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ORIGINAL ARTICLE

Role of Serum S100 A12 (Calgranulin C) as a Diagnostic and follow-up Marker in Egyptian children with Inflammatory bowel disease

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Abstract

Background: ***IBD, which includes both Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, intermittent inflammatory bowel illness that relapses frequently. A noninvasive indicator of gut inflammation, calc granulin-C (S100A12) has been found to be high in a number of chronic inflammatory conditions, including rheumatoid arthritis, cystic fibrosis, and, more recently, inflammatory bowel disease (IBD).***

Aim and Objective: ***To assess the efficacy of serum S100A12 as a diagnostic and follow-up marker in Egyptian children suffering from inflammatory bowel disease (IBD).***

Patients and methods: ***This study was carried out on 60 children classified into three groups: chronic disease group in remission (n=20), newly diagnosed group (n=20), and control group (n=20). The following was done for all patients: detailed history, complete general examination, local abdominal examination, examination of other systems, and endoscopy findings. Serum S100A12 level Enzyme-linked Immunosorbent Assay Kit was used for quantification.***

Results: ***Our study found statistically noteworthy increased mean values of CRP and ESR in the newly diagnosed group compared to the chronic disease group. Our study showed highly statistically noteworthy increased mean values of Serum S100A12 in the Newly diagnosed group, followed by the chronic disease group, and the lowest value in the control group. There was a statistically significant positive correlation between fecal calprotectin and Serum S100A12 in the group with chronic disease cases and newly diagnosed cases.***

Conclusion: ***Serum s100A12 may be included in the diagnosis of IBD.***

Keywords: Inflammatory bowel diseases; Ulcerative colitis; Crohn's disease; S100A12; Calgranulin C

1. Introduction

Episodic inflammation of the intestines is a characteristic feature of the chronic and sometimes life-threatening condition known as inflammatory bowel disease (IBD). Crohn's disease and ulcerative colitis are two basic kinds of idiopathic intestinal disease that are characterized by their distinct locations and varying degrees of involvement in the intestinal wall. Both conditions have a genetic tendency and great morbidity, and neither is treatable. Lastly, both raise the chance of colon cancer.[1]

S100A12 belongs to the S100 protein family, which includes at least twenty-five low molecular weight (9-14 kDa) proteins in humans. Because these proteins are 100% soluble in ammonium sulfate at normal pH, they go by the moniker S100. Moore initially identified the S100 proteins in 1965. Later, other members of this family were located and described.

The majority of these proteins are encoded by genes within a narrow region of 1q21.[2] IBD has been examined in relation to S100A12.[3] Hashem et al. [4] assessed serum S100A12 as a diagnostic marker in patients with inflammatory bowel disease to evaluate its efficacy. They concluded that UC and CD can be detected noninvasively with serum S100A12.

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The objective of this study is to assess the efficacy of serum S100A12 as a diagnostic and monitoring indicator for inflammatory bowel disease (IBD) in children from Egypt.

2. Patients and methods

A total of 60 children were recruited from the Paediatric Department of the Faculty of Medicine at Al-Azhar University Hospitals (specifically Al-Hussein and Sayed Galal Hospitals) to participate in this case-control study. Additionally, participants were also selected from the Outpatient Clinic of Gastroenterology within the Paediatric Department.

Out of the sixty children who took part in this study, three groups were created: Group I consisted of twenty healthy children who served as a control group. Group II consisted of twenty children who were diagnosed with IBD and were in remission, as determined by the IBD index. Group III included twenty children newly diagnosed with IBD.

Inclusion criteria: Egyptian children. Age <18 years, children of both sexes, confirmed endoscopic, radiographic, histological, and conventional clinic criteria.

Exclusion criteria: Patients with positive stool cultures, a medical history of significant gastrointestinal surgeries, particularly those involving resection and anastomosis, non-steroidal anti-inflammatory drugs, and individuals suffering from conditions involving active inflammation.

2.1.Methods:

History taking includes personal data and history. General examination includes Vital indicators including blood pressure, pulse, temperature, respiration rate and head, neck, upper limb and lower limb. Local abdominal examination including inspection, palpation, percussion and auscultation. Examination of other systems. Anthropometric measures and routine laboratory tests include acute phase reactants, total blood counts (ESR and CRP), and fecal calprotectin. Finally, endoscopy and biopsy measurements of serum S100A12 were also done.

