectin as a stand-in marker forMH (2).

Comparison of ulcerative colitis, Crohn's disease, irritable bowel syndrome

	UC	**CD**	**IBS**
Age	Any	Any	Any, but more in young
Gender	M = F	M = F	Female preponderance
Population distribution	Incidence in Western countries: 10–20 per 100,000 Prevalence in Western countries: 100–200per100,000	Incidence in Western countries: 5–10 per100,000 Prevalence in Western countries: 50–100per100,000	About 20% but only 10% consult GPs
Ethnic group	Any	Any; more common in Ashkenazi Jews	Not reported
Genetic factors	HLA-DR103associated with severe disease	CARD 15/NOD-2 mutations predispose	Not reported
Risk factors	More common in non-/ex-smokers; appendectomy protects	More common in smokers (RR = 3)	History of psychological stress
Diagnosis	Clinical confirmed by biopsy	Biopsy	Clinical. Diagnosis supported by symptoms for more than 6months; worsened by stress;

	UC	CD	IBS
			FBC & ESR normal
Anatomical distribution	Colon only; begins at anorectal margin with variable proximal extension Proctitis (rectum); proctosigmoiditis (rectum and sigmoid colon); pancolitis (whole colon)	Any part of GI tract; perianal disease common; patchy distribution – 'skip lesions' Sites involved (in order of frequency): terminal ileum & right side of colon, colon alone, terminal ileum alone, ileum & jejunum	Colonoscopy
Extraintestinal manifestations	Common	Common	Associated with other conditions like dysmenorrhoea, non-ulcer dyspepsia, 'fibromyalgia'
Presentation	Bloody diarrhoea Proctitis – rectal bleeding, mucus discharge, tenesmus Proctosigmoiditis – bloody diarrhoea with mucus; some develop fever, lethargy and abdominal discomfort Extensive pancolitis – bloody diarrhoea with passage of mucus. Severe case – anorexia, malaise, weight loss & abdominal pain, studied case is toxic with fever, tachycardia & signs of peritoneal inflammation	Variable; pain, diarrhoea, weight loss all common Ileal CD: there can be subacute or even acute intestinal obstruction. Diarrhoea – watery but no blood or mucus Crohn's colitis: identical to UC but rectum spared and presence of perianal disease. Many presents with symptoms of both small bowel and colonic disease. In few, isolated perianal disease, vomiting from jejunal strictures & severe oral ulceration	Recurrent colicky abdominal pain or cramping, relieved by defecation Abdominal distension Episodes of diarrhoea but can have more of a constipation pattern Patients well, no weight loss
Histology	Inflammation limited to mucosa; crypt distortion, cryptitis, crypt abscesses, loss of goblet cells	Submucosal or transmural inflammation common; deep fissuring ulcers, fistulas; patchy changes; granulomas	Normal

(17)

A chronic inflammatory gastro-intestinal condition is what is known as inflammatory bowel disease. Crohn's disease & ulcerative colitis are the 2main disorders associated with IBD. The most popular, invasive, & subjective diagnostic method for inflammatory bowel disease is endoscopy. Consequently, tissue degradation protein fragments, which have been detectable in serum, may serve as impartial instruments for IBD diagnosis. Currently, leukocyte antigens including neutrophil granulocytes & yeast glycans are the targets of antibodies used in serological biomarkers for IBD diagnosis & evaluation of consequences. The most widely utilised faecal biomarker for separating people with irritable bowel syndrome from those with inflammatory bowel disease is faecal calprotectin. Direct biomarkers of extracellular matrix induced by local tissue inflammation could provide an alternative class of biomarkers that could help with early diagnosis, tracking the progression of a disease, & determining the effectiveness of medical interventions (15).

The epithelial cell layer that covers the extracellular matrix that is made up of fibroblasts, interstitial matrix, & basement membrane makes up the intestinal mucosa. Increased protease activity, such as matrix metalloproteinase & neutrophil elastase, facilitates the breakdown of the matrix into smaller peptide fragments throughout an inflammatory state, as seen inIBD, when leukocyte & fibroblast infiltration modifies ECM turnover. These protein fragments, which can be detectable & represent harmful disease processes, are discharged into the bloodstream (17).

