https://doi.org/10.22416/1382-4376-2022-32-6-53-59
UDC 616.34-002-072.85:612.361

Diagnostic Possibilities of Determining the Level of Faecal Calprotectin in Clinical Practice

Arkadiy A. Sheptulin*, Svetlana S. Kardasheva, Anastasya A. Kurbatova

Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

Aim: to analyze the publications devoted to the modern possibilities of determining the level of faecal calprotectin (FCP) in the diagnosis of various diseases.
Key points. In patients with already established diagnosis of inflammatory bowel diseases (IBD), dynamic monitoring of the level of FCP allows to assess the course and prognosis of the disease, as well as the effectiveness of treatment. The determining of FCP helps in the primary diagnosis of IBD (ulcerative colitis, Crohn's disease, microscopic colitis), contributing to their differentiation from functional bowel disorders, as well as in assessing the course of diverticular intestinal disease and celiac disease. The possibility of using FCP as a marker of colorectal cancer (CRC) and adenomatous polyps of the colon is also discussed.
Conclusion. Determining the level of FCP plays an important role in the diagnosis and assessment of the course of a number of gastroenterological diseases (primarily IBD). The significance of FCP as a marker of CRC requires further research.
Key words: faecal calprotectin, inflammatory bowel diseases, functional bowel disorders, colorectal cancer
Conflict of interest: the authors declare no conflict of interest.

For citation: Sheptulin A.A., Kardasheva S.S., Kurbatova A.A. Diagnostic Possibilities of Determining the Level of Faecal Calprotectin in Clinical Practice. Russian Journal of Gastroenterology, Hepatology, Coloproctology. 2022;32(6):53–59. https://doi.org/10.22416/1382-4376-2022-32-6-53-59

Диагностические возможности определения уровня фекального кальпротектина в клинической практике

А.А. Шептулин*, С.С. Кардашева, А.А. Курбатова
ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации, Москва, Российская Федерация

Цель публикации. Провести анализ публикаций, посвященных современным возможностям определения уровня фекального кальпротектина (ФКП) в диагностике различных заболеваний.
Основные положения. У больных с уже установленным диагнозом воспалительных заболеваний кишечника (ВЗК) динамический контроль уровня ФКП позволяет оценить течение и прогноз заболевания, а также эффективность лечения. Определение ФКП помогает при проведении первичной диагностики ВЗК (язвенного колита, болезни Крона, микроскопического колита), способствуя их разграничению с функциональными расстройствами кишечника, а также в оценке течения дивертикулярной болезни кишечника и целиакии. Обсуждается также вопрос о возможности использования ФКП как маркера колоректального рака (КРР) и аденоматозных полипов толстой кишки.
Заключение. Определение уровня ФКП играет важную роль в диагностике и оценке течения ряда гастроэнтерологических заболеваний (прежде всего ВЗК). Значение ФКП как маркера КРР требует дальнейших исследований.
Ключевые слова: фекальный кальпротектин, воспалительные заболевания кишечника, функциональные расстройства кишечника, колоректальный рак
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Шептулин А.А., Кардашева С.С., Курбатова А.А. Диагностические возможности определения уровня фекального кальпротектина в клинической практике. Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2022;32(6):53–59. https://doi.org/10.22416/1382-4376-2022-32-6-53-59

Faecal calprotectin (FCP) is a calcium- and zinc-binding protein with a molecular weight of 38 kDa, which is released from neutrophils and monocytes when they die. It accounts for about 60 % of the protein contained in these cells. The level of FCP correlates with fecal excretion of neutrophils labeled with the radioactive isotope indium-111. Its concentration, determined by enzyme immunoassay, remains stable and can be used as a biomarker in the diagnosis of various gastroenterological diseases and the assessment of their course [1, 2].

First of all, in patients with a confirmed diagnosis of **inflammatory bowel disease (IBD)**, the determining the level of FCP can be used to non-invasively assess of *the activity of the course of ulcerative colitis (UC) and Crohn's disease (CD)* [3, 4]. It has been shown that in patients with exacerbation of UC and CD, the level of FCP is significantly higher than in healthy, and correlates with the Mayo index, the index of endoscopic activity of UC and the level of C-reactive protein [5, 6]. In patients with UC in remission the concentration of FCP does not differ from that in the control group [5].

