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Shiha, M.G. orcid.org/0000-0002-2713-8355, Yusuf, A. and Sanders, D.S. (2024) Role of endoscopy in the diagnosis of coeliac disease: a narrative review. Translational Gastroenterology and Hepatology, 9. 51. ISSN 2415-1289

https://doi.org/10.21037/tgh-23-122

Review Article

Role of endoscopy in the diagnosis of coeliac disease: a narrative review

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Contributions: (I) Conception and design: MG Shiha, DS Sanders; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: MG Shiha, A Yusuf; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Coeliac disease (CD) is a common autoimmune disorder triggered by gluten consumption in genetically predisposed individuals. CD is characterised by chronic inflammation in the small bowel mucosa with an influx of lymphocytes, followed by crypt hyperplasia and villous atrophy. The gold standard test to diagnose CD is endoscopy with duodenal biopsies. However, variations in practice between endoscopists can lead to missed diagnoses. This review aims to discuss the role of endoscopy in the diagnosis of CD, highlighting the performance measures of endoscopy in CD and the advancement in endoscopic techniques for the optical diagnosis of villous atrophy.

Methods: We searched PubMed and Google Scholar from their inception to December 2023 for relevant articles on the role of endoscopy in CD. Two authors reviewed these references, and relevant studies were included in the discussion section of this review.

Key Content and Findings: We provide an up-to-date assessment of the diagnostic accuracy of endoscopic markers of CD and the performance of enhanced endoscopic imaging to identify villous atrophy during endoscopy. We propose a set of benchmarks for endoscopy in CD and discuss the potential role of artificial intelligence (AI) in the endoscopic diagnosis of CD.

Conclusions: Performing high-quality endoscopy and identifying strategies to reduce inter-endoscopist variations may reduce missed diagnoses. Adopting advanced endoscopic techniques and embracing new technologies such as AI could enhance diagnostic accuracy and improve patient care.

Keywords: Coeliac disease (CD); endoscopy; biopsy; transglutaminases

Received: 08 November 2023; Accepted: 01 March 2024; Published online: 09 May 2024.

doi: 10.21037/tgh-23-122

View this article at: https://dx.doi.org/10.21037/tgh-23-122

Introduction

Coeliac disease (CD) is the most common autoimmune enteropathy, affecting approximately 1% of the population worldwide (1). CD is characterised by an immune-mediated response to gluten, a protein commonly found in wheat, barley and rye, resulting in intestinal villous atrophy in genetically predisposed individuals (2). This leads to nutritional deficiencies due to the malabsorption of nutrients and a wide array of gastrointestinal and extraintestinal symptoms. The diagnosis of CD typically involves a combination of serological testing with tissue-transglutaminase or endomysial antibodies, followed by

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Table 1 The search strategy summary

Items	Specification
Date of search	November & December 2023
Databases and other sources searched	PubMed & Google Scholar
Search terms used	We used combinations of the following subject heading terms and keywords "celiac disease" OR "coeliac disease" AND "endoscopy" OR "capsule endoscopy" OR "artificial intelligence"
Timeframe	From inception to 18 December 2023
Inclusion criteria	All study types, including review articles and systematic reviews published in English
Selection process	The literature search was conducted by M.G.S. and A.Y.

endoscopy with duodenal biopsies for those who have positive serology or high clinical suspicion of CD (3).

Increasing awareness about the diverse presentations of patients with CD and the increasing accuracy of serological tests led to a significant rise in the incidence and prevalence of CD over the past two decades (4). Despite this, it is estimated that most people with CD remain undiagnosed or experience substantial delays in diagnosis (5).

In this review, we aim to discuss the role of endoscopy in the diagnosis of CD and the advancement in endoscopic techniques to identify villous atrophy. We present this article in accordance with the Narrative Review reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-122/rc).