The mucous lining the healthy intestinal tissue is undamaged and helps shield the epithelium layer from things like germs. Both the mucus layer & the epithelial cell layer are damaged throughout the inflammatory phase of IBD, which increases the infiltration of germs. Enhanced proteinase activity (MMP & NE) & enhanced leukocyte infiltration—such as that of macrophages & neutrophil granulocytes—will follow from this. Increased proteinase activity remodels the extracellular matrix, producing fragments of elastin (EL-NE), biglycan (BGM), & typeV collagen (C5M). Moreover, elevated cellular turnover causes an increase in local tissue calcium levels. Vimentin produced from macrophages is citrullinated more as calcium levels rise. The following are abbreviations: CIT-vimentin (citrullinated vimentin), NE (neutrolphil elastase), and MMP (maxtrix metalloproteinase) (6).

We have demonstrated recently that the chronic inflammation associated with IBD affects the extracellular matrix of intestinal tissue, leading to higher turnover of tissue & the release of fragments of tissue into the bloodstream. Therefore, the fundamental relationship between the ECM and IBD can be related to the pathogenic mechanism that causes the chronic inflammation in IBD, rather than just being a result of it. Thus, other extracellular matrix proteins, such as biglycan, elastin, & typeV collagen, which have been expressed in the human colon tract & have vital roles in the ECM, may be relevant to inflammatory bowel disease (17).

Biglycan is a proteoglycan that is necessary for maintaining the extracellular matrix because it facilitates the assembly of collagen fibrils & elastic fibres. As a result, typeV collagen contributes to the structure & quality of the extracellular matrix by organizing & forming the fibrils of other collagens in the interstitial matrix. The elastic fibres formed in the extracellular matrix that give tissue its elasticity primarily consist of elastin. Released into the bloodstream, certain NE-fragments of elastin may be quantified as a biomarker of NE activity & tissue repair (15).

The biomarkers VICM had been linked to CD, & BGM, EL-NE, & Pro-C5 had been linked to UC. With an AUC of nearly 1, VICM & BGM were used to achieve good clinical accuracy in differentiating between UC & CD. It's interesting to note that, when compared to healthy donors, type V collagen, Pro-C5, & its degradation, C5M, were shown to be higher in IBD & IBS studied cases. Because IBD is characterized by a chronic inflammatory state, it had been hypothesized that the C5M & Pro-C5 biomarkers would be higher in people with the disease than in those with IBS. With excellent diagnostic accuracy, the combination of biomarkers C5M, Pro-C5, & EL-NE had been the best for distinguishing among donors in good health & those with IBS. These findings would suggest that some IBS studied cases can have micro-inflammation, which could then result in more ECM remodeling in IBS studied cases (17).

Prometheus Laboratories has developed a biomarker diagnostic platform that combines 17serological, genetic, & inflammatory biomarkers. This platform can give clinicians a tool to help diagnose & classify IBD studied cases into treatment & risk groups for more efficient patient care. Nevertheless, only three of the serological biomarkers—pANCA, ASCA-IgA, & ASCA-IgG—may be fully explained by the diagnostic accuracy of the SGI diagnostic platform. Furthermore, biglycan fragments are a ligand for toll-like receptors-2/4 in particular & can function as a chemokine. TLR-4 expression varied among CD & UC studied cases; CD studied cases showed the strongest staining at the apical pole of the epithelial cells, whereas UC studied cases had the strongest TLR-4 expression at the basolateral pole, with some UC studied cases exhibiting apical staining. Therefore, the finding that UC studied cases, regardless of the degree of disease activity, exhibit elevated levels of degraded biglycan (BGM) can corroborate the theory that biglycan fragments ligand TLR-4 & contribute to UC studied cases' persistent, chronic inflammation (16).

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