T. Rokkas et al. [1] conducted a meta-analysis of 25 studies involving 2,822 patients with IBD and 298 healthy persons in the control group. The sensitivity of determining the level of FCP in the diagnosis of the active stage of IBD was 85 %, specificity — 75 %, and in patients with UC these indicators were higher than in patients with CD (respectively, sensitivity 87.3 % and 82.4 %, specificity — 77.1 % and 72.1 %). The highest sensitivity (90.6 %) was noted at the level of FCP < 50 ug/g, the greatest specificity (78.2 %) — with its level > 100 ug/g. Recommendations of the Russian Gastroenterological Association (RGA) and the Association of Coloproctologists of Russia (ACR) for the diagnosis and treatment of adult patients with ulcerative colitis also consider it appropriate to determine the level of FCP for non-invasive assessment of the activity of the inflammatory process on the background of treatment [7].

Other data was obtained by S. Conroy et al. [8], who performed colonoscopies in 97 persons with a level of FCP > 50 ug/g and 49 persons with its values < 50 ug/g. In the first group IBD was detected in 7.2 % of cases, in the second — in 6.1 %. With a threshold value of FCP > 50 ug/g, its sensitivity in the diagnosis of IBD was 72.7 %, specificity — 64.9 %, positive predictive value — 5.41 %, negative — 98.9 %. The authors concluded that there was a low sensitivity and specificity and a low positive predictive value of this method.

It is of interest to evaluate the level of FCP as a criterion determining the feasibility of subsequent *performance* of *videocapsular endoscopy* in patients with suspected CD with lesions of the small intestine. A meta-analysis of 7 studies involving 463 patients with suspected CD with lesions of small intestine found a correlation between the concentration of FCP and inflammatory changes in the small intestine in patients with CD detected by videocapsular endoscopy. The highest negative predictive value (91.8 %) was observed in patients whose FCP level was < 50 ug/g [9].

In turn, T. Sipponen et al. [10] observed 84 patients with suspected CD with lesions of the small intestine who underwent videocapsular endoscopy and concluded that the determining the level of FCP has low sensitivity (59 %) for the diagnosis of CD with lesions of small intestine and moderate specificity (71 %), and therefore considered the use of this method in the screening of inflammatory changes in the small intestine in patients with CD inappropriate.

Works have also been published on the importance of determining the level of FCP *in assessing the prognosis of the course of IBD*. It was shown that the risk of relapse in patients with CD and UC increased, respectively, by 2 and 14 times, if the level of FCP in patients with clinical remission of these diseases exceeded 150 ug/g [11]. P. Molander et al. [12] studied the possibility of using the determining the level of FCP as a predictor of the development of exacerbations of IBD in 49 patients with UC and CD who achieved remission as a result of biological therapy with inhibitors of tumor-necrotizing factor-α. Within 12 months exacerbations of IBD occurred in 31 % of patients. These patients had a constantly elevated level of FCP, on average, for 3 months before the onset of exacerbation. Persistent normal level of FCP was predictor of clinical and endoscopic remission. According to C.G. Björkesten et al. [13], the mainteinance in patients with CD during 1 year after the start of biological therapy an elevated level of FCP indicated the ineffectiveness of treatment, the need to increase the dose of drugs or the addition of corticosteroids, and also an increased risk of surgical interventions.

A significant number of works are devoted to the importance of determining the level of FCP in *the differential diagnosis between IBD* (and in the broad sense — organic bowel diseases) and *functional bowel disorders*, such as irritable bowel syndrome (IBS), etc. [2, 14]. A. Banerjee et al. [15] came to the conclusion that the determining the level of FCP in patients with chronic diarrhea allows to make a differential diagnosis between IBD and IBS, to exclude the presence of IBD and, thus, to avoid colonoscopy. At a normal level of FCP endoscopic and histological signs of inflammatory changes in patients were absent.

