

# Current noninvasive modalities in Crohn's disease monitoring

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## Abstract

Crohn's disease (CD) is characterized by a remitting and relapsing course. Longstanding active CD may result in accumulating intestinal damage and disease-related complications. In contrast, mucosal healing is associated with significant improvement in the health-related quality of life, longer periods of disease remission and lower risk of disease progression, complications, hospitalizations, intestinal surgeries, as well as a lower risk of developing colorectal cancer. Mucosal healing, the new treatment endpoint in CD, made necessary the development of noninvasive, accurate, objective and reliable tools for the evaluation of CD activity. Ileocolonoscopy with biopsies remains the reference standard method for the evaluation of the colonic and terminal ileal mucosa. However, it is an invasive procedure with a low risk of complications, allowing the investigation of only a small part of the small bowel mucosa without being able to assess transmural inflammation. These disadvantages limit its role in the frequent follow up of CD patients. In this review, we present the currently available biomarkers and imaging modalities for the noninvasive assessment of CD activity.

**Keywords** Crohn's disease, monitoring, disease activity

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## Introduction

Until now, there has been no single diagnostic test able to interpret symptoms and signs, evaluate treatment efficacy, guide patient management, predict the clinical course, disease behavior and the development of disease-related complications in patients with Crohn's disease (CD). Thus, patient management is based on the assessment of disease activity, location, extent, and the presence of complications or extraintestinal manifestations [1].

Mucosal healing is becoming the treatment goal and therapeutic endpoint in CD, partially replacing the role of clinical and biochemical markers that, in a significant proportion of patients, were demonstrated to underestimate disease activity and correlate poorly with endoscopic findings [2-4]. In detail, mucosal healing is a recently introduced complex concept and, despite the lack of an accepted definition, it could be defined

as the disappearance of inflammatory endoscopic lesions [5]. Mucosal healing is associated with significant improvement in health-related quality of life, a lower risk of disease progression, as well as a lower risk of colorectal cancer [4,6,7].

Endoscopy and cross-sectional imaging modalities are invaluable tools in CD monitoring [8]. Upper gastrointestinal CD involvement is optimally evaluated with upper gastrointestinal endoscopy, whereas ileocolonoscopy, despite its inability to determine transmural inflammation, allows the direct visualization of the inflamed intestinal mucosa, tissue sampling, and malignancy screening [9]. Moreover, the development of endoscopic indices—CD endoscopic index of severity (CDEIS), Simple Endoscopic Score for CD (SES-CD), Rutgeerts score—has enabled the objective and reliable quantification of mucosal inflammation [10-12].

On the other hand, there are several considerations regarding the role of ileocolonoscopy in CD monitoring: a) the inflammatory insult in CD is transmural; b) whilst the small bowel is predominantly affected, as 70% of patients have ileal or ileocolonic disease, conventional endoscopes enable the visualization of only a short segment of the terminal ileum mucosa; c) in a small proportion of patients the terminal ileum cannot be reached or is inaccessible due to ileocecal valve stricturing; d) the inflamed mucosa is characterized by a patchy distribution which may result in a false negative endoscopic study; e) patients may feel uncomfortable with the colonoscopy procedure, as it requires bowel preparation; and lastly, f) it carries a low risk of complications [9,13-15]. For all these reasons, ileocolonoscopy is less than ideal for the frequent follow up of CD patients.

The technologic innovation of capsule endoscopy allowed the minimally invasive evaluation of the entire small and

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large bowel mucosa, with a superior diagnostic performance in the detection of proximal and mild small bowel disease in comparison to other modalities [16,17]. However, capsule endoscopy does not allow the acquisition of tissue samples, it carries a small but considerable risk of procedure-related complications (e.g. capsule retention, intestinal perforation), it requires bowel preparation and it is contraindicated in selected cases [17]. Moreover, it is a time-consuming procedure, a small but considerable proportion of patients will have an incomplete examination, whilst it only allows the evaluation of the intestinal mucosa, without being able to provide information regarding transmural inflammation, disease behavior (stricturing or penetrating disease) and disease-related complications [17,18], the assessment of which is largely based on the use of cross-sectional imaging modalities [19].

