ORIGINAL RESEARCH

Evaluation of fecal protein S100A12 in patients with inflammatory bowel disease

Fengming Yi[I], **Long Feng**[I], **Jianbing Wu**[I]

[I] Department of Oncology, Second Affiliated Hospital of Nanchang University, Nanchang 330006, P.R. of China

BACKGROUND AND OBJECTIVE: The diagnosis and evaluation of inflammatory bowel disease is quite complex. An ideal, noninvasive marker for this disease is quite urgently needed. Fecal S100A12 is a member of the S100 protein family and is secreted by activated neutrophils. We aim to evaluate it as a biomarker for inflammatory bowel disease patients in China.

METHODS: Fecal S100A12 was measured in 18 Crohn's disease, 21 ulcerative colitis, and 17 healthy controls. Diagnostic value was evaluated by receiver operating characteristic (ROC) analysis in comparison with C-reactive protein and erythrocyte sedimentation rate. The correlation between fecal S100A12 and clinical characteristics was also evaluated.

RESULTS: We found significant increases ($p<0.01$) in the diagnostic value of S100A12 in both Ulcerative Colitis and Crohn's Disease when compared to healthy controls. In ulcerative colitis, fecal S100A12 correlated with fecal occult blood ($p=0.02$, $r=0.55$); in Crohn's disease, it correlated with disease duration, albumin and platelet levels ($p=0.01$, $r=-0.53$; $p<0.01$, $r=-0.65$; $p=0.04$, $r=0.45$. respectively). No correlation occurred between fecal S100A12 and other clinical conditions.

CONCLUSION: Fecal S100A12 is valuable in distinguishing inflammatory bowel disease patients versus healthy controls. However, the sensitivity and specificity are limited when compared with that described in western countries. The correlation between S100A12 and clinical characteristics is limited as well. More research is need to better explore this interaction in Chinese patients.

KEYWORDS: Crohn's disease, ulcerative colitis, S100A12 .

Fengming Y, Long F Jianbing W. Evaluation of fecal protein S100A12 in patients with inflammatory bowel disease. MedicalExpress (São Paulo, online). 2017 June; 4(3):M170303

Received for Publication on February 5, 2017; **First review** on April 12, 2017; **Accepted for publication** on May 2, 2017; **Online on** May 12, 2017

E-mail: ivandoctor@163.com

INTRODUCTION

Inflammatory bowel diseases (IBD) are idiopathic, life-long, chronic intestinal conditions characterized by periods of remission and recurrent relapses. The two main types of IBD are ulcerative colitis (UC) and Crohn's disease (CD). The diagnosis, prognosis, assessment of disease activity and severity, in addition to outcome of therapy, are aspects that continue to present challenges for physicians. They might be defined based upon endoscopic, histological, and radiological investigations, with histological findings being of paramount importance.[1] Clinical indices tend to be too complex and time consuming for daily routine practice, and are hindered by inaccuracy due to subjective components. Endoscopy is costly, invasive, and has been associated with morbidity, and rarely, with mortality.[1] Various noninvasive tests have been studied in the past to screen for patients with gastrointestinal inflammation, but with limited accuracy and sensitivity.[2]

Clearly, a simple, reliable, reproducible, and non-invasive test, with the ability to differentiate IBD from other gastrointestinal conditions is needed as a clinical investigative tool. Fecal biomarkers of intestinal inflammation are attractive in the clinical routine as they could provide a non-invasive examination that can help screening patients with mild symptoms such as abdominal

DOI: 10.5935/MedicalExpress.2017.03.03

Copyright © 2016 MEDICALEXPRESS. This is an open access article distributed under the terms of the creative commons attribution Non-Commercial License (creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non commercial use, distribution and reproduction in any medium, provided the original work is properly cited.

pain or diarrhea. Furthermore, the measurement of such biomarkers can be repeated to follow up inflammation or to detect early sub-clinical activity.[3] Potential specific roles for these markers include the detection of gut inflammation in individuals presenting with undifferentiated gut symptoms, evaluation of the success of anti-inflammatory therapies and the confirmation of mucosal healing. Key criteria for such indicators consist of high sensitivity and specificity, good acceptability, low cost, and ease of collection and measurement.