Methods

The details of the search strategy for this narrative review are provided in *Table 1*. We searched PubMed and Google Scholar from their inception to December 2023 for relevant articles on the role of endoscopy in CD. Two authors (M.G.S. & A.Y.) reviewed these references and relevant studies were included in the discussion section of this review.

Discussion

Endoscopic markers of CD

The loss of small bowel folds in patients with CD was first recongised in the 1930s. The "moulage sign" by Kantor described the featureless appearance of the dilated jejunal loops following the introduction of contrast media, resembling a tube into which wax has been poured (6). Decades later, the advent of endoscopy allowed the direct visualisation of the small bowel mucosa and the acquisition of duodenal biopsies to confirm the diagnosis of CD. The earliest reported endoscopic features of CD were scalloping and loss of duodenal folds (7,8). Initially routine duodenal biopsies were being taken at endoscopy for all patients with non-specific gastrointestinal symptoms. Bardella *et al.* reported a low diagnostic yield of routine duodenal biopsies in patients with dyspepsia presenting to endoscopy, with only 3 cases out of 517 (0.5%) found to have villous atrophy (9). A similar low prevalence of CD was found in a large Finnish study of open-access endoscopy, where routine duodenal biopsies confirmed CD in 0.7% of 5,347 patients with dyspepsia and in 0.6% of 2,974 patients with reflux symptoms (10). Therefore, owing to the low diagnostic yield and the high associated costs, routine duodenal biopsies were not recommended for patients with non-specific gastrointestinal symptoms and low pre-test probability of CD. Currently, endoscopic markers of CD such as scalloping, mosaic pattern, loss of duodenal folds, fissuring, nodularity, and erosions, are well described (*Figure 1*) (11). Obtaining duodenal biopsies during routine endoscopy in patients with endoscopic markers of CD has been shown to increase the diagnostic yield from 0.1% to 0.8% (12). However, the accuracy of these markers in predicting villous atrophy has been disappointing, especially in patients with partial villous atrophy, with a sensitivity ranging between 50–78.4% (9,13-17) (*Table 2*). Despite this, the recognition of endoscopic markers of CD remains important. In a recent study, almost 1 in 10 patients with newly diagnosed CD had at least one non-diagnostic endoscopy where no duodenal biopsies were taken in the 5 years prior to diagnosis (26). It is likely that some of these patients had endoscopic markers of CD at the index endoscopy, which were not recognised by the endoscopists, leading to significant delays in