Due to the relapsing and remitting clinical course of CD, the development of noninvasive, accurate, objective and reliable diagnostic modalities for the evaluation of mucosal inflammation would allow prompt identification of disease exacerbation, especially in the pediatric and adolescent population, where there are concerns over the use of potentially harmful procedures and sedation. As landmark studies have demonstrated that treatment decisions based on a tight control monitoring strategy with noninvasive biomarkers lead to improvement in endoscopic and clinical outcomes [20], the aim of this review was to present and analyze the currently available tools for the noninvasive evaluation of CD activity.

## Materials and methods

A thorough search was performed in PubMed from 2000 up to June 2020, to identify articles that describe biomarkers and other diagnostic methods for the evaluation of CD activity. The search for relevant studies was performed using the follow search string: (“*Crohn’s disease*”) AND (“*assessment*” OR “*evaluation*” OR “*monitoring*” OR “*follow-up*” OR “*follow up*”) AND (“*mucosal inflammation*” OR “*inflammation*” OR “*activity*” OR “*disease activity*”). The search was supplemented with the addition of suitable articles cited in the reference lists of the included studies. A list of the key studies regarding the diagnostic performance of the currently available and emerging modalities in CD activity assessment can be found in Table 1.

## Biomarkers

The discovery of a noninvasive marker that could reflect the complex condition of mucosal healing is really difficult. Nevertheless, a significant amount of research has been dedicated to identifying a minimally invasive, low cost, easy to determine, objective and reproducible biomarker that enables disease prognosis and the assessment of treatment response. The most used and most studied biomarkers in CD monitoring are C-reactive protein (CRP) and fecal calprotectin (FC). Among their advantages are availability and low cost.

## CRP

CRP is an acute phase protein produced in the liver in response to circulating inflammatory cytokines. According to the results of a recent meta-analysis, despite the low sensitivity (49%), a CRP level >5 mg/dL was demonstrated to be highly specific (>90%), with an area under the curve (AUC) of 0.72, in the discrimination of endoscopic activity [21]. However, its use in the assessment of CD activity has several limitations: any inflammatory condition may result in CRP elevation, its production is related to the patient’s characteristics, whilst the patient’s genetic profile affects the CRP level, with up to 25% of CD patients being unable to produce significant CRP levels despite endoscopic activity [22,23]. Thus, although further diagnostic investigation is warranted in patients with abnormal CRP, its interpretation in CD monitoring should be made cautiously.

## FC

FC, a protein released by activated neutrophils in the intestinal chyme in response to intestinal inflammation, can be quantified and is the most studied fecal biomarker of inflammation. It resists proteolysis for up to 7 days at room temperature and can be measured from a small fecal sample [24]. A cutoff point of <250 µg/g is a useful surrogate marker for mucosal healing in CD [25]. In detail, FC sensitivity and specificity in the prediction of endoscopic activity is dependent on the cutoff level used: a cutoff value between 50-100 µg/g results in high sensitivity and specificity [26,27], with FC levels below 50 µg/g practically eliminating the possibility of mucosal inflammation.

FC was shown to have 87%, 67% and 0.85 pooled sensitivity, specificity and AUC, respectively, in the diagnosis of endoscopic activity [21].

Nevertheless, FC is unable to determine the cause of inflammation, whereas abnormal levels can be associated with gastrointestinal neoplasms and microbial gastrointestinal infections. Finally, FC was demonstrated to perform better in patients with colonic mucosa inflammation [28], which may limit its use in patients with small bowel CD.

## Other biomarkers

Of the numerous biomarkers [29-67] continually being discovered (Table 2), some are attracting great interest due to their high diagnostic accuracy and ease of use. Below we present the most promising biomarkers based on their diagnostic performance, availability and ease of use.

