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Fecal Calprotectin in Children Can Differentiate Between Different Gastrointestinal Diseases

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Abstract

BACKGROUND: Calprotectin is a 36 kDa member of the S100 family of proteins. It is derived predominantly from neutrophils and has direct antimicrobial effects and a role within the innate immune response. Calprotectin is found in various body fluids in proportion to the degree of any existing inflammation and its concentration in feces is about 6 times that of plasma. Measurement of fecal calprotectin is a useful surrogate marker of gastrointestinal inflammation. It has a high negative predictive value in ruling out inflammatory bowel disease (IBD) in undiagnosed, symptomatic patients and high sensitivity for diagnosing the disease making it useful as a tool for prioritizing endoscopy. In patients with known IBD, fecal calprotectin can be a useful tool to assist management, providing evidence of relapse or mucosal healing to enable therapy to be intensified or reduced.

AIM: The present study aimed to discuss the use of calprotectin for the diagnosis of IBD and some of the other ways in which the test may be useful in the management of gastroenterology patients.

METHODS: A cross-sectional study on children with significant gastrointestinal diseases attending to pediatric department at Menoufia University, with a total number of 180 patients in addition to 30 normal children as control according to sample size calculation. The children are allocated into seven groups according to the final diagnosis to Group (1): 30 patients with IBD, Group (2): 20 patients with eosinophilic colitis, Group (3): 30 patients with *Helicobacter pylori* infection, Group (4): 40 patients with functional constipation, Group (5): 30 patients with cow milk allergy, Group (6): 30 patients with Celiac disease, and Group (7): 30 normal children as control.

RESULTS: In cow milk protein allergic patients with marked GI presentation in the form of bloody diarrhea and/or abdominal distension, the mean fecal calprotectin (FC) was 1260 ± 625 μg/g. FC has decreased after 2−4 weeks of elimination of cow milk products to 420 ± 190 μg/g. Patient with inflammatory bowel disease had mean FC 4640 ± 850 μg/g, decreased after medical treatment and resolution of symptoms to 1360 ± 520 μg/g. In *H. pylori* infection detected by upper GI endoscopy and histopathology with positive stool antigen the mean FC was 78.9 ± 25.1 μg/g. Celiac disease patients had mean fecal calprotectin 456 ± 123 μg/g. Eosinophilic esophagitis had mean fecal calprotectin 4.2 ± 2.9 μg/g. Functional constipation patients had mean fecal calprotectin 23.6 ± 21.8 μg/g. Normal control children had mean fecal calprotectin 4.1 ± 6.9 μg/g.

CONCLUSION: According to the results of previous studies, fecal calprotectin can be considered as a biomarker to differentiate between IBS and organic gastrointestinal disorders. However, due to the limitations of pre-analysis, a low fecal calprotectin concentration may not necessarily be considered as the reason for the absence of IBD.

Introduction

Calprotectin is a calcium and zinc-binding protein. It constitutes> 60% of cytosolic proteins in the neutrophils also found in smaller parts in the cytosol fluid of monocytes and macrophages. It has antimicrobial effects against bacteria and fungi. Calprotectin was first isolated in the 1970s. Reports of calprotectin started in the 1990s and early 2000s, which focused mainly on its role to monitor inflammatory bowel disease (IBD). It can be measured in different body fluids, such as urine, plasma, saliva, feces, synovial fluid, and liquor. It contains one light chain that binds calcium and zinc and two heavy chains [1].

Fecal calprotectin measurement is mostly used to screen for the possibility of inflammatory bowel disease, IBD. There is no consensus of the most accurate cutoff for raised values and cut-offs of > 50 mg/kg, ≥ 100 mg/kg, and ≥ 250 mg/kg are most frequently used [2].

Gastrointestinal inflammation is associated with the release of calprotectin in a large amount due to increased permeability of the gastrointestinal mucosa. Some studies suggest calprotectin can differentiate between functional and organic gastrointestinal disorders [3].

