SERUM CALPROTECTIN – A POTENTIALLY NOVEL BIOMARKER IN INFLAMMATORY BOWEL DISEASE

Sérový kalprotektín – potenciálny nový biomarker pri nešpecifických črevných zápalových ochoreniach

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Abstract

Persistent inflammation in inflammatory bowel disease (IBD) leads to progressive damage to the gastrointestinal tract, resulting in potentially severe outcomes such as the need for surgical interventions or managing life-threatening conditions. Diagnosis relies on invasive endoscopy and fecal calprotectin (FC) monitoring, which have limitations, particularly regarding patient compliance. This highlights the urgent need for a non-invasive, easily determinable, and accurate biomarker for diagnosing and monitoring IBD. Our review covers recent data on serum calprotectin (SC), a well-studied novel biomarker, assessing its diagnostic accuracy and laboratory methodologies. Pilot studies highlight SC's potential in IBD, with promising sensitivity (Sn) and specificity (Sp) rates. Despite its diagnostic promise, SC cannot yet replace FC due to limited evidence. The primary limitations include the monocentric nature of studies, small patient cohorts, the absence of longitudinal monitoring, and in some cases, missing endoscopic assessments. While ELISA dominates laboratory methods, emerging evidence suggests the advantages of point-of-care testing (POCT), pending further validation. Future establishment of SC´s role in regular clinical practice will require extensive validation through multicentric studies with comprehensive designs and proactive biomarker monitoring. However, based on the evidence accumulated so far, SC might potentially serve as a complementary biomarker and/or in assessing the activity of extraintestinal manifestations in patients with IBD *(Tab. 1, Ref. 55). Text in PDF www.lekarsky.herba.sk.*

KEY WORDS: inflammatory bowel disease, Crohn´s disease, ulcerative colitis, serum calprotectin, fecal calprotectin, point-of-care testing.

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Abstrakt

Pretrvávajúci zápal pri nešpecifických črevných zápalových ochoreniach (IBD) vedie k progresívnemu poškodeniu gastrointestinálneho traktu, čo môže mať za následok závažné následky, ako je potreba chirurgických zákrokov alebo zvládanie život ohrozujúcich stavov. Diagnóza a následný klinický manažment sa opierajú o invazívnu endoskopiu a monitorovanie fekálneho kalprotektínu (FC), ktorého stanovenie má limitácie predovšetkým v nedostatočnej compliance zo strany pacientov. Aktuálnou je potreba nového biomarkera, ktorý by bol neinvazívny, jednoducho stanoviteľný a mal dobrú diagnostickú presnosť pre diagnostiku a monitoring IBD. Naša práca poskytuje prehľad recentných dát o sérovom kalprotektíne (SC), intenzívne skúmanom novom biomarkeri, hodnotí jeho diagnostickú presnosť a použité laboratórne metódy. Pilotné štúdie poukazujú na potenciál SC pri IBD, s priaznivými hodnotami senzitivity (Sn) a špecificity (Sp). Napriek jeho diagnostickému potenciálu však SC zatiaľ nedokáže nahradiť FC pre limitovanú evidenciu. Medzi hlavné limitácie patria monocentrická povaha štúdií, malé pacientské kohorty, absencia dlhodobého sledovania a v niektorých prípadoch chýbajúce endoskopické hodnotenia. Hoci ELISA dominuje medzi laboratórnymi metódami, nové dôkazy naznačujú výhody stanovenia v mieste poskytovania zdravotnej starostlivosti (POCT), ktoré však ešte vyžaduje ďalšiu validáciu. Budúce zavedenie SC do bežnej klinickej praxe bude vyžadovať rozsiahlu validáciu prostredníctvom multicentrických štúdií s komplexným dizajnom a proaktívnym monitorovaním biomarkera. Na základe doteraz dostupných dôkazov by však SC mohol potenciálne slúžiť ako doplnkový biomarker a/alebo na hodnotenie aktivity extraintestinálnych manifestácií u pacientov s IBD *(tab. 1, lit. 55). Text v PDF www.lekarsky.herba.sk.*

KĽÚČOVÉ SLOVÁ: nešpecifické črevné zápalové ochorenia, Crohnova choroba, ulcerózna kolitída, sérový kalprotektín, fekálny kalprotektín, point-of-care testovanie.

