



Mini Review

The Role of Confocal Laser Endomicroscopy in Disorders of Gut–Brain Interaction: A Narrative Review



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Abstract

Disorders of gut–brain interaction (DGBIs) encompass some of the most common gastrointestinal disorders and affect up to 40% of the general population. Despite their inherent heterogeneity and diverse clinical manifestations, many of the underlying pathophysiological mechanisms overlap among different DGBIs. Activation of the gastrointestinal mucosal immune system at a low level (“low-grade inflammation”) and impairments in gut epithelial barrier structure and function have been reported to play a key role in the pathophysiology of multiple DGBIs, but these alterations cannot be detected using routine clinical testing. Confocal laser endomicroscopy (CLE) is an established, readily available technology that can be added to standard gastrointestinal endoscopy, enabling “real-time” microscopic evaluation of the gastrointestinal surface epithelium. CLE has been found to be capable of identifying gastrointestinal mucosal abnormalities that are reflective of epithelial barrier impairment and/or low-grade immune activation. Over the past several years, multiple intriguing studies have utilized CLE as a clinically applicable tool to evaluate the intestinal mucosa in patients with various DGBIs. The aim of this narrative review is to summarize the available literature on the role of CLE in patients with DGBIs and to provide a perspective on the use of this technology in DGBIs.

Introduction

The disorders of gut–brain interaction (DGBIs) encompass several common gastrointestinal syndromes that, in aggregate, affect up to 40% of the general population.^{1,2} Irritable bowel syndrome (IBS), functional dyspepsia (FD), functional constipation and diarrhea, among others, represent some of the most common DGBIs. Despite their inherent heterogeneity and the wide constellation of gastrointestinal symptoms in various DGBIs, many of the proposed underlying pathophysiologic mechanisms overlap among different DGBIs.^{3,4} Another common feature of DGBIs is the lack of identifiable abnormalities to explain symptoms on routinely applied diagnostic evaluations, including standard gastrointestinal endoscopy.^{5,6} Since individuals with DGBIs report chronic symptoms, often with fluctuating intensity, they are frequently subjected to repeated (“normal”) endoscopic evaluations, resulting in the po-

tential for procedural complications, patient dissatisfaction, high cost, and an associated burden on the healthcare system.⁷

The pathogenesis of DGBIs is complex and heterogeneous, with contributions from a variety of peripheral and central mechanisms, including impairments in gastrointestinal motility, visceral sensation, gut immune activation, intestinal permeability, microbiota, brain-gut interactions, and psychosocial distress.⁸ Furthermore, a variety of factors such as diet, stress, and acute gastrointestinal infections have been implicated in triggering the development of DGBIs by affecting many of these pathophysiological mechanisms.^{9–13} Activation of the gastrointestinal mucosal immune system at a low level (“low-grade inflammation”) and impairments in gut epithelial barrier structure and function have been proposed to play a key role in the pathophysiology of multiple DGBIs and were associated with various “triggers” (e.g., food exposure, infection, stress).^{12,14,15} For example, multiple studies report microscopic intestinal inflammation, most commonly identified by increased eosinophil and mast cell counts on histologic samples from patients with FD and IBS.^{16–18} In addition, higher levels of cytokines (e.g., interleukin-1 β , tumor necrosis factor α) and enhanced homing of small-bowel T lymphocytes have been found in patients with FD, which has been associated with greater severity of dyspeptic symptoms and delayed gastric emptying.¹⁹ Impairments in intestinal epithelial barrier structure and function have also been reported in multiple DGBIs, including FD and IBS.^{11,15,20,21} For example, greater mucosal permeability was measured using an

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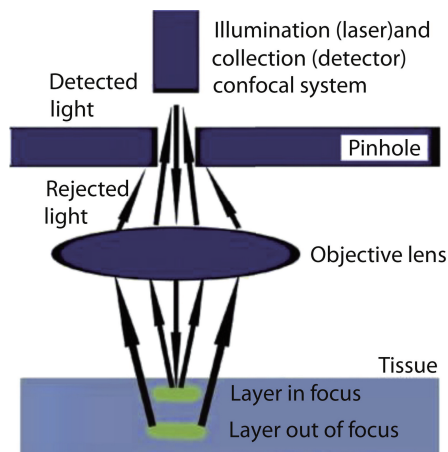


Fig. 1. Basic technical principle of confocal laser endomicroscopy. Reprinted with permission from ASGE (American Society for Gastrointestinal Endoscopy).²⁷

Using chamber in duodenal biopsy samples from FD patients when compared with asymptomatic individuals.²⁰ Overall, these findings draw a connection between mucosal immune activation, gut barrier function, and symptoms in subgroups of patients diagnosed with DGBIs. Consequently, identifying these gastrointestinal mucosal abnormalities may be beneficial in improving the clinical management of these patients based on their underlying pathophysiology. Unfortunately, there is a lack of clinically applicable tools that can reliably detect subtle gastrointestinal mucosal inflammation and/or epithelial barrier impairment.