## Fecal hemoglobin

The detection of fecal hemoglobin, via ELISA, fecal occult blood testing (FOBT), and fecal immunochemical testing (FIT), has been proposed as an alternative biomarker for the

**Table 1** Key studies regarding the diagnostic performance of the currently available and emerging modalities in the assessment of CD activity

Diagnostic method	Study [Ref.]	SENS	SPEC	PPV	NPV	AUC	Correlation with endoscopic findings
<b>Serum biomarkers</b>							
CRP	Mosli MH, 2015 [21]	49%	92%	NA	NA	0.72	NA
Serum BAFF	Zhang P, 2016 [52]	59%	93%	NA	NA	0.79	NA
Serum amyloid A	Ishihara S, 2018 [29]	68%	83%	NA	NA	0.77	r=0.64
Serum amyloid A	Yarur AJ, 2017 [30]	64%	95%	NA	NA	0.77-0.81	NA
<b>Fecal biomarkers</b>							
Fecal calprotectin	Mosli MH, 2015 [21]	87%	67%	NA	NA	0.85	NA
Fecal BAFF	Xie C, 2019 [51]	85%	91%	84%	92%	NA	NA
Fecal BAFF	Fu Y, 2017 [48]	84%	100%	100%	64%	NA	r=0.58
FIT	Mooiweer E, 2014 [50]	73%	79%	NA	NA	0.89	r=0.44
FOBT	Fu Y, 2017 [48]	41%	93%	90%	49%	0.79	NA
<b>Composite biomarker tests</b>							
EHI index (early-stage CD)	D'Haens G, 2019 [76]	97.1%	69.0%	NA	NA	0.88	NA
EHI index (moderate-to-severe CD)	D'Haens G, 2019 [76]	83.2%	36.6%	NA	NA	0.62	NA
Combination of Eotaxin-1, SAA, IL-6, IL-8	Bourgonje AR, 2019 [75]	90.7%	68.4%	86.7%	NA	0.84	NA
<b>Computed tomography</b>							
CTE	Horsthuis K, 2008 [81]	84.3%	95.1%	NA	NA	NA	r=0.70
Low-dose CTE	Rosenfeld G, 2018 [98]	85-94%	84-97%	NA	NA	NA	NA
Dual-energy CT	De Kock I, 2019 [100]	NA	NA	NA	NA	0.96	NA
Dual-energy CT	Kim YS, 2018 [99]	NA	NA	NA	NA	NA	r=0.74
<b>Magnetic resonance imaging</b>							
MaRIA index	Buisson A, 2017 [106]	73.9%	82.1%	NA	82.1%	NA	NA
MaRIA index	Rimola J, 2009 [107]	NA	NA	NA	NA	0.89	r=0.82
Clermont score	Buisson A, 2017 [106]	74%	81.3%	NA	82.4%	NA	NA
Diffusion-weighted imaging MRI	Stanescu-Siegmund N, 2017 [113]	97.4%	99.2%	NA	NA	NA	NA
<b>Ultrasound</b>							
SICUS	Pallotta N, 2005 [117]	100%	98%	NA	NA	NA	NA
CEUS	De Franco A, 2012 [127]	86-97%	83%	NA	NA	NA	NA

CD, Crohn's disease; SENS, sensitivity; SPEC, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CRP, C-reactive protein; FIT, fecal immunochemical test; FOBT, fecal occult blood test; BAFF, B-cell activating factor; EHI, endoscopic healing index; IL, interleukin; CT, computed tomography; MRI, magnetic resonance imaging; SICUS, small intestine contrast ultrasonography; CEUS, contrast-enhanced ultrasound; NA, not available

investigation of mucosal inflammation [48-50]. In particular, FIT is a low cost, easy to perform and widely available modality, allowing the objective and reliable evaluation of disease activity through the quantification of hemoglobin concentration in the feces, demonstrated to have 74% sensitivity, 84% specificity, 72% positive predictive value (PPV), 84% negative predictive value (NPV), and an AUC of 0.81 [50]. Although its diagnostic accuracy was shown to be comparable to that of FC, it has been shown to perform better in patients with colonic disease [68]. Despite the limited data regarding its role in CD patients, FOBT was demonstrated to predict mucosal inflammation with 65% sensitivity, 93% specificity, 97% PPV and 43% NPV [48].