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Introduction

Inflammatory bowel disease (IBD), primarily including ulcerative colitis (UC) and Crohn's disease (CD), is a group of chronic, progressive, and recurrent inflammatory disorders of the gastrointestinal tract. These conditions are diverse, presenting a wide array of intestinal and extraintestinal symptoms. Despite thorough research, the precise pathogenesis of these diseases remains poorly understood. Factors such as genetic predisposition, environmental triggers, disturbances in the gut microbiota, and immune system malfunctions are believed to contribute to their onset. Over the last three decades, the prevalence of both diseases has increased, affecting 0.3-0.5% of the population in economically advanced countries, with initial symptoms frequently emerging in younger demographics, particularly those aged 15-30. This significant impact on quality of life extends to the work and social engagements of those affected (1 – 4).

The diagnosis of IBD is complex, involving medical history and clinical examination, supplemented by paraclinical laboratory and imaging tests - particularly blood and stool tests, endoscopic examinations, and imaging methods such as ultrasound, MRI, or CT enterography, along with possible histopathological examination of affected sections of the gastrointestinal tract (5). Currently, the preferred biomarker used to aid in diagnosis and subsequent monitoring is fecal calprotectin (FC). FC can provide information about the response to treatment, detect intestinal inflammation, and guide the physician in treatment with the goal of achieving better clinical and possibly endoscopic outcomes. Its importance is significant in distinguishing difficulties associated with disease activity from functional disorders – such as irritable bowel syndrome (IBS), with which IBD may confound the diagnostic process. However, its use in clinical practice has limitations – for the patient, stool collection is restrictive, it cannot reliably differentiate IBD from other concurrent intestinal inflammation, and there is a need for more precise correlation with the degree of disease activity. The methodology of the collection and processing itself remains problematic, with day-to-day variability and consistency of the stool (6 – 8).

The goal of IBD treatment after achieving remission is to maintain it long-term alongside rigorous monitoring known as „tight control". This management strategy involves making treatment deisions based on careful observation of disease status indicators such as biomarkers, to improve treatment outcomes (9). Particularly, endoscopic remission (also known as mucosal healing - MH) is an important treatment goal, and its timely achievement is associated with better future outcomes for the patient. This includes reductions in hospitalizations, decreased risk of disease relapse and the need for surgical interventions (10, 11). Currently, IBD is monitored primarily using FC, disease activity questionnaires, but luminal assessment of inflammation in the intestines during endoscopy remains the gold standard. The need for repeated or frequent endoscopic examinations is associated with poor acceptance by patients due to the invasive nature and the need for bowel preparation, sedation, and the risk of complications. Additionally, it is a costly and time-consuming examination (12, 13). Clinical indexes reflect more of the symptoms reported by the patient and do not provide information on the extent and intensity of intestinal inflammation (13).

The prevalence of patients with CD and UC is gradually increasing, with an expected rise of at least 20 – 30% in the next decade. This will require increased demands for patient monitoring and also for new ways of monitoring treatment. In this context, telemedicine (remote monitoring using POCT and electronic health) appears as one of the most significant and promising projects for patients with chronic and as yet incurable diseases. This is further emphasized by the fact that a specific characteristic of IBD patients is that they are largely young people of working age, who may find the necessity of lifelong and regular visits to the doctor restrictive, but on the other hand, are interested in actively participating in the care of their health and are actively interested in their disease (14).

Given these facts, there is a significant need for new non-invasive biomarkers that would more accurately diagnose the disease, predict its progression, and correlate more precisely with the level of endoscopic activity, thus allowing for more effective clinical management. This need is particularly underscored in recent years based on experiences from the COVID-19 pandemic, or in connection with other possible pandemics, which can lead to a reduction in the number of examinations and the time a patient can spend in a healthcare facility. Over the past few years, research has therefore begun to intensively focus on the study of new serum biomarkers of protein and peptide nature or compounds containing sulfhydryl groups that could fill this missing element. Current trends are characterized by intense research into biomarkers such as leucine-rich alpha-2 glycoprotein, serum adropin, type VI collagen remodeling markers, elastin degradation markers, serum calgranulin C, serum amyloid A, serum cholinesterases, free thiols, and many others (13, 15 – 21).