Fecal markers of inflammation have the advantage of a more direct assessment of the gut mucosa. Over time, the presence of fecal white blood cells and the measurement of fecal a-1-antitrypsin have been widely available as indicators of gut inflammation; however, these tests have low sensitivity.[4]

S100A12 also known as calgranulin C, is a member of the S100 protein family. In humans, it consists of twenty five EF-hand (a helix-loop-a helix), calcium-binding proteins.[5] It is secreted by activated neutrophils and promotes inflammation through the activation of extracellular receptors for advanced glycation end products-binding protein (ENRAGE). Neutrophil influx into the intestinal mucosa is closely related to IBD activity, especially during early phases of inflammation. Neutrophil-derived S100A12 in tissue and exudates strongly correlates with inflammatory activity. Excretion of the protein into the gut lumen could reflect the number of neutrophils infiltrating the mucosa as well as their activation status.[6] S100A12, as a marker of neutrophil activation, is more restricted to granulocytes and is released during inflammatory conditions at the site of inflammation and abundant in the intestinal mucosa of patients with IBD. Over-expression at the site of inflammation and correlation with disease activity in a variety of inflammatory disorders underscore the role of this granulocytic protein as a proinflammatory molecule.[7,8] Once bacterial enteritis is ruled out, fecal S100A12 may be an excellent non-invasive marker of disease activity of IBD; it may be superior to other biomarkers including fecal calprotectin, which is derived from monocytes and potentially from epithelial cells, making it less specific for infiltrating neutrophils.

Fecal S100A12 performed as an exceptional screening marker for children with IBD, with superior sensitivity and specificity when compared to current blood tests. Though standard blood tests including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count, and albumin are traditionally used as inflammatory markers in patients with suspected IBD, they generally correlate poorly with histopathologic diagnosis.[9] Kaiser et al[7] recruited fecal specimens of 171 patients and 24 healthy controls. Fecal S100A12 distinguished active IBD from healthy controls with a sensitivity of 86% and a specificity of 100%. An excellent sensitivity of 86% and specificity of 96% was described for distinguishing IBD from irritable Bowel Syndrome. Fecal S100A12 was also elevated in bacterial enteritis but not in viral gastroenteritis. Therefore, Kaiser et al[7] concluded that fecal S100A12 correlated better with intestinal inflammation than fecal calprotectin or other biomarkers. A study by de Jong et al[10] showed that the sensitivity and specificity of S100A12 could reach up to 96% and 92% in children with IBD in comparison to healthy controls when the cut-off was greater than 10mg/kg. The sensitivity and specificity was 86% and 96% when compared to irritable bowel syndrome in adult patients.[7] It could be detected in serum, but its sensitivity and specificity are lower than in feces.[11]

In the present study, we aim to investigate fecal S100A12 in Chinese patients with inflammatory bowel disease and promote the application of this non-invasive tool in China.

METHODS AND MATERIALS

Patients and controls

Eighteen patients with CD, 21 patients with UC hospitalized in the Department of Gastroenterology of Zhongnan Hospital of Wuhan University were included in this study, from Dec/2011 to Sep/2012. Patients with the coexistence of other severe systemic or infectious diseases were excluded. The diagnosis of UC and CD was based on clinical, laboratory, imaging, endoscopic and histological examinations, and in accordance to the Chinese Medical Association diagnostic criteria for IBD.[12] Disease classification was according to the Montreal Classification.[13] Clinical disease activity of UC was assessed through the Truelove and Witts criteria;[14] Crohn's disease activity was assessed through the Harvey-Bradshaw Index (HBI).[15]

Simultaneously, 17 healthy volunteers (controls) who attended this center for constitutional examination of health were recruited in Zhongnan Hospital Medical Center of Wuhan University. All volunteers were unrelated to each other or to the patients from Hubei province, and had no history of IBD, chronic infectious diseases, immune-mediated, ischemic and radiation-induced diseases. The clinical profiles are presented in Table 1.

Ethics statement

The ethic committee of Zhongnan Hospital of Wuhan University approved the study. Informed Consent was signed by all participants involved in this study, along with permission for the use of the samples acquired for scientific research.

Pretreatment of feces

Feces was processed as follows: 4.9ml PBS buffer solution was added to 100mg wet weight of feces; this

