

Emerging technologies in upper gastrointestinal endoscopy and celiac disease

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SUMMARY

Despite advances in our knowledge of celiac disease, the most current and authoritative recommendations conclude that diagnosis requires at least four biopsy specimens to be taken from the duodenal area. These recommendations are based on the perception that classic endoscopic markers are not adequate to target biopsy sampling to sites of villous damage in the duodenum. In the past few years, newly developed procedures and technologies have improved endoscopic recognition of the duodenum. These advances make possible the real-time recognition of the duodenal villous pattern during an upper endoscopy procedure, and thereby have the potential to optimize diagnostic accuracy. It is, therefore, reasonable to hypothesize that upper endoscopy might have a more incisive role in the diagnosis of celiac disease than merely providing a means of obtaining biopsy specimens for histological analysis. This Review highlights the new technologies in the field of upper endoscopy that could be helpful for the diagnosis of celiac disease, including the water-immersion technique, chromoendoscopy, high-resolution magnification endoscopy, optimal band imaging, optical coherence tomography and confocal endomicroscopy.

KEYWORDS celiac disease, diagnosis, endoscopy, high resolution, magnification

REVIEW CRITERIA

PubMed was searched for papers published up to 31 May 2008 using the following terms in combination: "celiac disease" plus "chromoendoscopy", "confocal endoscope", "diagnosis", "duodenum", "endoscopy", "endoscopic markers", "high-resolution", "immersion technique", "magnification", "optical coherence tomography" and "villi". The reference lists of papers identified in the initial PubMed search were reviewed for further relevant publications. We did not perform meta-analyses and reviewed only articles published in English. The reference list was last updated in August 2008.

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INTRODUCTION

Celiac disease is a gluten-sensitive enteropathy that occurs in genetically predisposed individuals¹ and is characterized by chronic inflammation of the small intestinal mucosa that gradually leads to the development of villous atrophy.^{2,3} The prevalence of celiac disease is estimated to be 0.7–2.0% in most populations, including those in the US and Europe.⁴ Celiac disease typically results in malabsorption of most nutrients, but its clinical expression is highly variable and dyspepsia can be the only symptom.^{3,5}

The gold standard for the diagnosis of celiac disease is the histological demonstration of characteristic pathological changes that are categorized according to the Marsh classification and modifications thereof.^{3,6–11} As the small bowel mucosal damage associated with celiac disease can be unevenly distributed—with parts of the mucosa appearing normal and other parts severely diseased (so-called 'patchy villous atrophy')^{12–16}—it is important that multiple biopsy specimens are taken from the proximal small intestine during upper endoscopy.^{3,17–19} Indeed, 4–6 biopsies, including a duodenal bulb biopsy, are taken to ensure that villous atrophy is detected if it is present.^{9,13,19–21} In individuals in whom celiac disease is not suspected (i.e. those in whom symptoms are atypical or absent or those who have a patchy villous atrophy), there is the chance that biopsy specimens will not be taken and the diagnosis will be missed. The opportunity to make a diagnosis of celiac disease might, therefore, also depend on the endoscopic appearance of the duodenal mucosa.^{17,18}

Several endoscopic markers related to celiac disease have been identified. The presence of these endoscopic markers is often used to determine whether duodenal biopsies are indicated and possibly to target where biopsy specimens should be taken from.^{18–20,22–26} Endoscopic markers of celiac disease include the following: a reduction or absence of duodenal folds; scalloping, which is a notched and nodular appearance of the duodenal folds; evidence of submucosal vasculature; a

Table 1 Estimated sensitivity and specificity of the classic endoscopic markers of celiac disease.

Markers	Sensitivity (%)	Specificity (%)	References
Loss of duodenal folds	75	98	Maurino <i>et al.</i> (2003) ¹⁷
	88	83	Brocchi <i>et al.</i> (2002) ¹⁸
	73	97	McIntyre <i>et al.</i> (1992) ²⁵
	47	97	Oxentenko <i>et al.</i> (2002) ³⁰
Scalloping	29	94	Smith <i>et al.</i> (1998) ²⁶
	6	100	Oxentenko <i>et al.</i> (2002) ³⁰
	44	99	Shah <i>et al.</i> (2000) ³⁶
Nodularity	6	95	Oxentenko <i>et al.</i> (2002) ³⁰
Mosaic	12	100	Oxentenko <i>et al.</i> (2002) ³⁰
Any celiac disease marker	94	92	Maurino <i>et al.</i> (2003) ¹⁷
	88	100	Dickey and Hughes (1999) ²⁸
	59	92	Oxentenko <i>et al.</i> (2002) ³⁰
	37	NA	Lo <i>et al.</i> (2007) ⁵³