Serum calprotectin (SC) holds a dominant position in terms of the number of published pilot studies. The aim of our work is to provide a narrative review of published studies on this biomarker, focusing on its diagnostic accuracy, the laboratory methods used, and its evaluation in the context of established biomarkers like fecal calprotectin (FC) and CRP.

Methods

To create a narrative review, a search was conducted for published research studies indexed in scientific databases such as PubMed, Scopus, Embase, and via Google Scholar using specific keywords. Studies from

the period 2019 – 2023 that included a minimum of 30 subjects were included.

Results

Fecal calprotectin and other currently used biomarkers

The most commonly used biomarkers of intestinal inflammation in clinical practice are FC, CRP, and to a lesser extent, fecal lactoferrin (FL). FC, elevated in IBD, is particularly useful for distinguishing IBD from IBS, with reported cut-off values < 50 – 150 μg/g indicating IBS. It is widely used in monitoring the activity of IBD, although a consensus on the ideal cut-off is still lacking. In controlled clinical studies, values for remission are used up to 100 μg/g, while in real-world studies, values predominantly up to 250 μg/g are common (5, 8, 9, 11). The correlation coefficients of biomarkers with endoscopy ranged from 0.48 – 0.83 for FC and 0.19 – 0.87 for FL in IBD patients (22, 23). Stricter cut-off values of FC were associated with achieving histological healing in UC and transmural healing in CD (24 – 26).

An important feature of FC is its ability to predict relapse in patients in remission. A key insight in this regard was provided by a large meta-analysis that included 672 patients (318 with UC and 354 with CD), whose data came from 6 prospective studies assessing FC concentrations during remission. The combined Sn and Sp for FC in predicting relapse were 78% and 73%, respectively. The area under the receiver operating characteristic curve (AUROC) was 0.83, and the diagnostic odds ratio was 10.31. The ability of FC to predict relapse was comparable between UC and CD. Within CD, the predictive accuracy was higher for ileocolonic and colonic localizations (27).

Currently, the preferred treat-to-target (T2T) strategy using FC and CRP biomarkers was evaluated in the CALM study. It was the first prospective randomized controlled study to demonstrate that the T2T strategy using FC and CRP biomarkers (early escalation of biological therapy at FC ≥ 250 μg/g or CRP ≥ 5 mg/l) led to a higher rate of endoscopic remission in patients with Crohn's disease compared to a strategy based on the escalation of treatment based only on clinical symptoms. It was also shown that the combination of FC and CRP most accurately predicted disease relapse (28, 29). Long-term follow-up analysis (median 3 years) further showed that patients who achieved early endoscopic remission, i.e., at the end of the first year, had significantly lower incidence of serious complications such as strictures, fistulas, or mesenteric infiltrates, and a lower need for hospitalizations and surgical treatment (30).

Serum calprotectin

Currently, significant research is focused on the study of new serum biomarkers, aiming to identify those that offer a high degree of combined Sn and Sp, are user-friendly, and economically feasible for practical use. Serum calprotectin (SC) emerges as the most extensively studied serum biomarker in relation to the diagnosis of CD and UC, and clinical and endoscopic activity. An important subject of research is also its correlation with other biomarkers currently used, such as FC and CRP, and possibly erythrocyte sedimentation rate, neutrophil to lymphocyte ratio, albumin, and hemoglobin. Calprotectin (CP) is a heterodimeric protein belonging to the S100 protein family, consisting of S100A8 (molecular weight 10.8 kDa) and S100A9 (molecular weight 13.2 kDa) subunits, which bind calcium and zinc (31). It is evolutionarily conserved, widely expressed in neutrophils as their major component, constituting about 45% of their cytoplasmic proteins, and to a lesser extent in monocytes, macrophages, and certain epithelial cells, and is also known for its antimycotic activity against Candida albicans (32, 33). It plays a role in several physiological processes such as cell differentiation, immunoregulation, carcinogenesis, apoptosis, and inflammation (31, 34). In response to inflammatory stimuli, such as bacterial antigens or cytokines like TNF-α and IL-1β, CP expression can be induced in cells, further influencing inflammatory pathways (31, 35).