Table 1. Clinical profiles of the patients recruited and healthy controls

	UC	CD	HC
Age (years old)	36.22±10.11	34.19±11.76	29.71±10.08
Sex (M/F)	13/5	9/12	10/7
Disease duration (month)	41.11±43.51	55.64±71.63	
Disease activity (mild/moderate)	4/14	-	
HBI	-	3.71±2.31	
Location (E1/E2/E3)	4/5/9	-	
Location (L1/L2/L3)	-	10/9/2	
CRP (mg/L)	6.05±7.46	17.57±18.13	
ESR (mm/h)	14.67±11.12	30.33±28.52	
ALB (g/L)	41.94±3.78	38.64±4.45	
WBC ($\times10^9$/L)	6.82±2.72	6.09±2.71	
HGB (g/L)	128.33±17.96	102.52±14.23	
RBC ($\times10^{12}$/L)	4.11±0.58	3.73±0.76	
HCT (%)	35.41±9.96	30.69±4.17	
PLT ($\times10^9$/L)	222.71±37.90	288.14±109.08	
Occult blood (+/-)	11/7	7/14	

CD, Crohn's disease; UC, Ulcerative colitis; HC, Healthy control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw Index; ALB, albumin; WBC, white blood cells; HGB, hemoglobin; RBC, red blood cells; HCT, hematocrit; PLT, platelet.

was incubated in a water bath at 70 ºC for 5 min and subsequently centrifuged at 5000rpm for 1 min; 0.5ml of the supernatant fluid was collected.

ELISA of fecal S100A12

Enzyme linked immunosorbent assay(ELISA) kit CircuLex S100A12/EN-RAGE was used to detect fecal S100A12. Optical density (OD) of each specimen was assayed by microplate reader.

Statistical analysis

SPSS 13.0 software (SPSS for Windows version 13.0, Chicago, IL, USA) was used to conduct the statistical analysis. Measurement data are presented as mean ± standard deviation (SD), and categorical data are expressed as percentages and number of cases. Normality homogeneity tests for variance were performed for each group samples; Mann-Whitney U test was employed for nonnormal distribution or heterogeneity of variance. Whenever bi-variance exhibited normal distribution, the correlations of S100A12 and clinical characters were calculated by Pearson correlation test, otherwise by Speaman correlation test. To determine the accuracy of S100A12 measurements as a prognostic test the corresponding Receiver Operating Characteristic (ROC) curves were drawn by plotting sensitivity against 1-specificity. Overall accuracy of the marker in detecting IBD relapse was represented by area under the curve (AUC) with 95% confidence interval. Best cutoff point is defined as the maximum sum of sensitivity and specificity. A P value of 0.05 was considered statistically significant. $\chi2$ test with Yates continuity correction or Fisher's exact test was performed to compare measurement data. Odds ratio(OR) and 95% confidence intervals(CI) were calculated. All calculated P-values were two-sided.

RESULTS

Distribution of fecal S100A12 in 3 groups

The distribution of fecal S100A12 in 3 groups is shown in Figure 1. There are significant increases ($p < 0.01$) in both Ulcerative colitis and Crohn's Disease when compared to controls.

The diagnostic value for Ulcerative Colitis and Crohn's Disease.

Figure 2A shows the ROC curve of S100A12 in the diagnosis of UC. The sensitivity and specificity are 70.6% and 80.0% respectively at a cut-off of 0.95mg/kg. Compared to controls, the area under the curve is 0.78 (p=0.006) and the 95%CI is 0.622-0.947. Figure 2B shows the ROC curve of S100A12 in the diagnosis of CD. The sensitivity and specificity are 95.2% and 53.3% respectively, at a cut-off of 0.69mg/kg. Compared to controls, the area under the curve is 0.778 (p=0.005) and the 95%CI is 0.625-0.930).

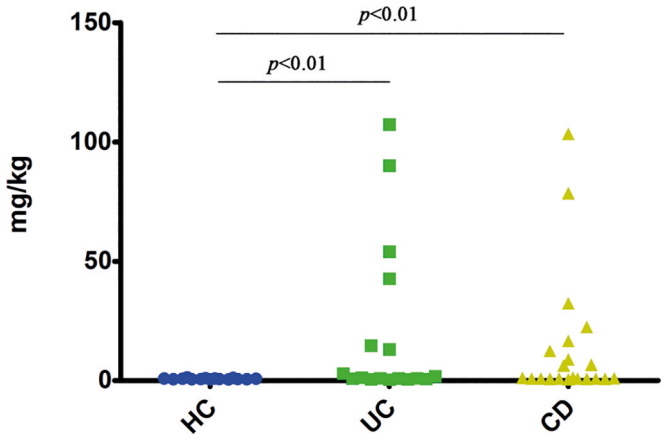

Figure 1. Distribution of fecal S100A12 in 3 groups

Sensitivity, specificity, Youden index, positive likelihood ratio(LR+) and negative likelihood ratio(LR-) of S100A12

As shown in Table 2, in Ulcerative Colitis, the Youden index(γ) for S100A12 is 0.506, which is higher than those for ESR and CRP. In Crohn's Disease, the Youden Index for S100A12 is 0.485, with no difference relative to ESR or CRP. The S100A12 positive and negative likelihood ratios are not relevant for either UC or CD.