Confocal laser endomicroscopy (CLE) is an endoscopic imaging modality that can be added to standard gastrointestinal endoscopy, allowing high-resolution, real-time scanning of the gut mucosa at a microscopic level.²² CLE is capable of dynamically visualizing abnormalities in the epithelial structure and function, including visualization of extrusion zones (“epithelial gaps”) left in the mucosal surface after intestinal epithelial cells have been shed.²³ These abnormalities are considered reflective of epithelial barrier impairment and/or “low-grade” immune activation—factors implicated in the pathophysiology of DGBIs. A variety of CLE parameters and scoring systems have been proposed to quantify these abnormalities (e.g., number/density of epithelial gaps, extravasation of intraluminal contrast/fluorescein, presence of cell shedding, etc.).^{22–30} Prior studies have found that CLE can detect microscopic abnormalities in endoscopically normal-appearing mucosa among patients with “organic” gastrointestinal disorders, such as inflammatory bowel disease (IBD) in remission,²⁴ microscopic colitis, and celiac disease.^{25,26} Over the past several years, several intriguing studies have utilized CLE as a clinically applicable tool to evaluate the intestinal mucosa in patients with various DGBIs. This narrative review aims to summarize the currently available literature on the role of CLE in patients with DGBIs.

Technical overview of CLE

CLE is an established technology that provides “real-time”, exceptionally high magnification and resolution endoluminal gut imaging.²² The technological principle of CLE is based on illumination of tissue with a low-power laser and detection of fluorescent light reflected from the tissue through a pinhole (Fig. 1).²⁷ The illumination

and collection systems are aligned in the same focal plane. The laser light is focused on a selected tissue depth, and reflected light is refocused to the detection system by the same lens. CLE has high spatial resolution and assesses tissue architecture at the focal plane since it only detects reflected light refocused through the pinhole. Images from the scanned area are reconstructed by a computer, which allows *in vivo* imaging of the visualized tissue segment.

CLE requires application of a contrast agent to enhance the fluorescence signal from the tissue and generate images with adequate resolution. Clinically, intravenous fluorescein has been utilized as a contrast agent, administered immediately before scanning at a dose of 2.5–5 mL, which allows CLE imaging for approximately 30 min.²⁸ Intravenous fluorescein distributes throughout the vasculature and allows microscopic visualization of the gut surface epithelium, including the cellular contour and lamina propria, although it does not stain cell nuclei.²⁹ Topical contrast agents for nuclear staining have been developed and applied via a spraying catheter during gastrointestinal endoscopy but are not typically used in clinical CLE applications.²² Currently, a probe-based CLE (pCLE) system is commercially available that uses a standalone confocal probe containing laser fibers that can be passed through the working channel of most conventional gastrointestinal endoscopes.³⁰ The pCLE system also includes a console with a laser scanning unit, light source, computer, and monitor, enabling real-time microscopic visualization of the epithelium that is projected in parallel with macroscopic images during standard gastrointestinal endoscopy (Fig. 2).³¹ Notably, CLE technology was initially applied using an endoscope-based CLE system, which is no longer commercially available, although some studies were performed using this system. While the two systems are generally comparable from a technical perspective, some differences have been identified (e.g., ease of operation and temporal resolution were preferable with the pCLE system).