Enzyme-linked Immunosorbent S100 Calcium Binding Protein A12 Assay Kit (S100A12). Homo sapiens, commonly referred to as humans, were produced by USCN Life Science Inc. A sandwich enzyme immunoassay kit has been developed for the quantitative measurement of S100A12 in human serum, plasma, tissue homogenates, cell culture supernates, and other biological fluids in vitro.

In our investigation, the blood levels of S100A12 were assessed in relation to the levels of established inflammatory markers and the clinical features of the patients.

Statistical analysis:

The recorded data was analyzed using version 23.0 of the statistical program for social sciences, developed by SPSS Inc. in Chicago, Illinois, USA. In instances where the quantitative data followed a parametric distribution, specifically a normal distribution, it was represented using the mean value accompanied by the standard deviation and range. Conversely, for non-parametric variables that did not adhere to a normal distribution, the median value was employed in conjunction with the interquartile range (IQR). Quantitative variables were represented in both percentage and numerical formats. The normality of the data was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests.

We conducted the following tests:

That independent-sample t-test was utilized to assess the difference between the two indicates that the Mann-Whitney U test was implemented to compare two groups in the context of non-parametric data. A one-way statistical analysis of variance (ANOVA) can be used to compare means within a dataset containing more than two distinct groups.

Post-Hoc test: Tukey's test was utilized to compare multiple variables simultaneously. In the context of comparing groups based on qualitative data, Fisher's exact test and the Chi-square test were preferred over the Chi-square test when the anticipated count in any given cell was below 5. In the event that either or both sets of variables exhibited skewness, the assessment of the degree of association between them was conducted utilizing Spearman's rank correlation coefficient (rs). Receiver operating characteristic (ROC) curve analysis was employed to assess the overall predictive ability of the parameter and identify the appropriate cut-off value. This analysis also allowed for the evaluation of sensitivity and specificity at the identified cut-off value.

Probability (P-value): A P-value was considered significant if it was below the threshold of 0.05. P-values below the threshold of 0.001 were considered to be very statistically significant. A p-value greater than 0.05 was considered to be insignificant.

3. Results

Table 1. Group comparison based on blood investigation.

BLOOD investigation	Chronic disease cases at follow up (n=20)	Newly diagnosed cases Groups (n=20)	Test value	P-value
HB (g/dl)				
Mean±SD	10.79±1.19	9.84±0.63	3.167	0.003*
Range	9.5-12.5	8.9-11		
TLC (1000/mm3)				
Mean±SD	11.86±3.20	10.37±2.38	1.670	0.103
Range	8.4-18	6.6-15		
Eosinophil%				
Mean±SD	1.30±0.41	1.15±0.33	1.276	0.210
Range	1-2	1-2		
PLT (1000/mm3)				
Mean±SD	469.00±149.05	403.70±82.68	1.713	0.095
Range	200-617	270-500		
CRP mg/l				
Mean±SD	6.20±2.53	14.40±5.45	7.386	<0.001**
Range	3-10	3-30		
ESR mm/h				
Mean±SD	10.0±3.97	18.20±7.05	6.583	<0.001**
Range	5-15	5-30		

t-Independent Sample t-test for Mean±SD; Significant (S): at p-value <0.05; Highly Significant (HS): at p-value <0.001; Insignificant at p-value >0.05.

Table 1. It was found that there exists a statistically significant disparity in the average Hb value between the group of individuals with chronic illness and the group of individuals who have just been diagnosed, with a p-value below 0.05. Furthermore, a notable disparity in the average CRP and ESR measurements was observed between the cohorts of individuals with newly diagnosed conditions and those with chronic illnesses, yielding a p-value below 0.05. Nevertheless, based on the obtained p-value (p>0.05), there is insufficient evidence to suggest a statistically significant distinction between the groups in relation to the variables HB (g/dl), TLC (1000/mm3), Eosinophil%, and PLT (1000/mm3)

Table 2. Comparison of the groups based on stool investigations.