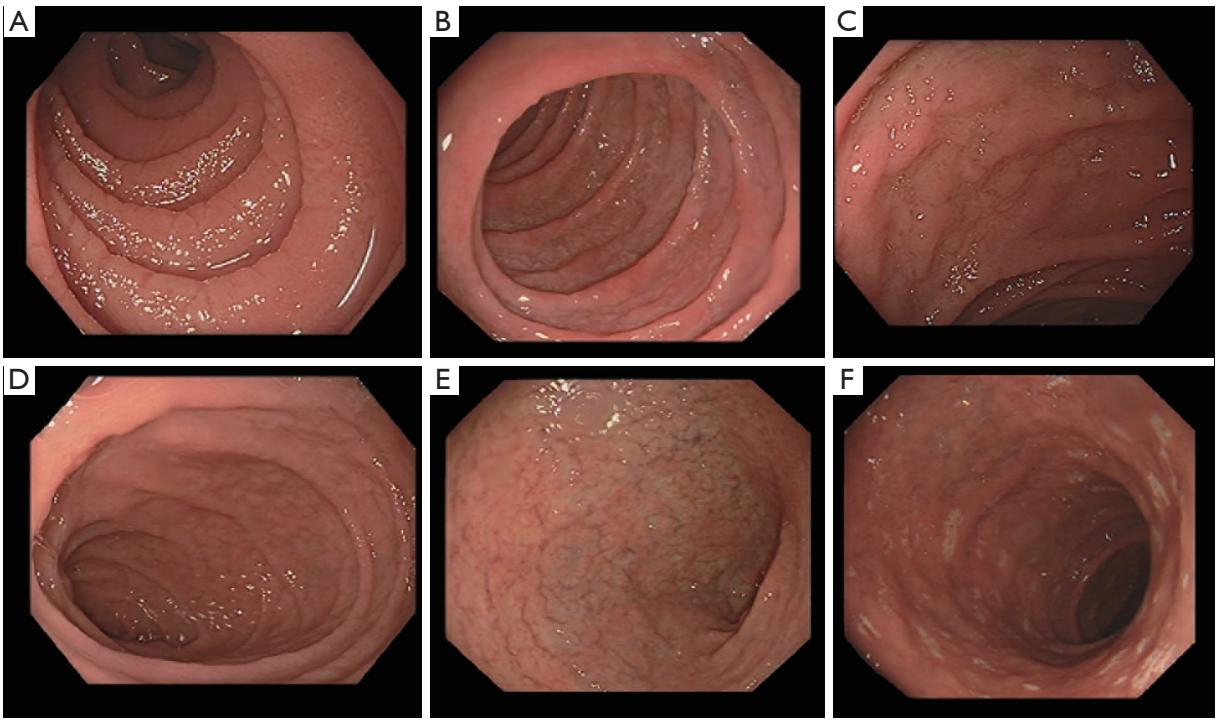

Figure 1 Endoscopic images of the duodenum in patients of coeliac disease showing features of (A) scalloping, (B) mosaic pattern and flattening of duodenal folds, (C) fissuring, (D) nodularity, (E) visible vascular pattern in the duodenal bulb, and (F) mucosal erosions.

Table 2 Accuracy of different endoscopic tools for the detection of villous atrophy in coeliac disease

Endoscopic tool	Sensitivity	Specificity	Studies
White-light endoscopy	50–78.4%	86.1–99.6%	Bardella *et al.* (9)
			Dickey *et al.* (13)
			Oxentenko *et al.* (14)
			Barada *et al.* (15)
			Penny *et al.* (16)
			Raju *et al.* (17)
Water immersion technique	85–90.9%	99–99.5%	Gasbarrini *et al.* (18)
			Cammarota *et al.* (19)
Dye-based chromoendoscopy	94%	99%	Niveloni *et al.* (20)
Magnification endoscopy	86.4–95%	74.4–99%	Raju *et al.* (17)
			Badreldin *et al.* (21)
			Banerjee *et al.* (22)
I-Scan	75–96%	63–86.8%	Penny *et al.* (16)
			Iacucci *et al.* (23)
Narrow band imaging	93%	95%	Shiha *et al.* (24)
Capsule endoscopy	89%	95%	Rokkas *et al.* (25)

Table 3 Suggested performance measures for endoscopy in patients with coeliac disease

Clinical domain	Suggested performance measures
Indication	Appropriate indication of upper GI endoscopy with available serology results
Completeness	Adequate photo-documentation of the duodenal bulb and the second part of the duodenum
Diagnosis	Adequate mucosal visualisation of the duodenum and the use of enhanced imaging
Accuracy	Obtaining ≥4 biopsies from the duodenal bulb and the second part of the duodenum using a single-bite technique
Documentation	Clear documentation of the presence or absence of endoscopic markers of coeliac disease

GI, gastrointestinal.

diagnosis (11). Moreover, documenting the presence of these markers during endoscopy may help with diagnosis in some cases where there are discrepancies between serology and histology results.