Clinical applications of CLE in DGBIs

Irritable bowel syndrome

Most of the literature on CLE in DGBIs has been acquired in patients with IBS. A study by Turcotte and colleagues was the first to utilize CLE in IBS patients (any subgroup) to quantify the presence of intestinal epithelial breaks/“gaps”.³² In this prospective, controlled study from a tertiary referral center, 16 IBS patients and 18 healthy controls were evaluated with pCLE in the terminal ileum during routine diagnostic colonoscopy. The study compared intestinal epithelial gap density (average number of epithelial breaks per 1,000 epithelial cells), determined by pCLE, between IBS patients and controls. The epithelial gap density by pCLE was deemed a surrogate of epithelial cell extrusion rate, representing a potential mechanism for the increased intestinal permeability observed in IBS.^{23,33} Indeed, the study found that IBS patients had a significantly higher density of epithelial gaps in the terminal ileum, as measured by pCLE, compared with healthy controls (median of 32 vs. 6 gaps/1,000 cells in IBS vs. controls, $P < 0.001$). The authors also compared epithelial gap density between IBS patients and a cohort of 27 IBD patients who, in a previous study, underwent colonoscopy with pCLE in the terminal ileum using the same protocol.³⁴ This comparison revealed that although gap density by pCLE is significantly higher in IBS patients compared with healthy controls, the increased gap density in IBS is significantly lower than in IBD patients (most IBD patients had active disease that did not involve the terminal ileum).

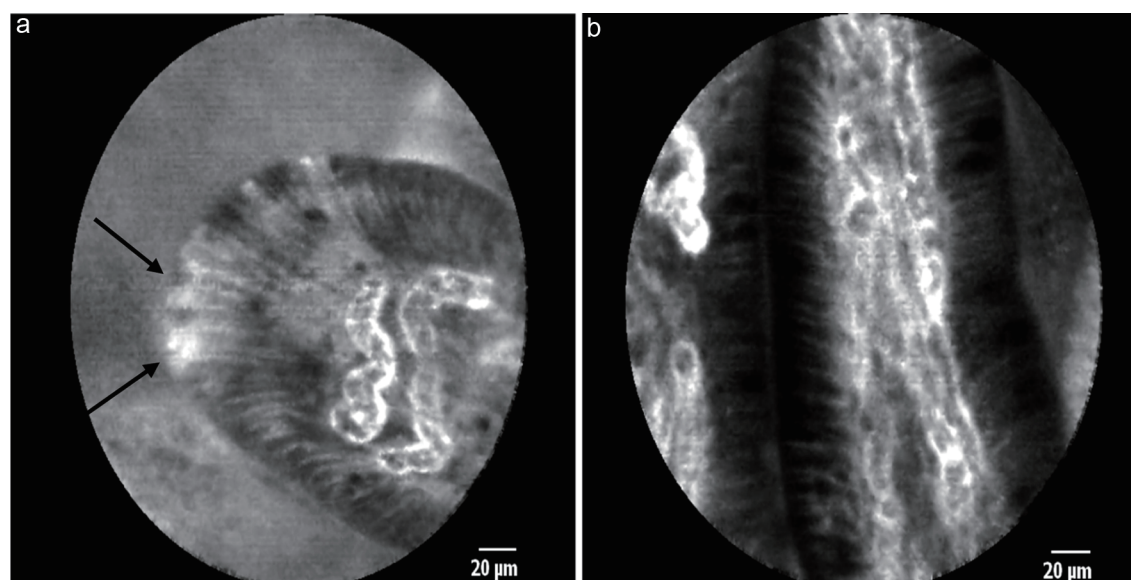


Fig. 2. Representative pCLE images of duodenal villi. (a) DGBI patient with several adjacent epithelial gaps (black arrowheads indicating epithelial gaps); (b) healthy individual without epithelial gaps. DGBI, disorder of gut-brain interaction; pCLE, probe-based confocal laser endomicroscopy. Adapted with permission from Nojkov *et al.*³¹

In another prospective, controlled, single-blind study from Ecuador, pCLE images and endoscopic biopsies were obtained from each colonic segment (cecum through rectum) in 37 IBS patients (any subgroup) and 37 controls (individuals undergoing colonoscopy for colorectal cancer screening).³⁵ This study evaluated multiple “inflammation criteria” on CLE (altered crypt architecture, epithelial gaps diameter, fluorescein leakage into the lumen, and dilation/branching of mucosal blood vessels) in parallel with histologic assessment of inflammation per the Geboes scale from biopsies in each colon segment.³⁶ The proportion of pCLE images with any “inflammatory” CLE criteria was reported per group. Signs of colonic mucosal inflammation were present in 65.8% of pCLE images from IBS patients compared with 23.4% of images from controls (odds ratio, 6.28; 4.14–9.52; $P < 0.001$), and 54% (20/37) of IBS patients had pCLE inflammatory changes in >3 colon segments. Similarly, a Geboes score > 0 (indicative of at least mild inflammation) was observed in 60.8% of biopsies from patients in the IBS group compared with 27.5% of biopsies from the control group. The authors reported overall high diagnostic accuracy of pCLE (sensitivity/specificity of 77–95% in different colon segments) for detecting inflammatory changes in IBS relative to histologic analysis of targeted colon biopsies. However, the Geboes histologic score used in this study was developed for assessment of inflammation in ulcerative colitis and has not been validated in patients with IBS. Furthermore, the applied CLE “inflammation criteria” in this study differed from the epithelial barrier density assessment used in the study by Turcotte and colleagues.³²