SC is a sensitive biomarker of both acute and chronic inflammation. Recent research has confirmed that elevated levels of SC have been present in various autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, ankylosing spondylitis, periodontitis, as well as in malignancies like myelodysplastic syndrome, carcinoma of the bladder, lungs, pancreas, prostate, and others (31). SC is particularly useful currently in the diagnosis and monitoring of disease activity in patients with familial Mediterranean fever, where it possesses relatively good Sp in detecting subclinical inflammation (36, 37).

Multiple pilot studies have demonstrated the significance of SC as a potentially sensitive biomarker for assessing disease activity in IBD or for establishing a diagnosis itself. One of the first significant studies on this topic, the STORI study conducted by Meuwis et al., found that SC had a profile very similar to CRP, with significant increases in active disease and good responsiveness to medical therapy. Findings from this study suggested that SC levels (> 5675 ng/ml), could be complementary to CRP (> 5 mg/l) and FC (> 250 μg/g) for relapse prediction specifically after infliximab withdrawal in Crohn's disease ($p = 0.0173$, 0.0024, and 0.0002; HR: 3.191, 3.561, and 4.120), highlighting its potential utility in monitoring disease activity and guiding treatment decisions (38).

In recent years, numerous studies have been conducted aiming to define the potential role of serum SC in the diagnostic and treatment algorithms for IBD. Among those aiming to comprehensively assess this biomarker - not only in distinguishing IBD diagnoses from healthy individuals or evaluating clinical activity, but also endoscopic activity mucosal healing (MH), several are notable. Veyrard et al. evaluated 119 patients in a prospective longitudinal study by periodically monitoring SC in patients in deep remission at baseline.

Patients were followed for 12 months or until relapse. SC levels were observed prior to and/or at the time of disease relapse to evaluate its diagnostic accuracy in predicting clinical relapse. The median SC levels at baseline were 3.15 μg/ml; during relapse, they increased to 4.45 μg/ml. In patients with clinical symptoms, SC demonstrated good predictive value for relapse (AUROC 0.764), with a Sn of 72% and a Sp of 77%, using a cut--off value of 4.45 μg/ml. SC performed better than CRP in detecting relapse but was less accurate than FC. Overall, SC increased during clinical and endoscopic activity and enabled differentiation between active IBD and IBS in patients with clinical activity of IBD. However, SC was not elevated during the follow-up of IBD patients in clinical remission before clinical relapse (41).

The POCT diagnostic approach was used in the prospective monocentric study by Bernardo et al. SC was assessed as a biomarker for predicting clinical remission and mucosal healing in a cohort of 82 IBD patients. The study highlighted SC's capacity to predict clinical remission with Sn of 65.6% and a Sp of 67.6% at a cut-off of 5.3 mg/ml, achieving an AUC of 0.67. Notably, SC's predictive accuracy was more favorable in UC than in CD. For mucosal healing, a threshold of 4.8 mg/ml provided a Sn of 61.9% and a Sp of 80.9%, with an AUC of 0.73. SC's performance was found to be comparable to that of FC and CRP in both UC and CD (6). In a detailed method comparison, the Bühlmann Quantum Blue® SC test, used in this study, demonstrated strong agreement with the Bühlmann SC ELISA. Analyzing 29 samples within the specified measuring range of the Quantum Blue® sCAL assay, each sample was tested ten times according to the assay procedure. These results were then compared with 1 – 4 duplicate values obtained using the Bühlmann SC ELISA. The correlation coefficient (R^2) between the two methods was 0.94, indicating a high degree of consistency. The regression equation derived from this comparison was $y = 0.93x + 0.51$ μg/ml, further underscoring the strong linear relationship between the assay results obtained by the Quantum Blue® system and those derived from the ELISA method (39).

In a pilot study examining SC in adolescent IBD patients, SC demonstrated a significant positive correlation with the endoscopic score ($r = 0.56$, $p = 0.01$), symptom score ($r = 0.64$, $p = 0.003$), and CRP ($r = 0.97$, $p < 0.0001$) across 19 samples from UC patients. Additionally, a significant relationship was also observed between SC and CRP in CD across 49 samples. These results underscore SC's potential as a biomarker for monitoring disease activity in adolescents with UC (7).