Nevertheless, physicians should be aware that fecal occult blood tests may produce false positive results in patients on nonsteroidal anti-inflammatory drugs, aspirin and red meat consumers, or false negative results in patients who consume high levels of vitamin C.

### B cell-activating factor (BAFF)

Another potential biomarker is fecal BAFF. BAFF is responsible for the formation and homeostasis of B cells, as well as the survival of autoimmune cells [69,70]. In addition, BAFF overexpression is associated with the development of autoimmune diseases [71]. Recently, it was demonstrated that, in patients with relevant gastrointestinal symptoms, fecal BAFF can be highly sensitive (84-85%) and highly specific (>90%) in the discrimination among patients with inflammatory bowel disease (IBD), those with irritable bowel syndrome, and healthy controls. Although the sensitivity of serum BAFF in the diagnosis of mucosal inflammation was demonstrated to be moderate (59%), it shows excellent specificity (93%) [48,51,52].

It should be noted that fecal BAFF measurement should be made under the appropriate clinical context, as abnormal levels

**Table 2** List of studied biomarkers for the assessment of Crohn's disease activity

<b>Serum biomarkers</b>
Adenosine deaminase
Blood-derived DNA methylation
C-reactive protein
Eotaxin-1
Eotaxin-3
Granzyme B
IL-6 and its soluble receptor components sIL-6R and sgp130
IL-1ra, IFN- $\gamma$ , TNF- $\alpha$ , IL-8, IL-10, IL-17A, IL-18, IL-33/ST2
MicroRNA-320a
Matrix metalloproteinases -3 and -9
Plasma osteopontin
Platelet indices
Platelet activation markers
PMN elastase
Red cell distribution width
Serum amyloid A
Serum free thiols
<b>Urine biomarkers</b>
Urine F2 isoprostanes
Urine leukotriene E4
Urine neopterin
<b>Fecal biomarkers</b>
Fecal B cell-activating factor
Fecal calgranulin C (S100A12)
Fecal Calprotectin
Fecal high mobility group box 1 protein
Fecal immunochemical test
Fecal lactoferrin
Fecal occult blood test
Fecal neopterin
Fecal pyruvate kinase
<b>Other</b>
Rectal nitrous oxide

IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; sgp, soluble glycoprotein

of fecal BAFF may be found not only in IBD, but also in other conditions, such as gastrointestinal neoplasms [51].

### Serum amyloid A (SAA)

Recently, 2 studies proposed SAA as a significant surrogate marker for the evaluation of CD activity. SAA is an acute phase protein, shown to correlate closely with endoscopic activity ( $r=0.64$ ,  $P<0.01$ ) [29], with an AUC between 0.77-0.81 [29,30] for the classification of macroscopic and microscopic mucosal inflammation.

### MicroRNA-320a

MicroRNAs are small non-coding RNA molecules responsible for RNA silencing and post-transcriptional regulation of gene expression [72]. In colitic mice, microRNA-320a levels were demonstrated to correlate with disease

activity [73], confirmed in a recent preliminary study with CD and UC patients [74]. In detail, microRNA-320a showed strong correlation with the SES-CD score in CD patients ( $r^2=0.76$ ;  $P<0.001$ ).

### Composite biomarker tests

In a recent study, the combination of certain biomarkers (eotaxin-1, SAA, interleukin [IL]-6, IL-8) was shown to be highly sensitive (90.7%) and accurate (AUC 0.84), with a PPV of 86.7% for the diagnosis of endoscopic activity in IBD patients, compared to the widely used clinical indices (Harvey Bradshaw index and Simple Clinical Colitis Activity Index), CRP and FC. Nevertheless, more studies are needed to elucidate the role of this composite biomarker in the assessment of CD activity [75].