A small study from China utilized CLE in addition to electron microscopy of mucosal biopsy samples to evaluate rectosigmoid epithelial cellular structure in 10 patients with IBS-diarrhea and 10 healthy controls.³⁷ Crypt arrangement, epithelial integrity, as well as fluorescein content in lateral intercellular spaces and in the gastrointestinal lumen were analyzed on CLE, although no quantitative data for these criteria are provided in this report. The study found no difference in CLE analysis of the epithelium between IBS-D patients and healthy controls, but architectural epithelial al-

terations were found on electron microscopy in IBS patients.

Other studies have utilized CLE in IBS patients to evaluate the intestinal mucosa in relation to endoscopic intraluminal application of various food constituents and to identify patients with “atypical”, presumably immune-mediated, food reactions.^{38–40} Fritscher-Ravens and colleagues were the first to introduce this concept of real-time intestinal mucosa CLE imaging before and immediately after endoscopic food application.^{38,39} In a pilot study of 36 IBS patients and 10 controls, four diluted foods known to induce symptoms (cow’s milk, wheat, soy, and yeast) were endoscopically administered into the duodenum after a (normal) baseline endoscopic/CLE exam.³⁸ The immediate post-food challenge CLE exam showed a real-time “response” in 22 of 36 IBS patients and in none of the 10 controls. Observed post-challenge CLE changes included increased density of epithelial gaps ($P = 0.001$), intraepithelial lymphocytes ($P = 0.004$), and widened intervillous spaces ($P = 0.0001$). After dietary restriction of the foods that induced these CLE changes, CLE-positive patients had 50% and 74% improvement in IBS symptoms at 1 and 12 months, respectively. In a subsequent, larger study of 108 IBS patients from the same group that applied the same “diagnostic” CLE criteria, 70% were found to be CLE-positive and most (61%) reacted to intraduodenal wheat.³⁹ CLE-positive patients had a significantly higher prevalence of atopic disorders compared with CLE-negative patients/controls ($P < 0.05$), and duodenal biopsy analysis in CLE-positive patients showed increased density of intraepithelial lymphocytes, upregulated claudin-2, and decreased levels of occludin. Furthermore, eosinophil degranulation and eosinophil cationic protein levels were higher in duodenal aspirates from CLE-positive patients than controls ($P = 0.03$), suggesting an “atypical” food allergy in these patients.

However, not all studies have found CLE to be accurate in identifying atypical mucosal reactions after intraluminal food application in IBS patients. A prospective, double-blind, multicenter study from Germany by Bojarski and colleagues specifically evaluated the accuracy of CLE in diagnosing wheat sensitivity among

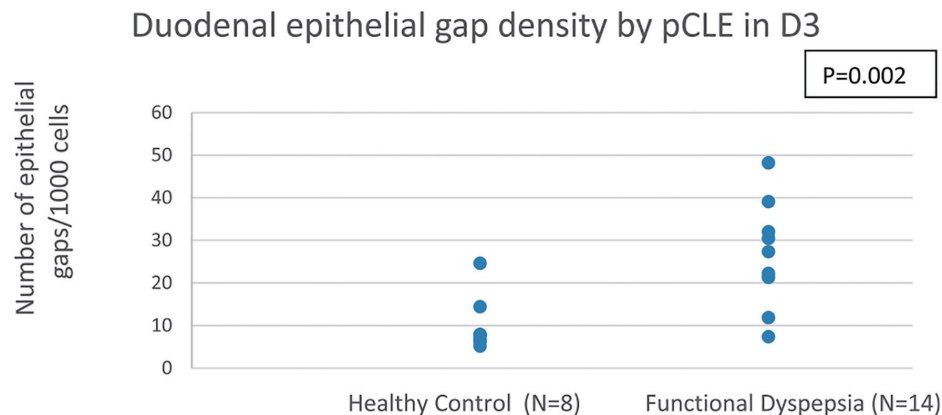


Fig. 3. Epithelial gap density assessed by probe-based confocal laser endomicroscopy (pCLE) in the third portion of the duodenum (D3) in healthy controls and functional dyspepsia patients. Reprinted with permission from Nojkov *et al.*³¹