Abbreviation: NA, not available.

mosaic pattern, which is the micronodular or cobblestone appearance of the mucosal surface; and mucosal fissures, crevices or grooves.^{17–20,22–26} Contradictory results concerning the value of these endoscopic markers of villous atrophy have been reported (Table 1). Among several studies, the overall sensitivity and specificity of endoscopic markers of celiac disease vary from 6% to 94% and from 83% to 100%, respectively (Table 1).^{17,18,26–35} Several possible explanations exist for the absence of endoscopic markers in patients with celiac disease. For example, such markers might actually be absent for degrees of enteropathy milder than subtotal or total villous atrophy (e.g. partial villous atrophy) and absent in cases in which the histopathological involvement of the duodenum is patchy.^{12,13,27,28} On the other hand, scalloping of duodenal folds has been reported in some patients who have moderate-to-severe enteropathy that is unrelated to celiac disease; scalloping has a positive predictive value of 69% for celiac disease and 96% for any duodenal mucosal pathology.³⁶

In clinical practice, the recognition of any mucosal features that are suspicious for celiac disease should alert the endoscopist to the need to take small intestinal biopsy specimens. However, the quite low sensitivity of these endoscopic features means that their absence does not exclude a diagnosis of celiac disease and biopsies should always be obtained when there is a suspicion that the disease might be present.

This Review focuses on the new methods and technologies that have been developed in the past

decade that can help evaluate villous morphology in real time during upper gastrointestinal endoscopy. A summary of the sensitivity and specificity values for the detection of villous alteration using these methods is reported in Tables 2 and 3.

THE WATER-IMMERSION TECHNIQUE

The water-immersion technique is a simple, quick and safe method of enhancing visualization of duodenal villi during standard upper endoscopy (Figure 1). We developed this technique as a procedure that could highlight duodenal villi,³⁷ and thereafter modified it to make it useful for clinical practice.³⁸ The water-immersion technique involves the removal of air from the lumen of the duodenum by suction followed by the rapid introduction of water (usually 90–150 ml).³⁸ The procedure adds about 25–30 s to the time required for a standard endoscopic examination.

The reliability of the water-immersion technique to enhance duodenal villous morphology was evaluated by our group in 396 consecutive patients who were undergoing upper gastrointestinal endoscopy for the investigation of dyspeptic symptoms.³⁸ For the detection of any villous abnormality (partial or total villous atrophy), the water-immersion technique achieved sensitivity, specificity and positive and negative predictive values of 99%, 99.5%, 83.3% and 99.7%, respectively. The sensitivity, specificity and positive and negative predictive values of the technique for the detection of total villous atrophy (flat mucosa) were 100%, 99.7%, 85.7% and 100%, respectively.

We have also analyzed the accuracy of water-immersion enhancement of villous profiles for the diagnosis and the follow-up of patients with celiac disease, including cases with patchy villous atrophy or villous abnormality limited to the duodenal bulb.^{21,39} The procedure was also trialed in children with suspected celiac disease, and achieved an optimal diagnostic accuracy of 100% for *in vivo* prediction of areas of the duodenum with villous damage.⁴⁰ We hypothesize that the water-immersion technique could have a role in reducing the number of biopsy specimens needed by targeting biopsy sampling to areas with villous damage, and, therefore, save on costs in children who have patchy villous atrophy.⁴⁰ We also believe that the endoscopic view obtained under water-immersion when complete duodenal villous atrophy is present is sufficiently specific to avoid the need for biopsy in patients at high risk of celiac disease.⁴¹

Table 2 Estimated sensitivity and specificity of the available endoscopic methods for the detection of any villous alteration.

Endoscopic tool	Sensitivity (%)	Specificity (%)	References
Water-immersion technique during standard upper endoscopy	90.9	99.5	Cammarota <i>et al.</i> (2004) ³⁸
Magnification endoscopy with chromoendoscopy	94	88	Siegel <i>et al.</i> (1997) ⁴⁷
Zoom endoscopy	90	62.9	Badreldin <i>et al.</i> (2005) ⁴⁹
Magnification endoscopy	95	99	Cammarota <i>et al.</i> (2004) ⁵⁰
Magnification endoscopy with water-immersion technique	95 100	98 91	Cammarota <i>et al.</i> (2004) ⁵⁰ Banerjee <i>et al.</i> (2007) ⁵²
Enhanced magnification endoscopy with acetic acid (3%)	96	NA	Lo <i>et al.</i> (2007) ⁵³
Optimal band imaging	100	100	Cammarota <i>et al.</i> (2008) ⁵⁸
Optical coherence tomography	100	100	Masci <i>et al.</i> (2007) ⁶⁵

Abbreviation: NA, not available.