A prospective study by Ferrer et al. involved 53 IBD patients who underwent colonoscopy as part of routine clinical practice. The study assessed SC, FC, and conventional blood test parameters. Notably, in UC patients, SC levels were significantly higher with endoscopic Mayo scores of 2/3 (median 10.39 mg/ml) compared to scores of 0/1 (median 4.07 mg/ml), underscoring SC's effectiveness as an inflammatory biomarker. The study demonstrated SC's high diagnostic performance in UC with an AUROC of 0.85, and Sn and Sp of 83.3% and 81.25%, respectively, for a cut-off of 4.4 mg/dl. However, SC did not show significant correlations with endoscopic findings in CD (40). Table 1 summarizes the studies on SC in the diagnosis and disease activity assessment of IBD.

Discussion

Our review summarizes a relatively high number of published studies focusing on serum calprotectin as a potentially new biomarker in the clinical management of IBD, which also indicates the growing importance and interest in this area. The studies vary in quality, and the majority are observational cross-sectional diagnostic studies with prospective parameter determination. The results, to varying extents within individual studies, confirmed its potential to distinguish IBD patients from healthy individuals, and the ability to correlate with clinical, endoscopic activity, and other inflammation biomarkers, primarily FC and CRP. The number of studies also confirmed our assumptions that current research in this area is very intense.

In our review, we cover 13 studies of SC, several of which confirmed a relatively good correlation of this biomarker's levels with clinical or even endoscopic activity. However, these data also bring some controversy as several studies did not demonstrate a correlation with activity in UC (44, 46, 47, 49) or in CD (40,42). Multiple studies showed a significant correlation of SC with CRP (7, 45, 47), whereas other studies did not show a significant correlation of SC with FC (6, 7, 38, 47, 51).

Considering these facts, it could be suggested that SC is more of a biomarker reflecting systemic inflammation rather than intestinal inflammation, unlike FC. This assumption is also supported by the fact that SC is released from neutrophils, monocytes, and macrophages as a result of stimulation by lipopolysaccharides or various cytokines such as TNF-α and IL-1β (47).

It is known that 25 – 40% of patients with IBD develop extraintestinal manifestations, including musculosceletal, ocular, hepatopancreatobiliary, renal, dermatological complications, and others (52). Considering the fact that elevated levels of SC have also been detected in several autoimmune diseases alone (31), this provides a basis for the assumption that SC could also be used in monitoring the activity of extraintestinal manifestations in IBD.

From our perspective, it remains one of the most promising serum biomarkers for potential future clinical adoption. An interesting study in terms of results and the laboratory method used is the work by Di Bernardo et al., who assessed SC through the currently desirable diagnostic concept – POCT. The Bühlmann Quantum Blue® rapid test based on the LFIA principle was used, along with the 2nd generation Quantum Blue® Reader, which provided quantification of results. This prospective monocentric study demonstrated that SC is a predic-

Table 1. Overview of clinical studies with serum calprotectin in the diagnosis and activity assessment of IBD.