Meta-analyses of multiple studies concluded the accuracy of Calprotectin in patients with active endoscopic inflammatory bowel diseases with high sensitivity (70%−100%) and specificity (44%−100%) [4].

Fecal calprotectin testing can support diagnoses of relapsing inflammatory bowel disease in children. It is elevated in inflammation of the gastrointestinal tract as cystic fibrosis and is the only biomarker elevated in cystic fibrosis compared to other

inflammatory stool markers, as it predicts colorectal and intestinal inflammation in children [5].

Fecal calprotectin is also elevated in adults with colorectal cancer or adenomatous polyp, in children with juvenile polyps, active celiac disease, eosinophilic and lymphocytic colitis, multiple food allergies, and cow milk allergy [6].

Aim of the study

The present study aimed to discuss the use of calprotectin for the diagnosis of IBD and some of the other ways in which the test may be useful in the management of gastroenterology patients.

Methods

Participants

A cross-sectional study on children with significant gastrointestinal diseases attending to pediatric department at Menoufia University, with a total number of 180 patients in addition to 30 normal children as control according to sample size calculation.

The children are allocated into seven groups according to the final diagnosis to Group (1): 30 patients with IBD, Group (2): 20 patients with eosinophilic colitis, Group (3): 30 patients with *H. pylori* infection, Group (4): 40 patients with functional constipation, Group (5): 30 patients with cow milk allergy, Group (6): 30 patients with Celiac disease, and Group (7): 30 normal children as control.

Children aged −4 years and diagnosed with gastrointestinal diseases are included in this study.

Children were excluded if their parents reported any signs of cold, flu, stomach discomfort, or similar problems in the last 2 weeks. In addition, children with a history of preterm birth, low or large birth weight, large or small weight for their age (<3rd percentile or >97th percentile), and positive results for stool virus or bacterial polymerase chain reaction were excluded from the study.

All patients were subjected to thorough medical history and demographic data (Age, Sex, Resident, etc.), then thorough clinical history with a thorough clinical examination which was done with special interest on weight, height, and nutritional status, and proper abdominal examination. Full blood count, liver function tests, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), Stool routine, culture and sensitivity, occult blood in stool, stool PH and reducing substances if needed, total Ig E, tissue transglutaminase IgA (TTG-IgA), endomysial antibodies (EMA), *H. pylori* stool Ag, upper GI, and lower GI endoscopies were done when needed. Fecal calprotectin is expressed as μg/g of feces. The stool samples were prepared and analyzed according to the manufacturer's instructions.

FC levels may vary with age. At present, an FC level below 50 μg/g is considered normal for children older than 4 years. To obtain the mean FC level of children under 4 years of age, we studied FC levels in healthy children at four kindergartens for 6 months. In this study, the cut/off the value of 50 μg/g of FC.

Fecal calprotectin measurement

The first method was described for the measurement of fecal calprotectin as an enzyme-linked immunosorbent assay (ELISA) which used a rabbit anticalprotectin antibody.

The stool samples were prepared and analyzed by a laboratory analyst according to the manufacturer's instructions (Calprest; Eurospital SpA, Trieste, Italy). A portion of each sample (40−120 mg) was measured and an extraction buffer containing citrate and urea was added in a weight per volume ratio of 1:50. The samples were mixed for 30 s by a vortex method and homogenized for 25 min. One milliliter of the homogenate was transferred to a tube and centrifuged for 20 min. Finally, the supernatant was collected and frozen at −20°C. In most cases, the time from sampling to preparation and freezing was estimated to be 1-3 d, except for a few samples that took 4-6 d before handling. The supernatants were thawed and analyzed later with Calprest, a quantitative calprotectin ELISA, for the determination of calprotectin in stools. The within assay coefficient of variation was 1.5%. Calprotectin was expressed as μg/g of feces.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution quantitative data were described using range (minimum and maximum), mean, standard deviation, median. The significance of the obtained results was judged at the 5% level.