The correlations of S100A12 and clinical profiles

As shown in Table 3, in Ulcerative Colitis, fecal S100A12 correlated with fecal occult blood (p=0.02, r=0.55). In Crohn's Disease, fecal S100A12 correlated with disease duration, plasma albumin and platelet count (p=0.01, r=-0.53; p<0.01, r=-0.65; p=0.04, r=0.45.respectively).

DISCUSSION

S100A12 is a member of S100 calcium binding protein family. Activated extracellularly,[16] it is a type of damage-associated molecular pattern protein. These endogenous molecules are released by activated or damaged cells under conditions of cell stress. S100A12 has also been shown to be produced by neutrophils, and it is believed that its expression in leukocytes is specifically restricted to granulocytes and monocytes;[7] it interacts with the multi-ligand RAGE, as a receptor transducing proinflammatory signals in the endothelial cells and cells of the immune system.[17]

Foell et al. provided the first demonstration of the expression of S100A12 in adults with Invlammatory Bowel Disease. This study delineated the tissue expression of S100A12 in the gut of individuals with CD and UC and measured circulating S100A12 in the serum of these patients. S100A12 was present in high levels in the inflamed mucosa and elevated serum levels were seen in the adults with CD and UC. Levels of S100A12 were also found to correlate with clinical indicators of disease activity.[18] S100A12 level was also significantly increased in Behçet's and Kawasaki disease (two other autoimmune diseases), and was correlated with disease activity.[17]

The focus of work to date has been upon defining S100A12 as a fecal marker of active gut inflammation, thereby establishing it as a tool in the assessment of children or adults presenting with undifferentiated symptoms. It is remarkably resistant to degradation by fecal bacteria, and stability of fecal specimens is acceptable for at least 7 days at room temperature.[10]

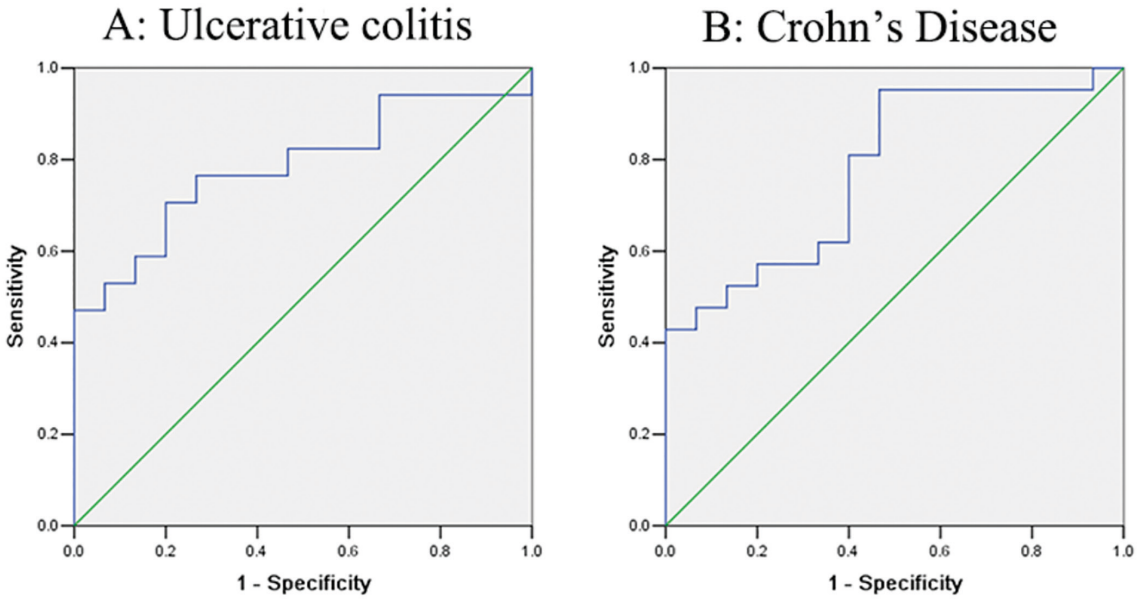

Figure 2. The ROC curves of S100A12 in the diagnosis of ulcerative colitis (A) and Crohn's Disease (B)