Table 3 Estimated sensitivity and specificity of the available endoscopic methods for the detection of total villous atrophy.

Endoscopic tool	Sensitivity (%)	Specificity (%)	References
Water-immersion technique during standard upper endoscopy	100	99.7–100	Cammarota <i>et al.</i> (2007) ²¹ , (2004) ³⁸ and (2006) ⁴¹
Magnification endoscopy	100	100	Cammarota <i>et al.</i> (2004) ⁵⁰
Magnification endoscopy with water-immersion technique	100	100	Cammarota <i>et al.</i> (2004) ⁵⁰
Enhanced magnification endoscopy with acetic acid (3%)	100 ^a	NA	Lo <i>et al.</i> (2007) ⁵³
Optimal band imaging	100	100	Cammarota <i>et al.</i> (2008) ⁵⁸
Optical coherence tomography	100	100	Masci <i>et al.</i> (2007) ⁶⁵

^aSensitivity calculated from data provided in the published study. Abbreviation: NA, not available.

The water-immersion technique not only enables the presence or the absence of duodenal villi to be detected *in vivo* but also provides excellent results in terms of operator learning curve, safety, tolerability, and diagnostic accuracy.^{21,38,39,41} We, therefore, believe that the water-immersion technique could potentially be used as a standard maneuver during upper gastrointestinal endoscopy to enhance the clinical diagnosis of celiac disease and alert the clinician to the need to take a duodenal biopsy. However, it should be noted that experience with the water-immersion technique has not been replicated by other groups; therefore, further data obtained in a wide range of clinical scenarios, including large multicenter studies, are required before this approach can be adopted.

CHROMOENDOSCOPY AND HIGH-RESOLUTION MAGNIFICATION ENDOSCOPY

Compared with standard endoscopy, chromoendoscopy with either indigo carmine or methylene blue provides additional information concerning the mucosal surface.^{42,43} The usefulness of chromoendoscopy with indigo carmine for the evaluation of celiac disease was first reported in 1976.²³ More than 20 years later, in a study by Niveloni *et al.*, chromoendoscopy and standard endoscopy achieved similar results for the detection of celiac disease.⁴⁴ The authors concluded that “The dye staining produces a better delineation of the classic endoscopic markers of the atrophic mucosa without providing additional information to the expert endoscopist.”⁴⁴

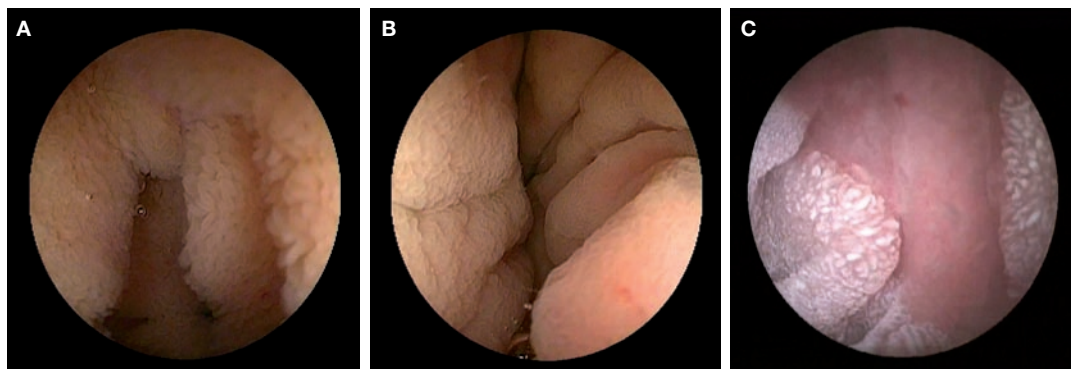


Figure 1 Visualization of duodenal mucosa by standard upper endoscopy in combination with the water-immersion technique. (A) Normal villous pattern. (B) Total villous atrophy. (C) 'Patchy' villous atrophy.