The used tests were

1. Chi-square test
   For categorical variables, to compare between different groups
2. Mann–Whitney test
   For abnormally distributed quantitative variables, to compare between two studied groups
3. One-Way Analysis of Variance (ANOVA)
   The one-way analysis of variance (ANOVA) is used to determine whether there are any statistically

significant differences between the means of three or more independent (unrelated) groups.

4. Two-sample t-test

Two-sample t-test (also known as the independent samples t-test) is a method used to test whether the unknown population means of two groups are equal or not

Ethical consideration

The study will be approved by the research scientific ethical committee in the Institute of Postgraduate Childhood Studies.

Ethical consent

Written informed consent will be obtained from the patients' parents or legal guardians after an explanation of the nature and aim of the study and its benefits for their children and adolescents and to the whole community as well as the expected risks that the candidates are subjected to if they participate in the study.

Privacy and confidentiality of the subjects

The entire patients' recorded data will be highly confidential. Patients' blood samples will be discarded after performing the required investigations and will not be used for any other purposes.

Ethical points

The study followed the ethical standards of the national liver institute - Menoufia University - Egypt, committee, and international Review Board (IRB) of the National Liver Institute. The study followed the ethical standards of the National Liver Institute – Menoufia University – Egypt, committee (IRB00003413).

Sample size

The sample size was calculated using the following equation:

$$n = \frac{Za^2 \times p \times q}{d^2}$$

N = Minimally accepted sample size, Z = level of confidence according to the standard normal distribution (for a level of confidence of 95%, z = 1.96), P = Estimated proportion of the population that presents the characteristic (when unknown we use p = 0.5), q = 1-P (in this study = 50%), d = Tolerated margin of error in this study = 0.08.

$$N = \frac{(1.96)^2 x 0.5 x 0.5}{(0.08)^2} = 150.06$$

(n) = 150

(n) = 150+30 (considering 20% dropout of study participants)

Sample size (n) = 180

Results

In cow milk protein allergic patients with marked GI presentation in the form of bloody diarrhea and/or abdominal distension, the mean fecal calprotectin (FC) was 1260 ± 625 μg/g. (Table 1) FC has decreased after 2−4 weeks of elimination of cow milk products to 420 ± 190 μg/g.

Table 1: Fecal calprotectin of the studied patients

Diagnosis	Fecal calprotectin (μg/g) (n = 180), mean ± SD
IBD	4640 ± 850
Cow milk allergy (GI presentation)	1260 ± 625
Helicobacter pylori infection	78.9 ± 25.1
Eosinophilic esophagitis	4.2 ± 2.9
Functional constipation	23.6 ± 21.8
Celiac disease	456 ± 123

IBD: Inflammatory bowel disease, GI: Gastrointestinal.

Patient with inflammatory bowel disease had mean FC 4640 ± 850 μg/g (Table 1), decreased after medical treatment and resolution of symptoms to 1360 ± 520 μg/g.

In *H. pylori* infection detected by upper GI endoscopy and histopathology with positive stool antigen the mean FC was 78.9 ± 25.1 μg/g. Celiac disease patients had mean fecal calprotectin 456 ± 123 μg/g. Eosinophilic esophagitis had mean fecal calprotectin 4.2 ± 2.9 μg/g. Functional constipation patients had mean fecal calprotectin 23.6 ± 21.8 μg/g. Normal control children had mean fecal calprotectin 4.1 ± 6.9 μg/g (Table 1).

The previous table shows diagnosis, the most type of diagnosis is functional constipation with 22% then IBD, cow milk allergy (GI symptoms), *H. pylori* infection and Celiac disease with 16.6%, and finally eosinophilic esophagitis with 11.1% as shown in Table 2 and Figure 1.