130 IBS patients.⁴⁰ In this study, results of CLE completed after intraduodenal wheat application (as an index test) were compared with symptomatic response to a gluten-free diet (GFD) as a reference standard for the diagnosis of wheat sensitivity. The same CLE criteria for identifying a positive reaction were used as in the studies by Fritscher-Ravens and colleagues (a combination of intraluminal fluorescein leakage and increased intervillous spaces or intraepithelial lymphocytes).^{38,39} After two months of a GFD, 56% (74/130) of IBS patients improved symptomatically, but CLE correctly identified only 51% (38/74) of these patients and was also positive in 33% (18/54) of patients who did not respond to a GFD. Based on these results, the authors concluded that CLE has low accuracy (against an empiric GFD trial) for diagnosing wheat sensitivity in IBS, and its use cannot be justified for this purpose.

Functional dyspepsia

CLE has been employed to assess the gastroduodenal mucosa in patients with FD.^{31,41,42} In a pilot controlled study performed at the University of Michigan, symptomatic FD patients ($n = 16$) and asymptomatic healthy individuals ($n = 18$) were assessed with esophagogastroduodenoscopy (EGD) enhanced by duodenal pCLE to evaluate between-group structural epithelial differences. Duodenal biopsies were obtained for standard histology, quantification of mucosal immune cells/cytokines, and immunohistochemistry for inflammatory epithelial cell death termed pyroptosis. Duodenal epithelial integrity was also evaluated by measurements of trans-epithelial electrical resistance (TEER) from biopsied mucosa in a subset of participants. The number of duodenal epithelial gaps on CLE per 1,000 epithelial cells was the primary outcome (same method applied in some IBS studies).^{32,33,38} The study found that FD patients had significantly higher epithelial gap density on CLE in the third portion of the duodenum compared with controls (26.9 ± 9.4 vs. 10.05 ± 6.5 , $P = 0.002$) (Fig. 3).³¹ These mucosal abnormalities corresponded to significant changes in duodenal biopsy samples from FD patients compared with controls, including impaired mucosal integrity by TEER ($P = 0.009$) and increased numbers of epithelial cells undergoing pyroptosis ($P = 0.04$). Furthermore, patients with FD demonstrated altered duodenal expression of claudin-1 and interleukin-6, supporting duodenal barrier impairment and immune activation in FD. There were no significant EGD findings or duodenal abnormalities on standard histology in either FD patients or asymptomatic individuals.

Another study by Ji and colleagues used pCLE to structurally evaluate the gastric epithelium in 58 patients with FD, 20 controls with *Helicobacter pylori* infection, and 20 healthy individuals.⁴¹ Electron microscopy and quantitative immunohistochemistry for mast cells were also performed on gastric biopsy samples. CLE analysis included semiquantitative evaluation (4-point grading scale) of fluorescein luminal leakage and cell shedding in images obtained from 10 standardized sites in the stomach. The study found that the endomicroscopic score for luminal leakage was significantly higher in FD patients than in healthy controls (3.69 ± 3.18 vs. 1.45 ± 1.27 , $P = 0.006$), but the cell shedding score did not differ between the two groups. Patients with *H. pylori* (“inflammatory controls”) had significantly higher pCLE scores (both for luminal leakage and cell shedding) compared with healthy controls and FD patients. Most pCLE alterations in FD were observed in the antrum. The study also found a positive correlation between the luminal leakage score and quantified mast cells in FD patients. Importantly, there was a good correlation between semiquantitative pCLE image analysis and electron microscopy findings ($r_s = 0.83$, $P < 0.01$). Dyspeptic symptom severity did not correlate with pCLE scores.