Similarly, another composite test, the endoscopic healing index [76], commercially available and known as the PROMETHEUS® Monitr™ Crohn's Disease Test, comprises 13 serum proteins (angiopoietin 1 and 2, CRP, SAA1, IL-7, extracellular matrix metalloproteinase inducer, matrix metalloproteinases 1, 2, 3 and 9, transforming growth factor  $\alpha$ , carcinoembryonic antigen-related cell adhesion molecule 1, and vascular cell adhesion molecule 1) and it was shown to distinguish endoscopic remission with excellent accuracy, in biologic-naïve, early CD patients (AUC 0.962). However, its diagnostic accuracy in chronic biologic experienced patients was shown to be only moderate (AUC 0.693), whilst it was not demonstrated to outperform the diagnostic accuracy of FC in both patient groups.

### Cross-sectional imaging modalities

The introduction of computed tomography (CT) enterography/enteroclysis (CTE/CTEc) and magnetic resonance enterography/enteroclysis (MRE/MREc) has contributed significantly to the diagnosis and evaluation of CD by allowing the visualization of the entire small intestine. In particular, cross-sectional imaging modalities were demonstrated to be highly reliable, objective and accurate in the classification of CD activity, allowing the evaluation of disease behavior, the identification of disease-related complications and the assessment of treatment response [77].

Both CT and MR require that patients are fasted 4-6 h prior to the study. Afterwards, 1.5-2 L hyperosmolar oral contrast solution is administered orally to the patient at regular intervals, over a period of approximately 40-60 min. Usually, the solution consists of mannitol, polyethylene glycol or a barium sulfate mixture containing a non-absorbable additive (e.g., sorbitol, polyethylene glycol). Additionally, patients may be given spasmolytics to reduce enteric peristalsis, i.e., hyoscine-N-butylbromide (Buscopan®) or glucagon [78,79].

Nevertheless, patients may feel discomfort associated with the procedure, as the use of hyperosmolar agents may result in abdominal pain, nausea, vomiting and diarrhea. In addition, the

use of hyoscine-N-butylbromide is contraindicated in patients with cardiac arrhythmia, narrow angle glaucoma or non-obstructive prostatic hypertrophy, whereas the use of glucagon is contraindicated in patients with pheochromocytoma. Lastly, cross-sectional modality procedures are costly and may require leave from work, whilst the documentation of disease remission and response to treatment may lag compared to endoscopic or clinical remission.

The difference between enterography and enteroclysis is that in the former the contrast agent is administered through the oral route, whereas in the latter, the contrast agent is administered through a nasojejunal tube, resulting in distention of the jejunum.

### CTE/CTEc

CTEc findings were demonstrated to correlate significantly with active mucosal inflammation ( $r=0.7$ ,  $P<0.0001$ ) [80]. In general, CT studies were shown to have 84.3% sensitivity and 95.1% specificity for the diagnosis of inflammatory bowel disease [81]. In particular, the results of one study with CD patients indicated that the performance of CTEc had 89% sensitivity, 100% specificity, 100% PPV, and 89% NPV in the discrimination of CD activity [82].

Characteristic CTE/CTEc findings in patients with active CD are the detection of transmural thickening, hyperdense mucosa, dilatation of the mesenteric veins (“comb sign”), fat wrapping and the presence of lymph nodes [77,83-85]. Despite the comparable diagnostic performance of both modalities, CTE is preferred to CTEc in the investigation of the small bowel, as it does not require the use of a nasojejunal tube to administer the contrast agent and exposes patients to less ionizing radiation. However, in cases where there is a need to examine the proximal small bowel/jejunum, CTEc is preferred.

Lastly, the diagnostic performance of CT enterography in the evaluation of CD activity is comparable to that of MRE [86-92]; nevertheless, given the concerns regarding patient exposure to ionizing radiation and complications associated with the use of intravenous contrast media [93-96], the use of MRE is preferred.