The optimal biopsy strategy

The villous atrophy in CD has a patchy distribution, and the severity of histological lesions may vary within the duodenal samples taken from individual patients (27). Villous atrophy may also be only confined to the duodenal bulb, known as ultra-short CD. Therefore, obtaining at least 3 duodenal biopsies, including a duodenal bulb biopsy, is required to ensure no cases of villous atrophy are missed (28). Whereas, a five-biopsy strategy is required for the recognition of the most severe histological lesions (28). A meta-analysis of 17 studies showed that duodenal bulb biopsies increased the diagnostic yield of CD by 5% [95% confidence interval (CI): 3–9%] (29). Current guidelines recommend that at least four duodenal biopsies are taken from the second part of the duodenum, and an extra 1 or 2 biopsies are taken from the duodenal bulb to optimise the diagnosis of CD (30). However, multiple studies have consistently shown that adherence to the biopsy guidelines occurs in less than 40% of cases, which is associated with an increased risk of missed diagnosis (26,31,32). Increasing awareness about the evidence supporting the biopsy guidelines and setting quality benchmarks for endoscopy in CD (*Table 3*) could lead to a significant improvement in the accuracy of endoscopy in CD and reduce the risk of post-gastroscopy CD.

Obtaining two biopsy specimens with each pass of the biopsy forceps increases the risk of specimen loss and reduces histological quality (33). A study comparing the single-biopsy and double-biopsy techniques in CD showed that the single-biopsy technique was associated with improved orientation of the duodenal biopsy specimens. However, there was no difference in the final Marsh scoring between the single- and double-bite biopsy techniques (34). These findings have not been replicated in other studies. In fact, a more recent study showed that there was no difference in the quality of the specimens between the single- and double-bite biopsy techniques (35). Further studies are needed to evaluate the optimal biopsy technique for CD. Another important factor to optimise the diagnosis is the correct orientation of the biopsy specimens. Non-oriented biopsies could lead to false-positive diagnosis of CD, even by expert pathologists (36). The correct orientation of biopsies begin in the endoscopy suite, with placing the biopsy specimens on a strip of paper in a straight line, with the luminal surface upwards (36). This technique aids the pathologists in making a more accurate diagnosis.

Endoscopic tools and techniques

Given the limitations of traditional white-light endoscopy in detecting villous atrophy, different novel endoscopic tools and techniques have been investigated, as summarised in *Table 2*.

Water immersion

Filling the duodenum with water during endoscopy enhances the visualisation of the intestinal villi (18). This technique, known as water immersion, is easy to perform and safe. It involves aspirating air from the duodenum, followed by the infusion of 100–200 mL of water (*Figure 2*) (19). A prospective study of 396 patients with dyspepsia, the sensitivity, specificity, positive and negative predictive values of the water immersion technique to detect villous atrophy were 90.9%, 99.5%, 83.3%, and 99.7%, respectively (19). Although this technique appears to be highly accurate and cost-effective, it is rarely used in routine clinical practice,

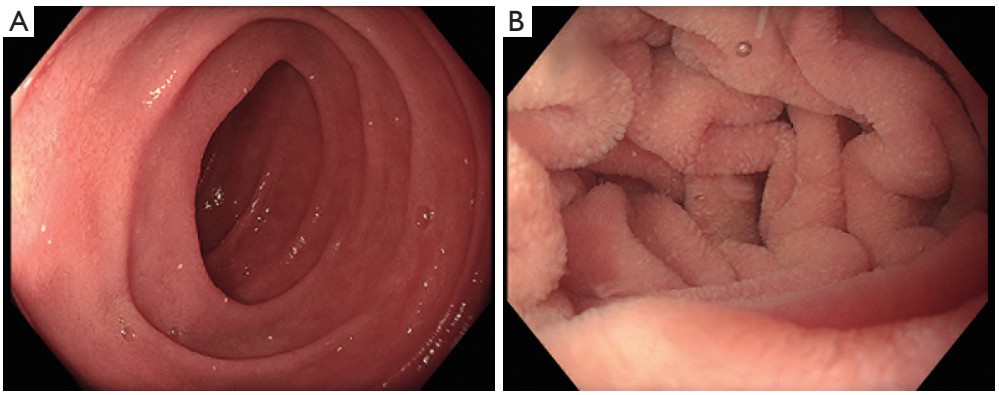

Figure 2 Endoscopic images of the duodenum with (A) air insufflation and (B) water immersion.

probably due to perceptions of it as time-consuming (19).