Table 2: Number and percent of the diagnosis in studied patients

Diagnosis (total cases 180)	n (%)
IBD	30 (16.66)
Cow milk allergy (GI symptoms)	30 (16.66)
Helicobacter pylori infection	30 (16.66)
Eosinophilic esophagitis	20 (11.11)
Functional constipation	40 (22.22)
Celiac disease	30 (16.66)

IBD: Inflammatory bowel disease, GI: Gastrointestinal.

The previous table shows fecal calprotectin, the most type of diagnosis with high fecal calprotectin is IBD with 4640 then cow milk allergy (GI symptoms) with 1260, Celiac disease with 456, *H. pylori* infection

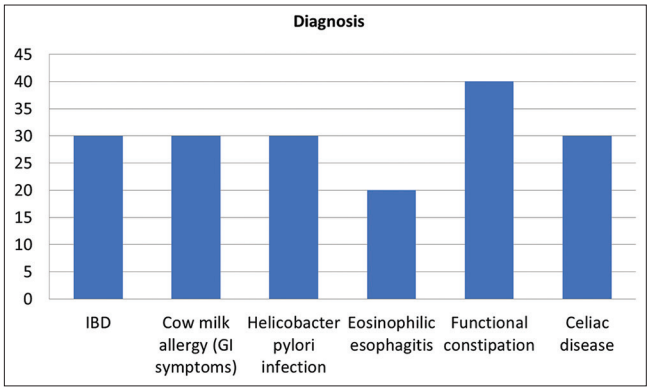

Figure 1: Number and percent of the studied patients

with 78.9, functional constipation with 23.6, and finally eosinophilic esophagitis with 4.2 as shown in Table 1.

The previous table show fecal calprotectin, the most statistical significant type of diagnosis with high fecal calprotectin is IBD with p = 0.0001 then cow milk allergy (GI symptoms) with p = 0.001, *H. pylori* infection with p = 0.01, eosinophilic esophagitis, and functional constipation with p > 0.5, and finally Celiac disease with p = 0.01 as shown in Table 3.

Table 3: Calprotectin level in diseased groups and normal control group

Diseased groups	Calprotectin level in diseased groups, mean ± SD	Calprotectin level in control group (n = 30), mean ± SD	p
IBD (n = 30)	4640 ± 850 μg/g	4.1 ± 6.9 μg/g	0.0001
Cow milk allergy (GI presentation) (n = 30)	1260 ± 625 μg/g		0.001
Helicobacter pylori infection (n = 30)	78.9 ± 25.1 μg/g		0.01
Eosinophilic esophagitis (n = 20)	4.2 ± 2.9μg/g		> 0.5
Functional constipation (n = 40)	23.6 ± 21.8 μg/g		> 0.5
Celiac disease (n = 30)	456 ± 123 μg/g		< 0.1

The statistical test used: Two-sample t-test. p ≤ 0.05 considered statistically significant (95% CI). CI: Confidence interval, SD: Standard deviation, IBD: Inflammatory bowel disease, GI: Gastrointestinal.

The previous table show sensitivity and specificity in the diagnosis types according to calprotectin level, the most sensitivity and specificity of diagnosis with high fecal calprotectin is IBD with 98%, 91% respectively then Celiac disease with 92%, 60%, functional constipation with 89%, 81%, cow milk allergy (GI symptoms) with 84%, 66%, eosinophilic esophagitis with 83%, 83%, and finally *H. pylori* infection with 80%, 82%, as shown in Table 4.