Stool investigations	Chronic disease cases at follow up (n=20)	Newly diagnosed cases Groups (n=20)	Test value	P-value
Blood (RBCs)				
No	6 (30.0%)	4 (20.0%)	0.533	FE0.465
Yes	14 (70.0%)	16 (80.0%)		
PUS				
No	8 (40.0%)	10 (50.0%)	0.404	FE0.525
Yes	12 (60.0%)	10 (50.0%)		
Mucus				
No	6 (30.0%)	8 (40.0%)	0.440	FE0.507
Yes	14 (70.0%)	12 (60.0%)		
Stool Culture				
No Growth	20 (100.0%)	20 (100.0%)	0.000	1.000
Fecal calprotectin (ug/g)				
Mean±SD	115.10±30.52	758.90±165.35	16.194	<0.001**
Range	80-187	471-1380		

x2: Chi-square test for Number (%) & Fisher's exact test, when suitable p-value>0.05 is insignificant;
t-Independent Sample t-test for Mean±SD

In Table 2. A statistically significant rise in the mean was detected. The objective of this study was to assess the value of fecal calprotectin in a group of newly diagnosed cases compared to a group with chronic disease. The statistical analysis revealed a significant difference between the two groups, with a p-value of less than 0.001. However, when examining stool investigations related to blood, pus, mucus, and stool culture, no statistically significant differences were observed between the groups, with a p-value greater than 0.05.

Table 3. Comparison between groups according to colonscopy finding.

Colonscopy finding	Chronic disease cases at follow up (n=20)	Newly diagnosed cases Groups (n=20)	Test value	P-value
Pancolitis	8 (40.0%)	6 (30.0%)	0.429	0.513
Distal colitis	6 (30.0%)	4 (20.0%)	0.520	0.471
Patchy colitis	6 (30.0%)	6 (30.0%)	0.000	1.000
Ulcer	6 (30.0%)	10 (50.0%)	1.625	0.202
Ilieitis	6 (30.0%)	6 (30.0%)	0.000	1.000
Rectosigmoidal colitis	0 (0.0%)	4 (20.0%)	4.333	0.037*

x2: Fisher's exact test where suitable, p-value>0.05 is not significant, and Chi-square test for Number (%)

Table 3. shows, The prevalence of Rectosigmoidal colitis was found to be significantly greater in the newly diagnosed group, with 4 patients (20%) affected, compared to the chronic illness group, where no occurrences of Rectosigmoidal colitis were observed. This difference was found to be statistically significant, with a p-value of 0.037.

Table 4. Comparison between groups according to upper endoscopy finding and biopsy result.

	Chronic disease cases at follow up (n=20)	Newly diagnosed cases Groups (n=20)	Test value	P-value
Upper Endoscopy Finding				
Duodenitis	4 (20.0%)	6 (30.0%)	0.222	0.638
Esophagitus	4 (20.0%)	0 (0.0%)	4.032	0.045*
Gastritis	4 (20.0%)	14 (70.0%)	4.569	0.033*
Hiatus Hernia	2 (10.0%)	2 (10.0%)	0.000	1.000
Pan	0 (0.0%)	2 (10.0%)	0.625	0.429
Biopsy Result				
Duodenitis	2 (10.0%)	8 (40.0%)	1.804	0.179
H Pylori Gastritis	2 (10.0%)	6 (30.0%)	0.937	0.333
Non Specific Gastritis	2 (10.0%)	8 (40.0%)	1.804	0.179

x2: Fisher's exact test and Chi-square test for Number (%), when applicable; p-value >0.05 indicates insignificance, p-value <0.05: indicates significance, and p-value <0.001: indicates highly significan

Table 4. showed that, The frequency of esophagitis was found to be significantly higher in the chronic group compared to the newly diagnosed group, as indicated by a p-value of less than 0.05. The newly diagnosed group exhibited a statistically significant higher occurrence of gastritis compared to the chronic group, as indicated by a p-value of less than 0.05. However, no statistically significant distinction was observed between the groups in terms of biopsy results, with a p-value more than 0.05.

Table 5. Comparison of the groups based on serum S100A12.

Serum S100A12	Chronic disease cases at follow up (n=20)	Newly diagnosed cases Groups (n=20)	Control Group (n=20)	Test value	P-value
Mean±SD	148.22±24.41B	335.26±108.68A	103.17±37.45 C	65.804	<0.001**
Range	109.7-210.5	180.1-527.1	63.7-195		
Tukey's test					
GI vs. GII		GI VS. GIII		GII VS. GIII	
<0.001**		0.040*		<0.001**	

In a single way, an analysis of variance test was run for Mean±SD, and a post-hoc test was used to compare groups many times. The Tukey test. Various capital letters denote a significant difference between the means in the same row at (p<0.05); **p-value <0.001 is extremely significant.