Table 2. The diagnostic value of S100A12 when compare with CRP and ESR

	Sensitivity	Specificity	FPR	FNR	γ	LR+	LR-
UC vs. HC							
CRP	27.8%	100.00%	0.0%	72.2%	0.278	-	0.722
ESR	44.4%	100.00%	0.0%	55.6%	0.444	-	0.556
S100A12	70.6%	80.0%	20.0%	29.4%	0.506	3.530	0.368
CD vs. HC							
CRP	47.6%	100.0%	0.0%	52.4%	0.476	-	0.524
ESR	57.1%	100.0%	0.0%	42.9%	0.571	-	0.429
S100A12	95.2%	53.3%	46.7%	4.8%	0.485	2.039	0.090

CD, Crohn's disease; UC, Ulcerative colitis; HC, Healthy control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FPR, False positive rate; FNR, False negative rate; γ, Youden index; LR+, positive likelihood ratio; LR-, negative likelihood ratio.

Table 3. The correlation of S100A12 and clinical characters in IBD patients

	S100A12(UC) p(r)	S100A12(CD) p(r)
Sex	0.17(0.34)	0.33 (0.22)
Age	0.90(0.40)	0.35 (-0.22)
Disease duration	0.14(0.36)	0.01 (-0.53)*
Disease activity	0.14(0.36)	
HBI(CD)	-	0.19 (0.30)
Location	0.89(0.04)	0.21(0.29)
Behavior(CD)	-	0.21(0.29)
CRP	0.06(0.46)	0.10(0.37)
ESR	0.36(0.23)	0.52(0.15)
ALB	0.43(-0.20)	<0.01(-0.65)*
WBC	0.39(0.22)	0.16(0.32)
HGB	0.29(-0.26)	0.81(-0.06)
RBC	0.30(-0.26)	0.36(0.21)
HCT	0.27(-0.28)	0.92(0.02)
PLT	0.95(0.02)	0.04(0.45)*
Occult blood	0.02(0.55)*	0.19(0.30)

CD, Crohn's disease; UC, Ulcerative colitis; HC, Healthy control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw Index; ALB, albumin; WBC, white blood cells; HGB, hemoglobin; RBC, red blood cells; HCT, hematocrit; PLT, platelet.

Van de Logt et al[19] figured out that S100A12 was a potentially novel biomarker for IBD, provided it could meet some characteristics, such as high sensitivity, high specificity, good compliance, low costs, ease of collection and detection.

de Jong et al[10] reported that fecal S100A12 had a sensitivity of 96% and a specificity of 92% (at a cutoff of 10 mg/kg) when distinguishing between healthy controls and the IBD group (mainly Crohn's Disease). These German investigators demonstrated that fecal S100A12 measurements could differentiate between 59 adults with IBD and 24 adults with Irritable Bowel Syndrome. S100A12 measurement provided a sensitivity of 86% and a specificity of 96% in this study. As happens in the pediatric experience, S100A12 performed better than calprotectin in this cohort. Fecal S100A12 levels also distinguished between active IBD and healthy controls, with a sensitivity of 81% for CD, and 91% for UC, and a specificity of 100% for both.[7] de Jong et al[10] utilized an in-house immunoassay to quantify fecal S100A12 levels in children with newly diagnosed IBD and in a small group of healthy control children. Elevated levels of fecal S100A12 were demonstrated in the children with IBD. Fecal S100A12 cut-off value of 10 mg/kg provided a sensitivity of 96% and specificity of 92% in distinguishing between children with IBD and normal healthy controls. In this cohort of patients, fecal S100A12 correlated with serum inflammatory markers and pediatric CD activity index scores. Kaiser et al.[7] investigated the utility of fecal S100A12 compared to fecal calprotectin as a marker for intestinal inflammation. Children diagnosed with IBD (n = 31) had elevated fecal S100A12 (median 55.2 mg/kg) and fecal calprotectin (median 1265 mg/kg) levels when compared to 30 children without IBD (median S100A12 1.1 mg/kg; median calprotectin 30.5 mg/kg). The sensitivity and specificity of fecal S100A12 for the diagnosis of IBD (cutoff 10 mg/kg) were both 97%, whereas fecal calprotectin had a sensitivity of 100% and a specificity of only 67%. Manolakis et al.[11] investigated S100A12 serum levels in 64 patients with ulcerative colitis (UC), 64 with Crohn's disease (CD) and 73 with Irritable Bowel Syndrome. UC and CD patients had significantly higher serum S100A12 levels compared to Irritable Bowel Syndrome patients (P = 0.001 for both comparisons). Moreover, a cut-off for serum S100A12 levels of 54.4 ng/mL could predict both UC and CD with a 66.7% sensitivity and a 64.4% specificity. When used to distinguish IBD from Irritable Bowel Syndrome in adult patients, serum S100A12 levels exhibited a moderate performance. On the other hand, serum S100A12 may serve as an inflammatory marker in IBD, since it is well correlated with CRP and serum amyloid A.[11]