The concept of CLE evaluation before and after endoscopic intraduodenal diluted food administration was also applied in FD in a recently published study from the University of Leuven in Belgium.⁴² In this randomized, crossover, double-blind, sham-controlled trial, 17 FD patients without food-specific IgE-mediated allergies completed baseline EGD with duodenal CLE followed by 29 repeat EGD/CLE procedures with duodenal nutrient exposure, performed per standardized protocol.⁴³ Six food solutions (wheat, soy, milk, egg white, fish, nuts) were administered in random order during repeat EGD/CLE procedures, and endoscopists were blinded to the administered foods. Interpretation of CLE images was performed in real time during the procedures, and images were assessed for the presence of intraluminal fluorescein leakage and appearance of luminal particles. The presence of these abnormalities in at least two of the four evaluated mucosal spots was considered a “positive” CLE reaction, an approach reported to be reproducible within and between different CLE evaluators.⁴⁴ Duodenal biopsies were obtained at each EGD after CLE and assessed for TEER, trypsinase, and eosinophil-derived neurotoxin (EDN) release. Fourteen patients completed a diet based on CLE reactions to individual foods as well as sham exclusion diets in a randomized, blinded order. The study found acute mucosal alterations after food

challenge in almost all (16/17, 95%) tested patients, and reactions were common to all tested foods (22–50% acute post-exposure CLE reaction per food item). These CLE abnormalities were not associated with changes in intestinal permeability (TEER), systemic tryptase, or tryptase/EDN release from duodenal biopsies. Furthermore, clinical response rates for FD symptom improvement did not differ between CLE-guided and sham diets (4/14 vs. 2/14, $P = 0.41$).

Unspecified DGBIs

There have been several recent uncontrolled studies that utilized CLE to assess heterogeneous patient populations with unspecified DGBIs, including individuals with chronic abdominal pain (e.g., “functional abdominal pain”), irregular bowel habits, and/or self-reported food sensitivities (e.g., “gastrointestinal adverse reaction to food”).^{45–48} An observational study by Gjini and colleagues evaluated 34 patients with chronic abdominal pain in the absence of organic disease using CLE and intraduodenal food exposure (soy, wheat, milk, egg, yeast) during upper endoscopy.⁴⁵ Spontaneous leakage of fluorescein into the duodenal lumen was considered a positive CLE reaction. The study found 68% of patients had a positive CLE response after food exposure (most commonly after soy and wheat), and 70% of these patients reported improvement in abdominal pain severity four weeks after following a diet restrictive of the food that triggered the CLE response. In another observational study from the same group in Germany, 84 patients with various DGBIs (IBS, functional abdominal pain, functional bloating, and functional diarrhea) were evaluated per the same protocol.⁴⁶ The study found that 28% of these patients had intraduodenal fluorescein leakage at baseline and 60% of participants had a positive CLE response to at least one intraduodenal food component. Analysis of duodenal biopsy samples found no differences in standard histology, mast cell/eosinophil counts, or markers of inflammation/IgE-mediated reactions between patients with positive and negative CLE responses. In a subsequent analysis from the same cohort, CLE findings and clinical response after a CLE response-based restrictive diet were analyzed relative to patients’ self-reported food intolerance(s).⁴⁷ This study found approximately 70% positive CLE responses to the duodenal food challenge regardless of self-reported food intolerance status. However, patients with self-reported food intolerance had a much higher rate of symptomatic improvement after CLE-guided dietary restriction compared with patients who did not report food intolerance (79% vs. 14%).

Lastly, a study by Rath and colleagues prospectively evaluated whether assessment of epithelial barrier integrity by CLE during colonoscopy can be used as a screening tool to identify patients with food allergy.⁴⁸ This study included 60 patients with self-reported food intolerances, and 27 (45%) of these patients were reported to have food allergy based on evaluation with symptomatic assessment (relative to food intake), food-specific IgE serologic testing, and skin-prick testing. All participants completed colonoscopy with pCLE in the terminal ileum and at two colonic sites (cecum and rectosigmoid junction). The Watson score was utilized to evaluate barrier dysfunction in the terminal ileum on CLE.²⁴ The study found that 26 of 27 (95%) patients with food allergy and 11 of 33 (33%) patients without food allergy had CLE changes suggestive of barrier dysfunction in the terminal ileum (Watson 2 or 3 score; $P < 0.0001$). The authors suggested a role for CLE imaging of the terminal ileum during routine colonoscopy to better stratify patients with self-reported food intolerances who might need diagnostic work-up for food allergy.