Table 5 . shows, The average value of Serum S100A12 in the Newly diagnosed group was significantly higher at 335.26±108.68 compared to the chronic disease group at 148.22±24.41B, and the control group had the lowest value at 103.17±37.45. This difference was found to be statistically significant with a p-value of less than 0.001.

Table 6. Correlation between fecal calprotectin (ug/g) and Serum S100A12 among study group, using Pearson Correlation coefficient (rs).

FECAL CALPROTECTIN (UG/G)	SERUM S100A12	
	Rs	p-value
CHRONIC DISEASE CASES GROUP	0.852	<0.001**
NEWLY DIAGNOSED CASES GROUPS	0.745	<0.001**

p-value>0.05 (NS); *p-value <0.05 S; **p-value <0.001(HS)

A statistically significant positive connection was found in table 6 between fecal calprotectin (ug/g) with Serum S100A12 in Chronic disease cases group and Newly diagnosed cases Groups, with r-value (r= 0.852 and 0.745) respectively, and p<0.001).

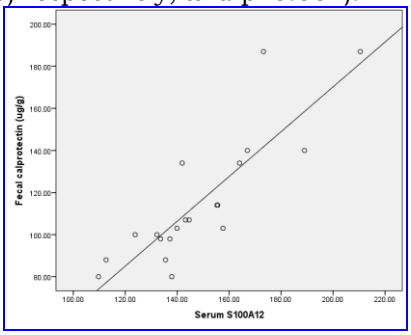

Figure 1. Correlation between fecal calprotectin (ug/g) and serum S100A12 in chronic disease group.

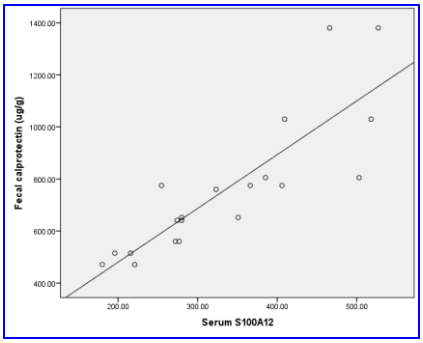

Figure 2. Correlation between fecal calprotectin (ug/g) and serum S100A12 in newly diagnosed group.

4. Discussion

The term "inflammatory bowel disease" (IBD) describes a group of inflammatory digestive tract illnesses that have a chronic, relapsing-remitting course. There are two primary types of IBD: ulcerative colitis (UC) and Crohn's disease (CD). Clinical symptoms, patient-reported outcomes, and inflammatory load are the main factors used to categorize individuals and determine the severity of the illness in UC and CD. These indicators are often created in a research context. One major challenge for researchers developing predictive biomarkers for IBD is the need for more consensus on valid, trustworthy and significant outcome measures.[5]

Calgranulin C, or S100A12, is a calcium-binding protein with proinflammatory characteristics. It has been shown to be a marker for inflammatory bowel illness and is substantially expressed in a number of inflammatory disorders. S100A12 may have the greatest capacity to initiate RAGE. The binding of S100A12 to RAGE has been demonstrated to elicit a proinflammatory response, both in vivo and in vitro. The reaction, as mentioned earlier, entails an augmentation in the synthesis of interleukin (IL)-6, IL-1, and tumor necrosis factor, with the activation of nuclear factor-kB. The inhibition of inflammation and atherosclerosis was accomplished through the implementation of RAGE blockade, employing anti-RAGE IgG or soluble RAGE, which acts as a decoy receptor, thereby impeding ligand interaction with RAGE.[6]

In the present study, the average age of patients diagnosed with chronic disease was found to be 6.40±2.97 years. Conversely, the average age of patients who were newly diagnosed with the condition was determined to be 8.98±3.47 years. Additionally, the average age of individuals in the control group was observed to be 7.40±2.10 years. There is no statistically significant difference observed between the groups under study with respect to age. Additionally, in the study of Lucaciu et al. [7] between healthy individuals and CD or UC patients, there were no statistically significant changes based on age or gender.