Study	Type	N	Laboratory methods	Results
Veyrard et al. 2022 (41)	OBS L	75 CD 44 UC	ELISA	SC levels were higher in active IBD and similar among groups of patients with IBS or in deep remission (3.05 µg/ml in IBS vs 2.99 µg/ml in remission vs 5.1 µg/ml in clinical relapse, p=0.04). SC was not as effective in predicting relapse as FC.
Carlsen et al. 2019 (7)	2 parts: OBS CS DS and OBS L	19 UC	ELISA	In UC, a positive correlation was observed between SC and endoscopic scores, symptom scores, and CRP (r=0.56, p=0.01; r=0.64, p=0.003; r=0.97, p<0.0001) in adolescents.
Bernardo et al. 2019 (6)	OBS CS DS	49 CD 33 UC	LFIA (POCT)	CR: AUROC = 0.67, cut-off of 5.3 mg/ml predicted CR with Sn of 65.6% and Sp of 67.6%; MH: AUROC = 0.73, cut-off of 4.8 mg/ml predicted MH with Sn of 61.9% and Sp of 80.9%.
Chen et al. 2021 (42)	OBS CS DS	64 CD 64 UC 64 HC	ELISA	For the diagnosis of CD, Sn and Sp were 87.3% and 89.7%, respectively. For the diagnosis of UC, Sn and Sp were 98.5% and 75.6%, respectively. In UC, SC levels correlated with clinical activity: 868.31±375.25 ng/ml during active disease and 701.58±278.88 ng/ml in remission (p<0.05).
Elshayeb et al. 2021 (43)	OBS CS DS	14 CD 36 UC 30 HC	ELISA	Patients with IBD had significantly higher average SC levels compared to non-IBD subjects. The AUROC was 0.99; cut-off of 925 ng/ml predicted the disease with Sn of 98% and Sp of 92%.
Ferrer et al. 2019 (40)	OBS CS DS	26 CD 27 UC	ELISA	Patients with active UC had significantly higher average median SC levels - 10.39 mg/ml compared to patients in remission - 4.07 mg/ml (p = 0.01). The AUROC was 0.85; cut-off of 4.4 mg/dl predicted active disease with Sn of 83.3% and Sp of 81.25%, no correlation in CD.
Udegbune et al. 2022 (44)	OBS CS DS	71 UC	ELISA	No correlation was demonstrated between SC lervels and clinical activity in UC; the median was 4534 (3387–6416) ng/ml for clinically active UC vs. 4031 (2401–5414) ng/ml for clinical remission (p = 0.1825).
Malham et al. 2019 (45)	OBS CS DS	84 UC	ELISA	FC and SC significantly correlated with clinical, endoscopic, and histological activity in UC, while PC showed a stronger correlation - (Rho=0.54, p=0.002), (Rho=0.39, p=0.0003), and (Rho=0.28, p=0.01) respectively.
Yasuda et al. 2023 (46)	OBS CS DS	74 CD 77 UC 22 HC	ELISA	Pediatric population: average SC levels in active CD were 2941 ng/ml, significantly higher than in remission – 962 ng/ml (p < 0.05) and healthy controls – 872 ng/ml (p < 0.05). In UC, no significant difference was observed between active UC and healthy individuals or those in remission.
Mori et al. 2021 (47)	OBS CS DS	105 CD 98 UC 92 HC	ELISA	Patients with UC (median 2.565 µg/ml, p < 0.001) and CD (2.565 µg/ml, p < 0.001) had higher SC levels compared to healthy individuals (1.04 µg/ml) and exhibited the highest levels during periods of high disease activity vs remission in CD, but not in UC.
Azab et al. 2022 (48)	OBS CS DS	20 CD 30 UC 20 HC	ELISA	SC levels correlated with the diagnosis of IBD – AUROC was 0.99, cut-off 48 ng/ml, Sn 98%, and Sp 95%; and with clinical activity/remission in UC – AUROC was 0.88, cut-off 104 ng/ml, Sn 73%, and Sp 93%; and in CD – AUROC was 0.97, cut-off 120 ng/ml, Sn 90%, and Sp 90%.
Townsend et al. 2019 (49)	OBS DS	109 IBD	ELISA – comparison of two commercially available assays	Patients with clinically active CD had significantly higher average SC levels compared to those in remission in both assays: 5507 vs 3830 ng/ml, p=0.0001 (Buhlmann) and 5131 vs 2994 ng/ml, p=0.0003 (Immunodiagnostics). This was not confirmed in UC.
Okada et al. 2019 (50)	OBS CS DS	40 CD 61 UC 101 HC	ELISA	Patients with IBD had significantly higher average SC levels compared to non-IBD subjects – UC (1.08×10^3 µg/l) and CD (1.30×10^3 µg/l) versus healthy controls (5.28×10 µg/l). The AUROC was 0.877 with cut-off of 5.8×10 µg/l, with Sn 79% and Sp 82%. In UC, SC correlated with clinical activity of the disease (r=0.342).

CR – clinical remission, Dx – diagnosis, ELISA – enzyme-linked immunosorbent assay, HC – healthy controls, LFIA – lateral flow immunoassay, MH – mucosal healing, OBS CS DS – observational cross-sectional diagnostic study with prospective parameter determination, OBS DS – observational prospective diagnostic study, OBS L – observational longitudinal prospective study, PC – plasma calprotectin, Rho – Spearman's correlation coefficient, r – Pearson's correlation coefficient

tive biomarker for clinical remission and mucosal healing in IBD patients. SC was not inferior in comparison to other biomarkers – CRP and FC in terms of predicting clinical remission and mucosal healing (6). This study used LFIA, a method that in general, thanks to the use of portable reading devices and continuous improvements in the characteristics of used labels, can achieve Sn comparable with ELISA (53). This is confir-

med by the the Bühlmann Quantum Blue® SC test as it demonstrated strong agreement with the Bühlmann SC ELISA (39).