### Low-dose CT

The development of a new low-dose ionizing radiation CT enterography technique was shown to be highly specific (84-97%) and sensitive (85-94%) in the detection of CD activity, with patients being exposed to a lower radiation risk compared to that of standard CTE [97,98].

### Dual-energy CT (DECT)

DECT has also been used in CD evaluation. DECT is an iodine-based CT imaging technique that improves tissue characterization by examining tissue behavior with 2 separate

X-ray energy beams. In a small number of studies, DECT was demonstrated to correlate strongly with CDAI ( $r=0.744$ ) [99], allowing the accurate discrimination between normal and affected bowel segments (AUC 0.96) [100], and enabling the quantification and objective evaluation of CD activity [101] as well as discrimination between fibrotic and inflammatory lesions [99].

### MR enterography

MR enterography is the main modality for the noninvasive evaluation of the small bowel in CD patients, as it allows high-contrast resolution, multiplanar capability and cine-imaging without exposing patients to ionizing radiation, enabling the objective, accurate and reproducible assessment of CD activity [102]. Moreover, it allows the inflammatory burden to be quantified via specific indices.

The use of contrast agents and bowel distention is crucial for the proper visualization of the bowel wall and the mesenteric veins. Characteristic findings of CD activity in MR are submucosal edema, enlarged bowel wall ( $>3$  mm), lymphadenopathy, fat wrapping and the “comb” sign [77,103].

The overall sensitivity and specificity of MR imaging in CD diagnosis were shown to be 78% and 85% respectively, whereas the evaluation of bowel movement may add valuable information for the diagnosis [104]. However, the performance of MRE in the identification of mucosal inflammation in the jejunum is limited by the suboptimal distention of the proximal small bowel [78].

### MR indices

Newly developed MR indices for the quantification of CD activity, namely the MR index of activity (MaRIA) and the Clermont score, offer reliability and objectivity in the assessment of disease activity [105]. The aforementioned indices are strongly correlated with the CDEIS, demonstrating high diagnostic accuracy in the prediction of mucosal ulceration during endoscopy (73.9% and 74.0%, respectively), high specificity (82.1% and 81.3%, respectively) and high NPV (82.1% and 82.4%, respectively) [106]. In particular, the MaRIA index was demonstrated to correlate closely with CDEIS ( $r=0.82$ ,  $P<0.001$ ), with a high AUC for the discrimination of active disease and the detection of ulcerative lesions (0.891 and 0.978, respectively) [107]. Nevertheless, their complexity means that their use is limited to clinical trials.

### Diffusion weighted imaging (DWI) MRI

DWI is a specific MRI technique, based on the random movement of molecules in fluids inside body tissues [108]. The impedance of water molecule diffusion is affected by the extent of tissue cellularity and the presence of intact cell membranes, and can be quantitatively assessed using the apparent diffusion

coefficient (ADC) value. The use of DWI alleviates the need for contrast agents during MRI, and it was shown to be a reliable alternative to intravenous gadolinium based MRI in the identification of inflammation, necrosis and malignancy [109]. The accuracy of DWI in the detection of CD activity was shown to be comparable or superior to that of MRE, whilst ADC values demonstrated excellent correlation with the Harvey-Bradshaw index, enabling the quantification of mucosal inflammation with excellent sensitivity and specificity (97.4% and 99.2%, respectively) [102,110-113].

## Ultrasound

The role of conventional ultrasound in the investigation of CD is limited. However, the use of high frequency ultrasound probes (5-17 MHz) permits the noninvasive and highly accurate investigation of small-bowel CD, disease-related complications, postoperative recurrence and disease monitoring in patients under treatment, with a diagnostic performance comparable to that of MRE [77,114,115]. CD findings during ultrasonography include the “target sign” (hyperechoic center with a sonolucent rim >0.5 cm), the failure of loop distention after oral contrast ingestion (“stiff loop”), bowel wall thickness  $\geq 3$  mm, small bowel dilation  $\geq 2.5$  cm, small bowel stenosis <1 cm, presence of fistulas, mesenteric enhancement, lymph nodes, and abscesses [116,117].