We found that inflammatory bowel diseases occur more frequently in men, with statistically insignificant gender differences between the groups under study.

According to Esmat et al.[8], The ratio of males to females was 1:1.15, suggesting a slight increase in the proportion of affected females compared to other global regions.

The study found that the newly diagnosed case group had a statistically significant higher mean value of fecal calprotectin ($p < 0.001$) than the chronic disease group. However, there was no statistically significant difference between the groups based on stool investigations, including blood, pus, mucus and stool culture ($p > 0.05$).

Furthermore, as assessed by Akutko et al. [9], can fecal calprotectin be used as a diagnostic tool to differentiate between non-inflammatory gastrointestinal tract disorders in children and Crohn's disease? The researchers found that children diagnosed with Crohn's disease exhibited significantly higher amounts of fecal calprotectin compared to the control group ($p < 0.001$). The

researchers concluded that the measurement of fecal calprotectin is a valuable tool for monitoring the clinical progression of Crohn's disease and distinguishing it from non-inflammatory gastrointestinal tract illnesses in pediatric patients. However, it does not provide significant benefits in evaluating the disease's activity and phenotype.

According to the findings of our study, the mean CRP value of the newly diagnosed group was significantly greater than that of the chronic illness group, as indicated by a p-value of less than 0.05. In addition, it was observed that children diagnosed with Crohn's disease exhibited significantly higher levels of C-reactive protein in comparison to the control group ($p < 0.001$) by Akutko et al.[9] The researchers reached the determination that C-reactive protein, erythrocyte sedimentation rate, and seromucoid exhibit utility in differentiating Crohn's disease in pediatric patients from other non-inflammatory gastrointestinal tract conditions, as well as in monitoring the clinical progression of the disease. However, these biomarkers do not possess efficacy in evaluating the disease's activity or phenotype.

The findings of our study indicate that the group of individuals who were recently diagnosed had a significantly higher average ESR value compared to the group with chronic disease. This difference was determined to be statistically significant, as evidenced by a p-value of less than 0.05. Additionally, Akutko et al.[9] discovered that children with Crohn's disease had erythrocyte sedimentation rates that were considerably greater than those of controls ($p < 0.001$).

Regarding S100A12, our study showed a highly statistically significant higher mean value of Serum S100A12 in the Newly diagnosed group was 335.26±108.68, followed by the chronic disease group was 148.22±24.41B, and the lowest value in the control group was 103.17±37.45, with p-value ($p<0.001$).

Hashem et al. [4] The present study assessed the utility of serum S100A12 as a diagnostic biomarker in persons afflicted with inflammatory bowel disease and irritable bowel syndrome. The study revealed a substantial increase in blood S100A12 levels among patients with ulcerative colitis (groups III and IV) as compared to patients with irritable bowel syndrome (group II) and the control group (group I). However, no significant difference was observed between patients with irritable bowel syndrome (group II) and the control group (group I). Additionally, it was shown that patients with high clinical activity index (CAI) and colonoscopic activity index had a noteworthy increase in serum S100A12 levels as compared to individuals with lower stages of disease activity as determined by CAI and lower colonoscopic activity index.

Carvalho et al.[10] It has been suggested that the optimal clinical application of S100A12 lies in differentiating between inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), wherein assessments of serum S100A12 are conducted alongside fecal S100A12 measurements.

A statistically significant positive association was found in our study between fecal calprotectin (ug/g) with Serum S100A12 in the Chronic disease cases group and Newly diagnosed cases Groups, with r-value ($r= 0.852$ and 0.745), respectively, and $p<0.001$).

Hashem et al.4 showed that serum S100A12 levels correlate significantly with other inflammatory parameters (ESR and CRP) in UC patients.

5. *Conclusion*

Our results support the notion that S100A12 overexpression is not limited to the walls of an intestine inhabited by IBD but rather is mirrored systemically and subsequently found in serum. Serum S100A12 levels are elevated in IBD patients and have a strong correlation with CRP, a "classic" measure of inflammation. However, serum S100A12 has little diagnostic usefulness when used alone; hence, combining it with a "palette" of other serological markers may actually increase overall diagnostic performance. As a result, serum s100A12 may be used to diagnose IBD..

Disclosure

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