Dye-based chromoendoscopy

Dye-based chromoendoscopy enables the detection of subtle mucosal abnormalities and has been shown to improve dysplasia detection in patients with long-standing inflammatory bowel disease (37). Conversely, the benefits of using chromoendoscopy in patients with CD are less clear. In a study by Niveloni *et al.*, dye staining with methylene blue did not provide additional diagnostic information to expert endoscopists, compared with conventional endoscopy (20). Another study by Bonatto *et al.* proposed an endoscopic classification incorporating chromoendoscopy, using 0.5% indigo carmine, with zoom magnification to confirm the presence of villous atrophy during endoscopy. The authors showed that this classification increased the agreement between endoscopy and histopathology. However, the agreement remained weak in less severe cases (38).

Magnification endoscopy

High-magnification endoscopes have the capacity to optically magnify images up to 150 times, enabling detailed assessment of the intestinal mucosa (39). Few studies evaluated the role of magnification endoscopy in the diagnosis of CD. The first study to report the accuracy of endoscopic magnification for the detection of villous atrophy showed impressive results with a sensitivity of 95% and specificity of 99% (40). However, a larger study by Raju *et al.* reported a lower sensitivity of 86.4% and a specificity of 74.4% (17). The high cost of the high-magnification endoscopes and the lack of added diagnostic benefit over conventional endoscopy, hindered their routine use in clinical practice.

Narrow-band imaging (NBI)

NBI is a widely available advanced imaging technique that filters specific wavelengths of light to enhance the visualisation of the mucosal surface architecture (*Figure 3*) (41). NBI is routinely used for the assessment of polyps, Barrett's oesophagus and early gastric cancers (42). However, it is rarely used for the assessment of duodenal mucosa outside expert centres and clinical studies. In a recent meta-analysis, we showed that NBI has a summary sensitivity of 93% (95% CI: 81–98%), and summary specificity of 95% (95% CI: 92–98%) to detect villous atrophy (24). Combining NBI with water immersion and magnification endoscopy may further improve the diagnostic accuracy (43,44). Using NBI in patients with suspected CD could help endoscopists target more accurate biopsies of potentially abnormal mucosa and reduce the reliance on multiple random biopsies. Furthermore, biopsies could be avoided in patients with low pre-test probability of CD and normal NBI findings (45).

Gulati *et al.* developed and validated a near-focus (NF)-NBI classification of villous atrophy in patients with suspected CD (46). This simple classification requires minimal training and could help expert and non-expert endoscopists in diagnosing villous atrophy during endoscopy. Yet, clinical validation of the (NF-NBI) in patients with a low- and high pre-test probability of CD is required.

Other endoscopic modalities

Several other endoscopic modalities have been investigated

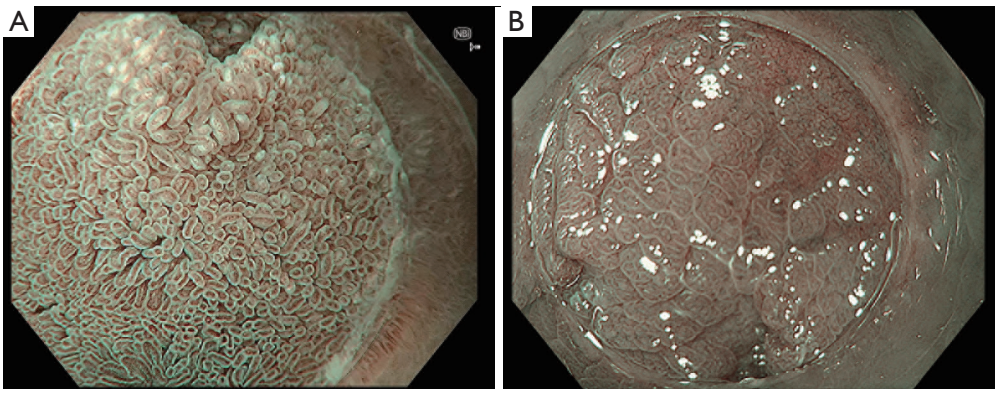

Figure 3 Near-focus narrow-band imaging of the duodenum showing (A) normal villi and (B) villous atrophy.