Wall thickening and increased vascularity of the thickened segments are the most significant findings in CD assessment, correlating strongly with disease activity [118-121]. In detail, wall thickness <3 mm is indicative of endoscopic remission and mucosal healing, with a sensitivity and specificity of 88% and 93%, respectively [118,119,121,122]. However, wall thickness can be associated with both inflammation and fibrosis.

### **Small intestine contrast ultrasonography (SICUS) and contrast-enhanced ultrasound (CEUS)**

The use of oral and intravenous ultrasound contrast agents has been demonstrated not only to improve image quality and diagnostic performance, but also to facilitate the discrimination between fibrosis and inflammation [77,104,123-125]. In detail, SICUS requires the ingestion of a polyethylene glycol solution, which results in bowel distention and better delineation of the wall layers, while the intravenous application of a contrast agent (CEUS) allows the assessment of tissue perfusion.

The sensitivity of conventional ultrasonography in the identification of small-bowel lesions was demonstrated to range between 57-96%, whereas SICUS was shown to increase sensitivity up to 96-100% [116]. Furthermore, SICUS detects postsurgical recurrence in CD patients with a sensitivity and specificity of 99% and 74%, respectively [126].

Similarly, the detection of hypervascularity and hyperperfusion in intestinal segments with the use of CEUS is strongly associated with disease activity in patients with established CD. Depending on the parameter used for the

evaluation of mural micro-vascularity (maximum peak intensity or wash-in slope coefficient), the use of CEUS was shown to result in high sensitivity (97% and 86%, respectively), as well as specificity (83% for both) [127]. Moreover, CEUS improves the assessment of disease activity [128-130] and allows the accurate prediction of postsurgical recurrence, with studies estimating its sensitivity, specificity and accuracy up to 98%, 100% and 98.3%, respectively [131,132].

## Doppler

In CD patients the affected wall segment is characterized by hyperemia and vascularization. The aforementioned bowel wall changes can be identified with power or color Doppler, which enables the characterization of the number and diameter of wall vessels [133]. The Limberg score is a semi-quantitative index, developed to assess CD activity. By evaluating vascularization with the help of the Doppler signal in thickened bowel segments (>4 mm), 4 grades of severity are assigned: a) Grade 1, no vascularization; b) Grade 2, segmental short stretches of vascularity; c) Grade 3, long stretches of vascularity; and d) Grade 4, long stretches of vascularity extending into the mesentery. Although the association of the Limberg score with the histologic activity was shown to be poor ( $\kappa=0.4375$ ), it demonstrated good correlation with endoscopic findings, in particular the SES-CD score ( $r=0.709$ ) [134-137].

Besides the role of Doppler ultrasonography in the evaluation of intestinal lesion vascularity, its use in the assessment of abdominal aortic and superior mesenteric artery (SMA) flow has been proposed as an adjunctive method in the evaluation of CD activity, as hyperdynamic mesenteric circulation is a characteristic of CD [144]. Despite the conflicting results of various studies, SMA measurements were not able to distinguish disease activity among patients, in contrast to aortic measurements, where significant differences correlated with disease activity confirming hyperdynamic circulation in CD [138-144].

## Positron emission tomography (PET)

PET has shown promising results in the assessment of CD activity, enabling the identification of inflammatory segments in the large and small bowel. In detail, the uptake of  $^{18}\text{F}$ -fluorodeoxyglucose from the inflamed bowel segments is proportional to the transmural inflammatory infiltrate, whilst the use of the standardized uptake value in PET enables CD activity grading.

Various studies have indicated that PET has excellent specificity and PPV, as well as good sensitivity and NPV in the prediction of bowel segments with moderate/severe inflammatory activity (82% sensitivity, 97% Specificity, 96% PPV, 88% NPV, 91% accuracy [145]). Nevertheless, the correlation of PET with endoscopic findings/SES-CD was shown to be moderate/low ( $r=0.48-0.62$ ) [146-148].