Table 4: Sensitivity and specificity in the diagnosis types according to calprotectin level

Diagnosis	Sensitivity (%)	Specificity (%)	AUC
IBD	98	91	0.991
Cow milk allergy (GI presentation)	84	66	0.872
Helicobacter pylori infection	80	82	0.949
Eosinophilic esophagitis	83	83	0.931
Functional constipation	89	81	0.944
Celiac disease	92	60	0.931

IBD: Inflammatory bowel disease, GI: Gastrointestinal

Discussion

There are different laboratory markers used to assess systemic inflammation, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). ESR and CRP cannot localize themselves in the gut. Calprotectin is the protein content of the cytosol in neutrophils. Intestinal inflammation leads to polymorphonuclear neutrophils migration to the intestinal mucosa. Inflammation causes disturbance of the mucosal architecture causing leakage of neutrophils; hence, calprotectin into the lumen and its subsequent excretion in feces.

In addition to detection of calprotectin in stool, calprotectin has been detected in different body fluids. Reference ranges in serum/plasma 0.12−0.66 mg/L, CSF calprotectin concentrations were 0.3 to 0.35 mg/L, Saliva: 22.0 mg/L. Calprotectin concentrations in urine 0.024 mg/L. In Meconium concentration of calprotectin 78.5−145μg/g. Fecal calprotectin (FC) ≤ 50.0 mcg/g is normal.

Increased FC can be related to inflammation, but not disease-specific, so in this study, we investigated the level of FC in different pediatric GI diseases.

It was well known that FC is a useful biomarker to accurately assess inflammation. In this study, mean FC in children was 17 patients with Crohn's disease and 13 patients with ulcerative colitis with 4640 ± 850 μg/g (Table 3).

Studies showed FC values >600 μg/g are strongly associated with IBD, although no consistent CP cutoff is established that would allow diagnosing IBD with high accuracy [7], [8].

Our study showed mean FC level in patients with GI presentations of cow milk allergy including abdominal distension and bloody diarrhea was 1260 ± 625 μg/g (Table 3), it was statistically significant when compared to the normal control group p = 0.001 (Table 3).

Other studies Lee *et al*. and Komraus *et al*. found the mean FC value before the CMP elimination diet was 886 ± 278 μg/g in the non-IgE-mediated group, the elevated level of FC in our results compared to their results may be explained because our cases were selected with more severe GI presentations [9], [10].

Patients positive for *H. pylori* by histopathology, rapid test during endoscopy (CLO test), and positive stool Ag for *H. pylori* had mean FC 78.9 ± 25.1 μg/g (Table 3), nearly the same findings reported by Dunlop *et al*., and Dale who reported mean FC 74.8 ± 67 μg/g. Explained mild elevation of FC in *H. pylori*-infected patients because fecal calprotectin represents gastric neutrophilic inflammation [11], [12].

The current study showed children diagnosed with Celiac disease had a mean FC 456 ± 123 μg/g, there was a statistically significant difference between celiac and normal control children (p < 0.1) (Table 3), this completely was indifference with other studies who found no significant difference, this difference in results may be due to age difference in both studies [13].

While other studies came in harmony with our study Shitrit *et al*., in which it was reported increased fecal calprotectin concentration may be considered a non-invasive marker that can help to diagnose celiac disease [14].

Eosinophilic esophagitis (EoE) (Table 3) patients enrolled in the current study showed mean fecal calprotectin 4.2 ± 2.9μg/g, which did not show statistical significance with FC of normal control children, the other studies who found increased FC, this because they studied eosinophilic gastrointestinal diseases as enteritis and colitis, whereas our study enrolled only eosinophilic esophagitis (EoE) [15], [16], [17].

Functional constipation is a common problem in children, this group of children enrolled in our study had a mean FC 23.6 ± 21.8 μg/g, (Table 3) it was statistically insignificant with FC level of normal children, other studies reported nearly the same with mean fecal calprotectin in children with functional constipation 0.5 to 100 μg/g [18], [19], [20], [21], [22].