Above all, fecal S100A12 provides very high sensitivity and improved specificity compared to fecal calprotectin for the detection of gut inflammation in

children. Although colonoscopy and upper gastrointestinal endoscopy remain essential in establishing a diagnosis of IBD and in defining the type of IBD, fecal S100A12 appears to be an ideal noninvasive screening test to select the children in whom these invasive and laborious investigations are required.[7]

In our study, in the diagnosis of UC, the sensitivity and specificity are 70.6% and 80.0% separately (cut-off: 0.95mg/kg). In the diagnosis of CD when compared to healthy controls, the area under the curve was 0.778 (p=0.005) and the 95%CI was 0.625-0.930. The sensitivity and specificity are 95.2% and 53.3% (cut-off: 0.69mg/kg). The cut-off is lower than previously reported, which may be due to differences between Westerners and Asians; the disease activity in patients recruited for this study is mild to moderate, the inflammation of the intestine is not severe. It is also possible that the lower sensitivity and specificity in our study may be related tothe small number of included patients.

In our Ulcerative colitis patients, the Youden index for S100A12 was 50.6%, which is higher than those for ESR and CRP. In our Crohn's Disease patients, no differences were found for the Youden Index between S100A12, ESR, and CRP. The S100A12 values of LR+ and the LR- were not very good for UC or CD.

In the study of Sidler et al,[7] fecal S100A12 did not correlate with ESR, CRP, platelet count, or serum albumin in children with CD. However, Dabritz et al[20] showed that fecal and serum S100A12 correlated positively with CRP, ESR, white blood cell count, and platelets; fecal but not serum S100A12 levels correlated negatively with hemoglobin. S100A12 performed not only as a promising marker for disease activity but also as a good marker for disease location and behavior in CD as well as for the extent of UC.[20] Indeed, in a previous study, we were able to show that in active CD, the release of S100A12 is strongly dependent on localization, with little release from sites of active ileal inflammation compared with colonic inflammation.[21] Serum S100A12 levels correlated with disease behavior in CD and were highest in patients with penetrating disease followed by stricturing and nonstricturing/nonpenetrating disease. Interestingly, fecal S100A12 concentrations did not significantly correlate with disease behavior in CD.[20] This may reflect the fact that the penetrating disease may lead to a more pronounced systemic inflammatory process such as the presence of abscesses and fistulae.

Accordingly, Sidler et al[2] found no correlation between fecal S100A12 and disease activity, measured by the PCDAI, whereas Kaiser et al[7] showed only a correlation between fecal S100A12 and PCDAI in children with a continuous, but not with a noncontinuous distribution of intestinal inflammation in CD.[7] A strong correlation between fecal S100A12 levels and endoscopically and histologically confirmed intestinal inflammation in both CD and UC. Our head-to-head comparison of fecal S100A12 and fecal calprotectin showed that fecal S100A12 was superior in distinguishing active IBD from Irritable Bowel Syndrome.

In our study, Fecal S100A12 correlated with fecal occult blood (p=0.02, r=0.55) in UC. However, in CD, fecal S100A12 correlated with disease duration, albumin and platelet (p=0.01, r=-0.53;p<0.01, r=-0.65; p=0.04, r=0.45, respectively). Fecal S100A12 is not correlated with disease location, behavior, activity and endoscopically or histologically diagnosed inflammation.

Turner et al[22] enrolled children presenting with acute severe UC in multiple pediatric units in North America; some were newly diagnosed and some had a longstanding diagnosis of UC. Serial stool samples were collected from these children and utilized to measure four fecal markers, including S100A12. The levels of these markers were evaluated for their values in predicting the response to initial medical therapy and other key outcomes. Fecal S100A12 levels were greatly elevated in these children. However, these levels did not correlate well with subsequent clinical response. Dabritz et al[20] included 147 adults and 34 children showed fecal S100A12 levels increased significantly in the relapse group. Time course analysis of fecal S100A12 before and after relapse showed a clear increase of S100A12 concentrations up to 6 months before clinical relapse. At 0.43mg/kg, the sensitivity and specificity of S100A12 for predicting relapse already 8 to 12 weeks earlier were 70% and 83%, respectively. Some data have also demonstrated that fecal levels of S100A12 fall following anti-inflammatory therapy, indicating that this marker could become a further easy way to assess response to therapy. Additional potential roles of S100A12 may be as indication of mucosal healing and in the prediction of potential relapse.[19] Furthermore, intense scientific research on S100 proteins has revealed a wide range of possibilities for novel S100- oriented therapeutic interventions. In the study of Hofmann et al. inhibition of the interaction of S100A12 with RAGE reduced inflammation in a murine model of colitis.[23]

The results of our research exhibit some limittations, such as small number patients we collected, and we expect to expand this information in future.