Finally, the use of PET technology suffers from significant limitations, as it exposes patients to ionizing radiation and

it is an expensive modality not widely available, requiring radiopharmaceuticals which are difficult and costly to produce.

In accordance with the joint, evidence-based, 2013 consensus of the European Crohn's and Colitis Organization and the European Society of Gastrointestinal and Abdominal Radiology [77], current evidence cannot support the use of PET in everyday clinical practice.

### CD monitoring in pregnant patients

CD mainly affects patients of reproductive age; thus, it is not uncommon for it to complicate pregnancy in selected cases. Nevertheless, disease activity evaluation in this population can be difficult. Firstly, although endoscopy is considered safe during pregnancy, it should be performed under strong indications and by experienced endoscopists, and it should be postponed until after the third semester when possible [149]. The use of capsule endoscopy is generally not recommended during pregnancy and its use should be restricted to urgent cases that cannot be postponed [150]. Noninvasive monitoring can also be problematic, as biomarkers of inflammation (CRP and erythrocyte sedimentation rate), hemoglobin and serum albumin may be affected in this patient group [151].

Similarly, the results of various studies regarding the role of FC in the evaluation of disease activity in pregnant CD patients are conflicting; thus, its use cannot be recommended [152]. The use of CT should be avoided in pregnant patients because of concerns about fetal radiation exposure. However, despite the concerns about a possible teratogenic effect of gadolinium contrasts, MRE with an adapted protocol for pregnancy is a reliable and safe imaging modality, as a fetal risk has not yet been proven [152,153]. Similarly, gastrointestinal ultrasonography is an accurate tool in disease monitoring during pregnancy enabling the detection of subclinical inflammation, especially in the majority of patients up to 20 weeks of gestation, where both the colon and the terminal ileum can be assessed with no risks for the fetus [154,155].

### Concluding remarks

The number of noninvasive tools for the evaluation of CD activity is continuously growing. Ileocolonoscopy with biopsies remains the reference standard method for the evaluation of mucosal inflammation and response to treatment. However, the transmural and patchy distribution of the inflamed bowel segments, as well as variations regarding disease location and disease behavior make the assessment of disease activity difficult.

CRP was demonstrated to correlate poorly with endoscopic activity, despite the high specificity of abnormal levels in the prediction of mucosal inflammation. Fecal biomarkers, and especially the most studied FC, have been shown to correlate closely with endoscopic activity, despite its higher diagnostic accuracy in the prediction of colonic mucosa inflammation. In the absence of FC, the detection of fecal hemoglobin can be used as a reliable alternative. Promising innovative biomarkers for the prediction of disease activity are fecal BAFF and SAA,

shown to have high diagnostic accuracy in the prediction of CD activity. The outcome of studies investigating the assessment of mucosal inflammation with the use of biomarker indices did not demonstrate a diagnostic advantage compared to the evaluation with FC alone. MR enterography is highly accurate for the detection of distal small bowel CD activity, whilst it allows the evaluation of transmural inflammation and disease-related complications. However, its diagnostic value decreases in proximal and early CD, whilst it is a costly, time-consuming procedure, requiring bowel preparation. The use of ultrasonography with contrast agents is gaining interest as a promising, minimally invasive, objective and highly accurate method in the evaluation of CD activity.

Despite the continuous development and progress regarding diagnostic methods for the assessment of CD activity, an ideal diagnostic modality is still lacking. Nevertheless, when endoscopy is not an option for the evaluation of disease activity, physicians should not rely solely on CRP levels and symptoms. In particular, disease activity should be assessed with objective and noninvasive tools, namely fecal biomarkers (e.g., FC), MR enterography and ultrasonography (SICUS or CEUS). The choice of these should be individualized according to the patient's disease phenotype and severity, as well as their expected disease course based on risk factors.

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