A meta-analysis of 28 studies showed that the determining the level of FCP can be used in the differential diagnosis between IBD and IBS. In the vast majority of cases, the level of calprotectin < 50 ug/g excludes the presence of IBD, but there were also false positive results when in patients with an elevated level of FCP the diagnosis of IBD was not confirmed. In patients with FCP values in the range from 50 to 150 ug/g IBD was also most often not detected, but they needed observation and re-examination [16].

According to another meta-analysis and a systematic review of 18 studies that included patients with organic diseases (among them 10 with IBD) and 16 studies that included patients with functional bowel disorders, the sensitivity of determining the level of FCP when conducting the differential diagnosis between them was 81 %, specificity was also 81 %. The sensitivity of the determining the level of FCP in the differential diagnosis of IBD and functional bowel disorders was 88 %, specificity — 72 % [17].

Already mentioned the joint recommendations of RGA and ACR for the diagnosis and treatment of adult patients with ulcerative colitis and the recommendations of RGA and ACR for the diagnosis and treatment of irritable bowel syndrome also consider it necessary to determine the level of FCP in the initial differential diagnosis between UC and functional bowel disorders (primarily with IBS) [7, 18].

Discussing the importance of determining the level of FCP in the differential diagnosis between IBD and functional bowel disorders, it should be noted that in one of the works it was revealed an increase in the level of FCP in 36.6 % of patients who fully met the Rome criteria for IBS and had a normal endoscopic picture of the colon [19]. An attempt to explain this fact was to point out the pathophysiological role of inflammation of the colon mucosa of a low degree of activity in patients with IBS and the association of elevated levels of FCP with these changes [20], although it would be more logical in such cases to revise the diagnosis of IBS and look for other reasons for the increase in the level of FCP, which, as the following presentation will show, can be many.

A clinically significant conclusion in the differential diagnosis between IBD and functional bowel disorders is that the normal results of the determination of FCP allow with a high degree of probability to exclude organic lesions of the bowel and, in the first place, IBD. Negative predictive value of this method in the diagnosis of IBD is, according to the literature, 98.1–99.6 % [8, 21, 22].

A number of papers are devoted to the importance of determining the level of FCP in the diagnosis of inflammatory changes of intestinal mucosa, which are often found in patients with *ankylosing spondylitis and spondyloarthritis*. So, R.D. Østgård et al. [23] observed 30 patients with ankylosing spondyloarthritis, divided into 2 groups of 15 people each: with elevated (>100 ug/g) and normal (<50 ug/g) levels of FCP. Inflammatory changes in the intestinal mucosa were found in the first group in 12 out of 15 patients, while in the group with normal levels of FCP — only in one.

M. Fauny et al. [24] conducted a systematic review of 7 studies that examined the possibilities of determining the level of FCP in the diagnosis of inflammatory changes in the intestinal mucosa in patients with ankylosing spondylitis and spondyloarthritis. The higher level of FCP in the studied works was noted in 21.1–70.7 % of patients. In such patients, in 11–80 % of cases, endoscopic signs of inflammation of the intestinal mucosa were noted, and in 41.7–100 % — histological. The authors concluded that FCP is a good marker of inflammatory changes of intestinal mucosa in this group of rheumatological patients.

Works on the diagnostic value of determining the level of FCP in patients with *microscopic colitis* have been published. U. von Arnim et al. [25] observed 23 patients with histologically confirmed microscopic colitis and 20 patients with IBS. In patients with an active course of microscopic colitis, the level of FCP was significantly higher than in patients with IBS and patients with microscopic colitis in the remission stage (in the latter, it did not differ from that in patients with IBS). The authors concluded that the determining the level of FCP can be a marker when doing the differential diagnosis between IBS and the active course of microscopic colitis.

S. Wildt et al. [26] compared the level of FCP in patients with exacerbation of collagen colitis, patients with remission of the disease and persons of the control group. In patients with an active course of collagen colitis the level of FCP was significantly higher than in patients with remission of disease, as well as in the control group, although in 38 % of patients with exacerbation of collagen colitis, the level of FCP remained normal, and this circumstance, according to the authors, limits the use of FCP as a marker of this inflammatory bowel disease.