Conclusion

According to the results of the previous studies, fecal calprotectin can be considered as a biomarker to differentiate between IBS and organic gastrointestinal disorders. However, due to the limitations of pre-analysis, a low fecal calprotectin concentration may not necessarily be considered as the reason for the absence of IBD. Nevertheless, it can be considered as a helpful test due to having relatively high sensitivity and specificity reported for this biomarker to differentiate between IBS and IBD. In the field of monitoring the IBD patients, some studies have reported a significant correlation between fecal calprotectin concentration and the endoscopic and histologic activities of IBD. Despite several promising results, recent studies have reported lower sensitivity and specificity rates for fecal calprotectin to predict endoscopic and histologic remission. Thus, despite its ease of measurement, fecal calprotectin cannot be considered as a reliable alternative for colonoscopy, to evaluate IBD endoscopic activity. However, under some conditions such as pregnancy and the COVID-19 pandemic, it may be helpful. Pre-analytical variables such as certain drugs or other diseases may have significant effects on the fecal calprotectin test results, and this issue should be considered more seriously in future studies. In recent years, some studies have reported that fecal calprotectin can be used to select treatment strategies. Altogether, given these promising results, which are particularly important regarding acute severe ulcerative colitis, future studies should focus more seriously on evaluating the predictive value of fecal calprotectin in this regard. In addition, investigating the efficacy of fecal calprotectin on some predicting events such as surgery, hospitalization, and disease-related death can be very helpful.

References

1. Mumolo MG, Bertani L, Ceccarelli L, Laino G, Di Fluri G, Albano E, *et al*. From bench to bedside: Fecal calprotectin in inflammatory bowel diseases clinical setting. World J Gastroenterol. 2018;24(33):3681. https://doi.org/10.3748/wjg.v24.i33.3681
   PMid:30197475
2. Yoo IH, Cho JM, Joo JY, Yang HR. Fecal calprotectin as a useful non-invasive screening marker for eosinophilic gastrointestinal disorder in Korean children. J Korean Med Sci. 2020;35(17):e120. https://doi.org/10.3346/jkms.2020.35.e120
   PMid:32356420
3. Balamtekın N, Baysoy G, Uslu N, Orhan D, Akçören Z, Özen H, *et al*. Fecal calprotectin concentration is increased in children with celiac disease: Relation with histopathological findings. Turk J Gastroenterol. 2012;23(5):503-8. https://doi.org/10.4318/tjg.2012.0366
   PMid:23161294
4. Capone P, Rispo A, Imperatore N, Caporaso N, Tortora R. Fecal calprotectin in coeliac disease. World J Gastroenterol. 2014;20(2):611. https://doi.org/10.3748/wjg.v20.i2.611
   PMid:24574734
5. Fahim SM, Das S, Gazi MA, Alam MA, Hasan MM, Hossain MS, *et al*. *Helicobacter pylori* infection is associated with fecal biomarkers of environmental enteric dysfunction but not with the nutritional status of children living in Bangladesh. PLoS Negl Trop Dis. 2020;14(4):e0008243. https://doi.org/10.1371/journal.pntd.0008243
   PMid:32324737
6. Kalach N, Bontems P, Raymond J. *Helicobacter pylori* infection in children. Helicobacter. 2017;22(1):e12414. https://doi.org/10.1111/hel.12414
   PMid:28891139
7. Demirbaş F, Çaltepe G, Abbasguliyev H, Kalaycı AG. Fecal calprotectin levels used as a noninvasive method for screening for chronic gastritis in pediatric patients. A descriptive study. Sao Paulo Med J. 2021;139(6):564-9. https://doi.org/10.1590/1516-3180.2020.0765.R1.0904221
   PMid:34406311
8. Beşer ÖF, Sancak S, Erkan T, Kutlu T, Çokuğraş H, Çokuğraş FÇ. Can fecal calprotectin level be used as a markers of inflammation in the diagnosis and follow-up of cow's milk protein allergy? Allergy Asthma Immunol Res. 2014;6(1):33-8. https://doi.org/10.4168/aair.2014.6.1.33
   PMid:24404391
9. Lee SH, Mainman H, Borthwick H, Dhar A. PTH-094 faecal calprotectin testing in primary and secondary care-are the current manufacturer's cut-off levels clinically useful? Gut. 2013;62(1):A249-9.
10. Komraus M, Wos H, Wiecek S, Kajor M, Grzybowska-Chlebowczyk U. Usefulness of faecal calprotectin measurement in children with various types of inflammatory bowel disease. Mediators Inflamm. 2012;2012:608249.
11. Dale I. Plasma levels of the calcium-binding Li leukocyte protein: Standardization of blood collection and evaluation of reference intervals in healthy controls.