over the years to improve the optical diagnosis of villous atrophy, including I-scan, optimal band imaging, confocal laser endomicroscopy, and optical coherence tomography (16,23,47-49). However, none of these techniques is used in clinical practice due to their high cost, limited availability, and the absence of clear clinical benefits.

Capsule endoscopy (CE) and enteroscopy

Video CE enabled the visualisation of the entire length of the small bowel and revolutionised the diagnosis of small bowel diseases (50). A meta-analysis of 6 early studies showed that CE had a pooled sensitivity of 89% (95% CI: 82–94%) and specificity of 95% (95% CI: 89–98%) to predict villous atrophy (25). Therefore, CE is not recommended for the diagnosis of CD (30). Nonetheless, it plays an important role in the diagnosis of complications, such as ulcerative jejunitis and small bowel malignancy in patients with non-responsive or refractory CD (*Figure 4*) (51). A sequential approach of CE as a first-line investigation, followed by device-assisted enteroscopy if CE detected complications, has been shown to have a high diagnostic yield in patients with suspected refractory CD (52,53). In a meta-analysis of three studies, the pooled diagnostic yield of push endoscopy and double-balloon enteroscopy for the diagnosis of small bowel malignancy and ulcerative jejunitis in patients with complicated CD was 27% (95% CI: 14.8–42.6%) (51).

Artificial intelligence (AI)

AI has the potential to revolutionise the optical diagnosis of villous atrophy during endoscopy. Scheppach *et al.* recently developed an AI algorithm to detect villous atrophy from endoscopic still images (54). The AI algorithm significantly outperformed expert and non-expert endoscopists for the detection of villous atrophy, and its performance remained stable even in difficult images with subtle changes. Yet, the overall sensitivity, specificity and accuracy of the AI algorithm to detect villous atrophy were 90%, 76% and 84%, respectively (54). More studies with larger and more diverse training datasets are needed to improve the accuracy of the deep learning algorithms. Given the rapid advancements in this field, real-time computer-aided detection of villous atrophy during endoscopy may be on the horizon.

Role of endoscopy in the no-biopsy era

Although endoscopy and biopsy has been long considered as the gold standard test to diagnose CD, recent evidence suggests that serology-based diagnosis in selected adult patients with markedly high tissue transglutaminase antibody levels (≥10 times the upper limit of normal) is highly accurate (55). This no-biopsy approach has been used in the paediatric population for over a decade (56). Yet, following the same approach to diagnose adults with CD has been a matter of an ongoing debate (57,58). Avoiding unnecessary endoscopy could lead to significant reductions in both the healthcare costs and the carbon footprint of endoscopy (59). However, it is important to recognise that less than a third of patients with suspected CD would fulfill the criteria for a serology-based diagnosis, and that most patients will still need endoscopy and biopsy to confirm the diagnosis. Furthermore, many patients may still want to have a histological confirmation of CD before adhering