Also of interest are the results of the determining the level of FCP in patients with **diverticular bowel disease**. A. Tursi et al. [27] compared the level of FCP in patients with asymptomatic diverticular disease, clinically manifest form of uncomplicated diverticular disease, acute uncomplicated diverticulitis, patients with IBS, as well as healthy individuals. In healthy persons and patients with IBS the level of FCP remained normal. In patients with asymptomatic diverticulosis it did not differ from that in the control

group and patients with IBS. The level of FCP in patients with acute uncomplicated diverticulitis and clinically manifest form of uncomplicated diverticular disease was significantly higher, than in healthy persons and patients with IBS (respectively, $p < 0.0005$ and $p < 0.005$) and correlated with the severity of the inflammatory changes of the mucous membrane lining the diverticulum. After treatment the level of FCP significantly decreased. The authors concluded that the determining the level of FCP can be used to detect inflammatory changes in patients with diverticular bowel disease. The recommendations of the RGA and ACR for the diagnosis and treatment of adult patients with diverticular bowel disease also consider it appropriate to determine the level of FCP in such patients to assess the course of the disease [28].

The results of the study of the level of FCP in patients **with celiac disease** deserve attention. M. Montalto et al. [29] determined the level of FCP in 28 adult patients with celiac disease and in 30 healthy volunteers and found that in untreated patients with celiac disease the level of FCP did not significantly differ from the control and did not depend on the presence of their clinical manifestations and severity of endoscopic changes in the intestinal mucosa.

However, in pediatric studies, it was shown that in children with newly diagnosed celiac disease the level of FCP was significantly higher than in healthy children and children with celiac disease who were on a gluten-free diet. In patients with clinical symptoms of the disease it was higher than in patients without them, and in untreated children with total atrophy of the villi of the small intestine the level of FCP was significantly higher than in children with partial atrophy. It has been concluded that the determining the level of FCP may serve as an additional diagnostic marker, which helps in the diagnosis of celiac disease, especially in children with gastrointestinal symptoms [30, 31].

Given the great value of early detection of patients with **colon adenomatous polyps and colorectal cancer (CRC)**, it is important to evaluate the determining the level of FCP as a possible screening marker of these diseases. J. Tibble et al. [32] determined the level of FCP in 62 patients with CRC and 29 patients with adenomatous colon polyps. In 90 % of patients with CRC it was elevated. At the same time, only 58 % of them had a positive fecal reaction to occult blood. The level of FCP in patients with adenomatous polyps of the colon was also elevated, but too a much lesser extent. The overall sensitivity and specificity of the determining the level of FCP in relation combined to CRC and adenomatous polyps of the colon, were 79 % and 72 %, respectively, while the sensitivity and specificity of the analysis of feces for occult blood in the recognition of these diseases were, respectively, 43 % and 92 %. The authors concluded that FCP as a non-invasive marker of CRC and colon adenomatous polyps is more sensitive, but less specific compared to the test for occult blood in the stool.

H. Ye et al. [33] conducted a meta-analysis of 20 studies examining the possibility of using the determining the level of FCP to screen patients with CRC. The sensitivity and specificity of this method were 83 % and 61 %, respectively; the Odds ratio (OR) of having a tumor when an elevated level of FCP was detected was 7.76, and adenomatous polyps of the colon — 1.27. The authors concluded that FCP cannot serve as a screening marker for CRC, but its determining is still appropriate, since it allows the stratification of patients with a high and low risk of developing CRC. In other works, it was found that the negative predictive value of the determining the level of FCP in the diagnosis of CRC and adenomatous polyps of the colon is 96.2–98.7 %, which gives reason to consider it as a marker that allows with a high degree of probability to exclude these diseases in cases of obtaining normal results of its determination [21, 34].

In a number of studies it has been shown that an increase in the level of FCP may be due to **the intake of drugs**. So, D. Lundgren et al. [35] examined 590 persons with a normal endoscopic picture of the colon mucosa, and 36 % of them showed an increase in the level of FCP > 50 ug/g. A significant correlation was found between an increase in the level of FCP and taking proton pump inhibitors (OR = 3,843), nonsteroidal anti-inflammatory drugs (NSAIDs) (OR = 2,411) and acetylsalicylic acid (OR = 2,934).