Future perspectives

CLE is an established, globally available technology that can be an adjunct to standard gastrointestinal endoscopy to enable microscopic evaluation of the gastrointestinal surface epithelium in real time.^{27,30} Prior research in animal models and patients with IBD found CLE capable of identifying gastrointestinal mucosal abnormalities that are reflective of epithelial barrier impairment and/or “low-grade” immune activation.^{23,24,49–53} These features enable exciting opportunities to apply CLE in patients with DGBIs, as these mechanisms have been found to be central in the pathogenesis of multiple DGBIs.^{11,15–21}

The currently available literature implementing CLE in patients with DGBIs is scarce and limited but is evolving. Preliminary controlled studies in both patients with IBS and FD,^{31,32,38} utilizing a standardized approach with in-depth analysis of CLE images, found evidence of increased epithelial gap density (increased rate of epithelial cell extrusion that has been associated with inflammatory conditions) in the small intestine of affected patients compared with asymptomatic controls. These data need further validation in larger, multicenter studies with well-defined DGBI patient populations and CLE procedural/analysis protocols. Parallel assessment of biopsied mucosa obtained from areas corresponding to CLE imaging will also enhance the strength of the evidence connecting CLE findings with proposed physiologic functions. Furthermore, standardization and validation of additional quantitative CLE analysis parameters may allow development of scoring systems with “diagnostic” thresholds specific for patients with individual DGBIs.

The role of CLE in the clinical management of patients with DGBIs has not yet been established. A significant proportion of completed work dedicated to CLE in DGBIs involves the concept of endoscopic intraduodenal food constituent application followed by immediate CLE assessment for acute post-exposure mucosal alterations and subsequent dietary restriction based on these results.^{38–40,42–47} While initial preliminary studies and subsequent^{38,39} uncontrolled observational reports found clinical benefits from this approach in a substantial proportion (>50%) of tested patients,^{45,47} two recent double-blind controlled studies were not able to replicate these findings.^{40,42} Furthermore, the pathophysiology explaining observed CLE abnormalities immediately after luminal food application remains unclear, and certain technical and interpretation questions related to the proposed CLE protocol require further study.⁴³

An alternative approach for clinical use of CLE in DGBIs is to utilize its ability to detect inherent microscopic mucosal abnormalities (alterations in epithelial barrier structure/function, “low-grade” immune activation) in subsets of patients and evaluate whether these findings are predictive of clinical response to selected therapies that are known to modulate these mechanisms (e.g., dietary interventions, microbiota manipulation). Such an approach has not been tested in clinical studies but may allow an opportunity to develop CLE as a clinically applicable biomarker and potentially provide a pathway toward personalized care in patients with DGBIs.

Limitations

There are numerous limitations of the currently available literature evaluating the application of CLE in patients with DGBIs. First, the number of available studies is small overall, most studies are from single centers, and many have relatively small sample sizes. Second, studies commonly include not-well-defined DGBI pa-

tient populations, analyze different outcomes, and are frequently uncontrolled. Technically, there is heterogeneity in applied protocols among many of the studies, including location of CLE evaluation in the gastrointestinal tract and interpretation criteria used to analyze the gastrointestinal epithelium. Furthermore, while the reproducibility of qualitative CLE image analysis for acute food-induced reactions has been evaluated in a single study,⁴⁴ the reproducibility of a well-defined CLE criteria set for in-depth quantitative evaluation of barrier integrity/microscopic inflammation needs further evaluation.

Conclusions

CLE is a readily available technology that can be added to standard gastrointestinal endoscopy to allow microscopic evaluation of the gut mucosa. Preliminary studies found evidence of “inflammatory” gut epithelial changes on CLE in patients with DGBIs. CLE has also been studied for evaluation of acute mucosal reactions after intraduodenal endoscopic food application, but studies report mixed results regarding the ability of this approach to predict clinical improvement from CLE-guided dietary restriction. Subsequent research will need to refine this concept and further validate the diagnostic accuracy of CLE in identifying DGBI patients with impaired epithelial barrier structure/function and/or low-grade inflammation. Additional pathways to explore the role of CLE as a clinical biomarker in patients with DGBIs are available and will need to be studied in future research.

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Conflict of interest

BN has been an Editorial Board Member of *Journal of Translational Gastroenterology* since 2023. The author declares no other conflict of interest related to this publication.

Author contributions

BN is the sole author of the manuscript, and approved the final version and publication of the manuscript.

Ethical statement

No new human or animal study was conducted for this narrative review. The clinical pCLE images in Fig. 2 were de-identified and reprinted with permission from the original publication. The author confirms that the use of these images complied with the ethical approval/consent requirements of the original study.

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