Scand J Clin Lab Invest. 1990;50(8):837-41. https://doi.org/10.3109/00365519009104950

PMid:2128131

12. Dunlop O, Bruun JN, Myrvang B, Fagerhol MK. Calprotectin in cerebrospinal fluid of the HIV infected: A diagnostic marker of opportunistic central nervous system infection? Scand J Infect Dis. 1991;23(6):687-9. https://doi.org/10.3109/00365549109024294

PMid:1815329

13. Mao R, Xiao YI, Gao X, Chen BL, He Y, Yang L, *et al*. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: A meta-analysis of prospective studies. Inflamm Bowel Dis. 2012;18(10):1894-9. https://doi.org/10.1002/ibd.22861

PMid:22238138

14. Shitrit AB, Braverman D, Stankiewics H, Shitrit D, Peled N, Paz K. Fecal calprotectin as a predictor of abnormal colonic histology. Dis Colon Rectum. 2007;50(12):2188-93. https://doi.org/10.1007/s10350-007-9038-x

PMid:17963005

15. Fagerberg UL, Lööf L, Myrdal U, Hansson LO, Finkel Y. Colorectal inflammation is well predicted by fecal calprotectin in children with gastrointestinal symptoms. J Pediatr Gastroenterol Nutr. 2005;40(4):450-5. https://doi.org/10.1097/01.mpg.0000154657.08994.94

PMid:15795593

16. Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. Gastroenterology. 2011;140(6):1817-26. https://doi.org/10.1053/j.gastro.2010.11.058

PMid:21530748

17. Montalto M, Gallo A, Santoro L, D'Onofrio F, Landolfi R, Gasbarrini A. Role of fecal calprotectin in gastrointestinal disorders. Eur Rev Med Pharmacol Sci. 2013;17(12):1569-82.

PMid:23832721

18. Yui S, Nakatani Y, Mikami M. Calprotectin (S100A8/S100A9), an inflammatory protein complex from neutrophils with a broad apoptosis-inducing activity. Biol Pharm Bull. 2003;26(6):753-60. https://doi.org/10.1248/bpb.26.753

PMid:12808281

19. Fagerberg UL, Lööf L, Lindholm J, Hansson LO, Finkel Y. Fecal calprotectin: A quantitative marker of colonic inflammation in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2007;45(4):414-20. https://doi.org/10.1097/MPG.0b013e31810e75a9

PMid:18030206

20. Weil D, Heurgue-Berlot A, Monnet E, Chassagne S, Cervoni JP, Feron T, *et al*. Accuracy of calprotectin using the quantum blue reader for the diagnosis of spontaneous bacterial peritonitis in liver cirrhosis. Hepatol Res. 2019;49(1):72-81. https://doi.org/10.1111/hepr.13239

PMid:30084186

21. Costa F, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, *et al*. Role of faecal calprotectin as non-invasive marker of intestinal inflammation. Dig Liver Dis. 2003;35(9):642-7. https://doi.org/10.1016/s1590-8658(03)00381-5

PMid:14563186

22. Shalaby MN, Sakoury MM, Abdi E, Elgamal S, Elrkbwey S, Ramadan W, *et al*. The impact of resistance training on gene expression of IGF1 and athletes' physiological parameters. Open Access Macedon J Med Sci. 2021;9(A):934-40. https://doi.org/10.3889/oamjms.2021.7215