H. Hovstadius [36] determined the level of FCP in 1263 persons with normal results of colonoscopy and found in 32 % of persons its elevated level. Further persons were observed for 3 years, without revealing any differences in the incidence of diseases of the lower gastrointestinal tract depending on the level of FCP. Most of them with elevated level of FCP compared with persons who had its normal level were significantly older (70 and 60 years, $p < 0.001$), more often took proton pump inhibitors (63 % and 26 %, $p < 0.001$), acetylsalicylic acid (60 % and 28 %, $p < 0.001$), NSAIDs (54 % and 33 %, $p < 0.003$).

Thus, an analysis of the available publications on the possibilities of determining the level of FCP in the diagnosis of various diseases and assessing their course gives grounds to conclude that a number of provisions and conclusions

concerning this issue can be considered quite proven, while others require their confirmation.

Of course, in patients with an already confirmed diagnosis of IBD, the determining the level of FCP in dynamics allows to control the course of the disease and the effectiveness of treatment. In addition, the determining the level of FCP can help in conducting a differential diagnosis between IBD (with the initial establishment of this diagnosis) and functional bowel disorders (primarily IBS). The use of this non-invasive method allows to assess the course of diverticular bowel disease and with a high degree of probability to suspect the development of diverticulitis. Determining the level of FCP can play an additional role in diagnosing celiac disease and assessing the effectiveness of its treatment.

At the same time, the significance of the determining the level of FCP as a marker of CRC and adenomatous polyps of the colon should apparently be considered insufficiently proven, given its insufficiently high specificity and positive predictive value. In addition, possible mechanisms for the increase of the level of FCP in such patients have not been deciphered. This also applies to the data about its increase in patients taking medications (proton pump inhibitors, NSAIDs, acetylsalicylic acid), which require confirmation and explanation. All this indicates the need for further research on the role of the determining the level of FCP in the diagnosis of various gastroenterological diseases.

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Information about the authors

Arkadiy A. Sheptulin* — Dr. Sci. (Med.), Prof., Chair of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Sklifosovsky Institute of Clinical Medicine, I.M. Sechenov First Moscow State Medical University (Sechenov University).
Contact information: arkalshep@gmail.com;
119435, Moscow, Pogodinskaya str., 1, bld. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

Сведения об авторах

Шептулин Аркадий Александрович* — доктор медицинских наук, профессор кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии Института клинической медицины им. Н.В. Склифосовского ФГАОУ ВО «Первый Московский государственный университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации
Контактная информации: arkalshep@gmail.com;
119435, г. Москва, ул. Погодинская ул., д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-1395-9566

* Corresponding author / Автор, ответственный за переписку

Svetlana S. Kardasheva — Cand. Sci. (Med.), Associate Professor, Department of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: svetlanakardasheva@gmail.com;
119991, Moscow, Pogodinskaya str., 1/1.
ORCID: https://orcid.org/0000-0002-5116-2144

Кардашева Светлана Станиславовна — кандидат медицинских наук, доцент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии Института клинической медицины им. Н.В. Склифосовского ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации,
Контактная информации: svetlanakardasheva@gmail.com;
119991, Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-5116-2144

Anastasya A. Kurbatova — Cand. Sci. (Med.), Assistant, Department of Internal Diseases Propedeutics, Gastroenterology and Hepatology, Sechenov First Moscow State Medical University (Sechenov University).
Contact information: maksnastia@gmail.ru;
119991, Moscow, Pogodinskaya str., 1/1.
ORCID: https://orcid.org/0000-0002-6154-8163

Курбатова Анастасия Александровна — кандидат медицинских наук, ассистент кафедры пропедевтики внутренних болезней, гастроэнтерологии и гепатологии Института клинической медицины им. Н.В. Склифосовского ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» (Сеченовский Университет) Министерства здравоохранения Российской Федерации,
Контактная информации: maksnastia@mail.ru;
119991, Москва, ул. Погодинская, д. 1, стр. 1.
ORCID: https://orcid.org/0000-0002-6154-8163

Submitted: 10.09.2021 Accepted: 20.01.2022 Published: 30.12.2022
Поступила: 10.09.2021 Принята: 20.01.2022 Опубликована: 30.12.2022