CONCLUSION

Fecal S100A12 appears to be a promising candidate as a biomarker for the early assessment of non-specific gut symptoms, permitting a more focused future investigation in those individuals most likely to have organic disease and an avoidance of invasive tests in those with a low likelihood of such pathology.

■ ACKNOWLEDGEMENTS

We thank the numerous individuals in IBD group who volunteered to participate in this study. The study was supported by Jiangxi provincial department of science and technology [grant number 2015BAB215007].

■ CONFLICT OF INTERESTS

Authors declare no conflict of interest regarding this project.

■ AUTHOR PARTIPATION

All three authors participated is all the stages of this project

AVALIAÇÃO DA PROTEÍNA FECAL S100Q12 EM PACIENTES COM DOENÇA INFLAMATÓRIA INTESTINAL

JUSTIFICATIVA E OBJETIVO: O diagnóstico e avaliação da doença inflamatória intestinal é bastante complexo. Um marcador ideal, não invasivo para esta doença é urgentemente necessário. O S100A12 fecal é um membro da família de proteínas S100 e é secretado por neutrófilos ativados. Pretendemos avaliá-lo como biomarcador para pacientes com doença inflamatória intestinal na China.

MÉTODOS: a proteína fecal S100A12 foi medida em 18 pacientes com Moléstia de Crohn, 21 pacientes com Colite Ulcerativa e 17 voluntários saudáveis (controles). O valor diagnóstico foi avaliado através da análise da característica de operação do receptor (ROC) em comparação com a proteína C reativa e com a taxa sedimentação eritrocitária. A correlação entre S100A12 fecal e características clínicas também foi avaliada.

RESULTADOS: Observamos aumentos significativos ($p < 0.01$) no valor diagnóstico de S100A12 tanto na Colite Ulcerativa quanto na Doença de Crohn quando comparados aos controles saudáveis. Na colite ulcerativa, a proteína S100A12 fecal correlacionou com sangue oculto fecal ($p = 0,02$, $r = 0,55$); Na doença de Crohn, correlacionou com a duração da doença, albumina e níveis de plaquetas ($p = 0,01$, $r = -0,53$; $p < 0,01$, $r = -0,65$; $p = 0,04$, $r = 0,45$, respectivamente). Não houve correlação entre S100A12 fecal e outras condições clínicas.

CONCLUSÃO: O S100A12 fecal é valioso para distinguir pacientes com doença inflamatória intestinal versus controles saudáveis. No entanto, a sensibilidade e especificidade é limitada quando comparada com a descrita nos países ocidentais. A correlação entre S100A12 e características clínicas é limitada. Mais pesquisas são necessárias para explorar melhor essa interação em pacientes chineses.