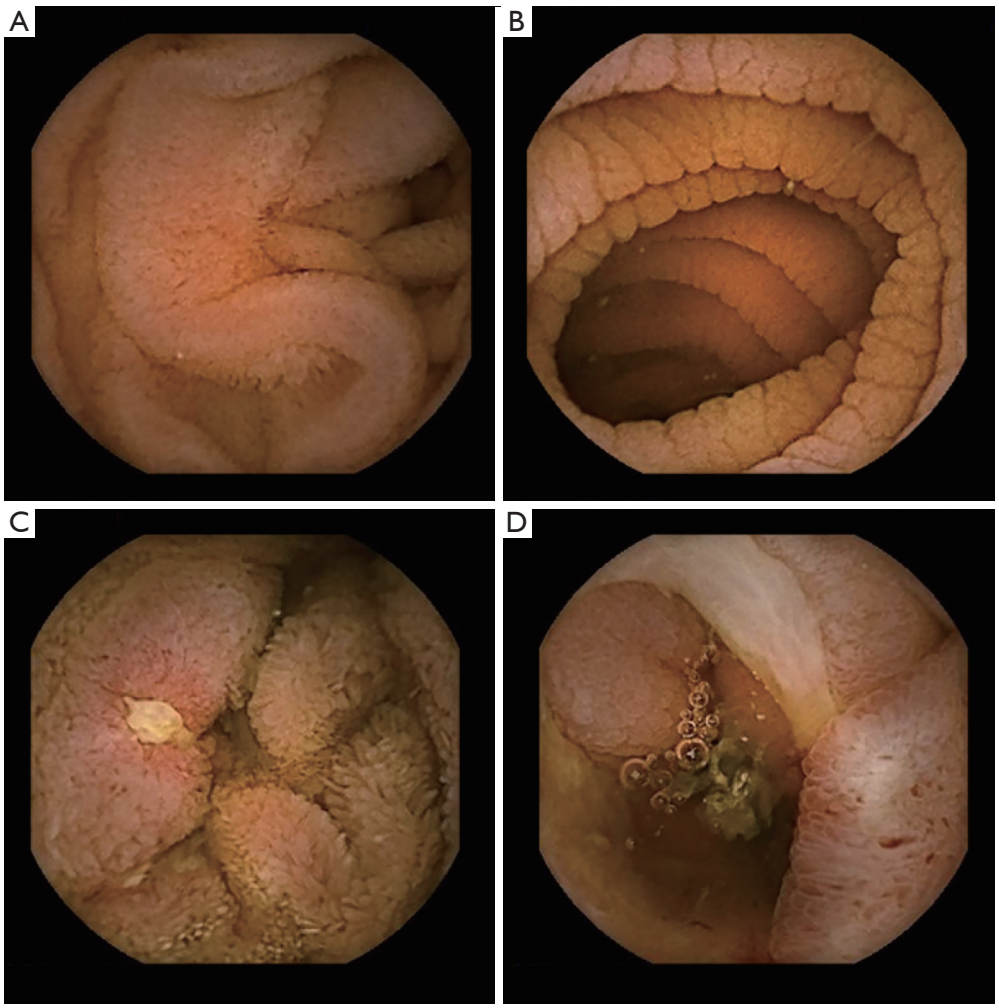

Figure 4 Capsule endoscopy images showing (A) normal villi, (B) scalloping, (C) ulcerative jejunitis, and (D) small bowel malignancy.

to a life-long gluten-free diet. Therefore, the decision to pursue endoscopy- versus serology-based diagnosis for CD should be tailored to individual patient preferences, clinical presentation, and risk factors. Future studies on the accuracy of endoscopic tools for the detection of villous atrophy in CD may yield different results if they only included patients with low and intermediate tissue transglutaminase antibody levels.

Conclusions

In conclusion, endoscopy plays a vital role in the diagnosis of CD. Performing high-quality endoscopy and adhering to the biopsy guidelines reduce the risk of missed diagnosis. Integrating enhanced endoscopic imaging and deep learning can further enhance the accuracy of the optical diagnosis of villous atrophy, potentially reducing the need for multiple random biopsies. This approach could improve patient outcomes and reduce healthcare costs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-122/rc

Peer Review File: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-122/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-122/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tgh-23-122
Cite this article as: Shiha MG, Yusuf A, Sanders DS. Role of endoscopy in the diagnosis of coeliac disease: a narrative review. Transl Gastroenterol Hepatol 2024;9:51.