On the other hand, one of the disadvantages of SC is that it was not sufficiently effective in predicting relapse (41). One way to improve the diagnostic accuracy of SC is by determining it from plasma. Malham et al. found that PC and SC significantly correlated with clinical, endoscopic, and histological activity in UC, with PC showing a stronger correlation (45).

Another possible approach in an effort to improve diagnostic accuracy is the simultaneous determination of multiple biomarkers. The determination of a combination of four serum biomarkers: SAA, IL-6, IL-8, and Eotaxin-1 predicted better endoscopic activity in IBD than CRP (54). The results of the studies presented in this review are significant despite the fact that SC have yet not reached the acceptance and status of FC in the diagnostic process and clinical management of IBD, which continues to be the most important biomarker, supported by recommendations (5).

The main limitations of the studies presented include their monocentric nature, a low number of patients, the absence of longitudinal monitoring, and in some cases, the lack of assessment of endoscopic activity. Nevertheless, according to current evidence, SC could potentially serve as a complementary biomarker and/or assist in evaluating the activity of extraintestinal manifestations in IBD patients (55).

As for the laboratory methods used, ELISA remains predominant, but one study mentioned in our review was conducted using POCT (LFIA). A significant challenge associated with POCT systems is achieving analytical validation standards comparable to those in clinical laboratories. Analytical requirements should be the same as those demanded in clinical laboratories (14). ELISA methods have been widely validated, even though the protocol is quite time-consuming and the results are reported later than in POCT methods.

POCT, while also validated, the extent and rigor can vary depending on the specific test. POCT devices are generally designed for ease of use and rapid results, often at the cost of some accuracy and Sn. Standardization can be challenging, as the simpler user interface and design can lead to greater variability between different users and environments compared to more controlled laboratory settings. POCT is optimized for speed and convenience, which can sometimes affect the limit of detection and overall precision. However, technological advancements are rapidly improving the capabilities of POCT devices, especially in Sn (53). FC, which is an established biomarker of IBD activity, already has a fairly extensive evidence record even within POCT measurements in the clinical setting (56 – 59).

Conclusion

Recent years have been marked by intense efforts to accumulate evidence in search of the ideal biomarker for diagnosing and monitoring IBD. An ideal biomarker should be non-invasive, affordable, standardized, with rapid results availability, and high diagnostic accuracy. Current research focuses on biomarkers of various types, with serum biomarkers being a significant area of interest. Among the large number of serum biomarkers studied, SC can be considered promising for further research and potentially later implementation in practice.

Considering the evidence accumulated so far, it may seem that FC is more directly linked to intestinal inflammation, whereas SC may be more useful in assessing systemic inflammation. Its future role might be as a complementary biomarker and/or in assessing the activity of extraintestinal manifestations in patients with IBD. Additional research is essential to establish SC' regular clinical application, define standardized diagnostic thresholds, and validate its use for prognosis and diagnosis, potentially replacing the widely researched FC.

Another scenario in the search for the ideal biomarker could be demonstrating the superiority of combining multiple biomarkers. In terms of laboratory methods, there is scope for more intensive research and validation of tests used in POCT due to their speed, economic affordability, simplicity, and the mobility of the reading device. The advantage of the POCT approach for patients is clear and lies in the ability to make immediate treatment decisions, thereby achieving better clinical outcomes, higher patient safety, and overall satisfaction. In this regard, the continuous improvement of the tests used in POCT in terms of Sn, quantification, and the ability to perform multiplex detection of multiple biomarkers simultaneously within a single test is also important. A fundamental requirement for confirming SC as a useful biomarker in IBD management will be the conduct of further validation multicentric studies involving a higher number of patients with a longitudinal design, assessment of endoscopic activity, and proactive monitoring of the biomarker.*

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