PALAVRAS-CHAVE: Doença de Crohn, colite ulcerativa, S100A12

■ REFERENCES

1. Judd TA, Day AS, Lemberg DA, Turner D, Leach ST. Update of fecal markers of inflammation in inflammatory bowel disease. J Gastroenterol Hepatol. 2011;26(10):1493-9. DOI: 10.1111/j.1440-1746.2011.06846.x.
2. Sidler MA, Leach ST, Day AS. Fecal S100A12 and fecal calprotectin as noninvasive markers for inflammatory bowel disease in children. Inflamm Bowel Dis. 2008;14(3):359-66. DOI: 10.1002/ibd.20336.
3. Pardi DS, Sandborn WJ. Predicting relapse in patients with inflammatory bowel disease: what is the role of biomarkers? Gut. 2005;54(3):321-2. DOI: 10.1136/gut.2004.048850.
4. Fischbach W, Becker W, Mossner J, Koch W, Reiners C. Faecal alpha-1-antitrypsin and excretion of 111indium granulocytes in assessment of disease activity in chronic inflammatory bowel diseases. Gut. 1987;28(4):386-93. DOI: 10.1136/gut.28.4.386.
5. Santamaria-Kisiel L, Rintala-Dempsey AC, Shaw GS. Calcium-dependent and -independent interactions of the S100 protein family. Biochem J. 2006;396(2):201-14. DOI: 10.1042/BJ20060195.
6. Carlson M, Raab Y, Seveus L, Xu S, Hallgren R, Venge P. Human neutrophil lipocalin is a unique marker of neutrophil inflammation in ulcerative colitis and proctitis. Gut. 2002;50(4):501-6. DOI: 10.1136/gut.50.4.501.
7. Kaiser T, Langhorst J, Wittkowski H, et al. Faecal S100A12 as a non-invasive marker distinguishing inflammatory bowel disease from irritable bowel syndrome. Gut. 2007;56(12):1706-13. DOI: 10.1136/gut.2006.113431.
8. Foell D, Roth J. Proinflammatory S100 proteins in arthritis and autoimmune disease. Arthritis Rheum. 2004;50(12):3762-71. DOI: 10.1002/art.20631.
9. Beattie RM, Nicholls SW, Domizio P, Williams CB, Walker-Smith JA. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. J Pediatr Gastroenterol Nutr. 1996;22(4):373-9. DOI: 10.1097/00005176-199605000-00006.
10. de Jong NS, Leach ST, Day AS. Fecal S100A12: a novel noninvasive marker in children with Crohn's disease. Inflamm Bowel Dis. 2006;12(7):566-72. DOI: 10.1097/01.ibd.0000227626.72271.91.
11. Manolakis AC, Kapsoritakis AN, Georgoulias P, Tzavara C, Valotassiou V, Kapsoritaki A, et al. Moderate performance of serum S100A12, in distinguishing inflammatory bowel disease from irritable bowel syndrome. BMC Gastroenterol. 2010;10:118. doi: 10.1186/1471-230X-10-118. 10.1186/1471-230X-10-118.
12. Chinese Medical Association. Consensus on diagnosis and treament of inflammatory bowel disease (2012.Guangzhou). Chin J Intern Med, 2012, 51: 818-31.
13. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006;55(6):749-53. DOI: 10.1136/gut.2005.082909.
14. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041-8.
15. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980;1(8167):514. DOI: 10.1016/S0140-6736(80)92767-1.
16. Donato R. Intracellular and extracellular roles of S100 proteins. Microsc Res Tech. 2003;60(6):540-51. DOI: 10.1002/jemt.10296.
17. Han EC, Cho SB, Ahn KJ, Oh SH, Kim J, Kim DS, et al. Expression of Pro-inflammatory Protein S100A12 (EN-RAGE) in Behcet's Disease and Its Association with Disease Activity: A Pilot Study. Ann Dermatol. 2011;23(3):313-20. DOI: 10.5021/ad.2011.23.3.313.

18. Foell D, Kucharzik T, Kraft M, Vogl T, Sorg C, Domschke W, et al. Neutrophil derived human S100A12 (EN-RAGE) is strongly expressed during chronic active inflammatory bowel disease. Gut. 2003;52(6):847-53. DOI: 10.1136/gut.52.6.847.
19. van de Logt F, Day AS. S100A12: a noninvasive marker of inflammation in inflammatory bowel disease. J Dig Dis. 2013;14(2):62-7. DOI: 10.1111/1751-2980.12012.
20. Dabritz J, Langhorst J, Lügering A, Heidemann J, Mohr M, Wittkowski H, et al. Improving relapse prediction in inflammatory bowel disease by neutrophil-derived S100A12. Inflamm Bowel Dis. 2013;19(6):1130-8. DOI: 10.1097/MIB.0b013e318280b1cd.
21. Foell D, Wittkowski H, Ren Z, Turton J, Pang G, Daebritz J, et al. Phagocyte-specific S100 proteins are released from affected mucosa and promote immune responses during inflammatory bowel disease. J Pathol. 2008;216(2):183-92. DOI: 10.1002/path.2394.
22. Turner D, Leach ST, Mack D, Uusoue K, McLernon R, Hyams J, et al. Faecal calprotectin, lactoferrin, M2-pyruvate kinase and S100A12 in severe ulcerative colitis: a prospective multicentre comparison of predicting outcomes and monitoring response. Gut. 2010;59(9):1207-12. DOI: 10.1136/gut.2010.211755.
23. Hofmann MA, Drury S, Fu C, Qu W, Taguchi A, Lu Y, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell. 1999;97(7):889-901. DOI: 10.1016/S0092-8674(00)80801-6.