A new generation of commercially available video endoscopes—the 'magnification' or 'zoom' endoscopes—can produce high-resolution and magnified images (up to 100–135 \times), and provide superior discriminatory details when compared with standard endoscopy.^{42,45} These video endoscopes are equipped with charged computed device chips with a density of up to 850,000 pixels, whereas conventional endoscopes have charged computer device chips with a density of 100,000–300,000 pixels. In general, video endoscopes are better able to evaluate the gastrointestinal mucosa than standard endoscopes.⁴⁶

Siegel *et al.* analyzed the value of magnification endoscopy (magnification range up to 35 \times) combined with chromoendoscopy (with sprayed indigo carmine) for the evaluation of duodenal villous patterns in a cohort of 34 patients with nutrient malabsorption or suspected celiac disease.⁴⁷ Patterns of villous atrophy were documented by histopathology in 17 of the 34 patients (6 with total villous atrophy and 11 with partial villous atrophy). Standard endoscopy detected only 6 of the 17 patients identified as having villous atrophy by histology (5 with total villous atrophy and 1 with partial villous atrophy). Compared with the histopathology results, the combined technique detected patterns of total villous atrophy in 5 out of 6 patients and patterns of partial villous atrophy in 10 out of 11 patients. The combination of magnification endoscopy with chromoendoscopy was particularly helpful for the evaluation of partial villous atrophy. Results showed that this combined technique had a sensitivity and specificity of 94% and 88%, respectively for the detection of any villous alteration.

In contrast to the findings of Siegel *et al.*, Kiesslich *et al.* found no difference in their ability to identify duodenal lesions (e.g. polyps, hyperplastic Brunner's glands, etc.) regardless of whether they used conventional endoscopy, chromoendoscopy, or magnification endoscopy (zoom magnification range 0–105 \times) combined with chromoendoscopy.⁴⁸ These authors did, however, recognize the superiority of chromoendoscopy combined with zoom endoscopy when villous atrophy is suspected.

In a prospective study by Badreldin *et al.*, a cohort of patients with celiac disease was analyzed to evaluate the potential of zoom endoscopy (when 10 ml of water was instilled using the sub-immersion technique) for the diagnosis of the various degrees of villous atrophy.⁴⁹ The method had a sensitivity of 90.7%, specificity of 62.9%, a positive predictive value of 83% and a negative predictive value of 77.2% for the detection of any degree of villous atrophy. The authors confirmed that the main area of disagreement between zoom endoscopy and histopathology for the detection of villous atrophy was when making the distinction between normal tall villi and morphologically normal but shortened villi, which depends on the assessment of villus height. However, the authors concluded that zoom endoscopy could be an effective method for assessing a severe degree of villous atrophy.⁴⁹

In a study of 191 patients with suspected duodenal disease, Cammarota *et al.* considered the usefulness of high-resolution magnification endoscopy plus or minus the water-immersion technique for the detection of villous atrophy. They showed a concordance of 100% between high-resolution magnification endoscopy used with the water-immersion technique and

histopathology for detecting the absence or the presence of villi (Figure 2).⁵⁰ The sensitivity, specificity, positive predictive value and negative predictive value of endoscopic magnification for the detection of total villous atrophy were all 100%, while those values were slightly lower for the detection of partial villous atrophy and normal villous patterns. Other reports have since suggested that there might be a role for magnification endoscopy in the detection of patchy villous atrophy.^{51,52}

In their study, Lo *et al.* described the endoscopic findings obtained in patients with celiac disease when enhanced magnification endoscopy (EME) was used.⁵³ EME involves the combined use of acetic acid instillation with magnification endoscopy. When compared with standard endoscopy, EME enables patterns of duodenal villous atrophy to be detected with increased accuracy.⁵³ In fact, in this study, EME enabled identification of abnormal mucosal patterns in 12 of 12 patients with celiac disease (100%), whereas standard endoscopy only enabled identification of classic features of villous atrophy in 7 of 12 patients (58%).

OPTICAL BAND IMAGING

Optical band imaging (OBI; also known as multiband imaging) technology is based on the selection of certain wavelengths from a reflected light signal that results in the generation of an enhanced and digitally constructed image.⁵⁴ This commercially available technology has the potential to provide the same contrast enhancement capabilities as traditional chromoendoscopy, but without the need to use staining agents.

The OBI system has been successfully used to identify neoplastic areas within Barrett's esophagus,⁵⁵ to recognize depressed-type early gastric cancer,⁵⁶ and to detect small colorectal lesions.⁵⁷ In addition, the OBI system has generated excellent results in terms of accuracy (100%) for the depiction of duodenal villous patterns in celiac disease (Figure 3).⁵⁸ A possible role for narrow band imaging in the detection of villous atrophy might also be speculated. Narrow band imaging uses filters to narrow the bandwidth of the transmitted light.^{59,60}

OPTICAL COHERENCE TOMOGRAPHY

Imaging with the use of optical coherence tomography (OCT) was first demonstrated *in vitro* in the human retina and atherosclerotic plaques in 1991.⁶¹ OCT measures the echo time delay

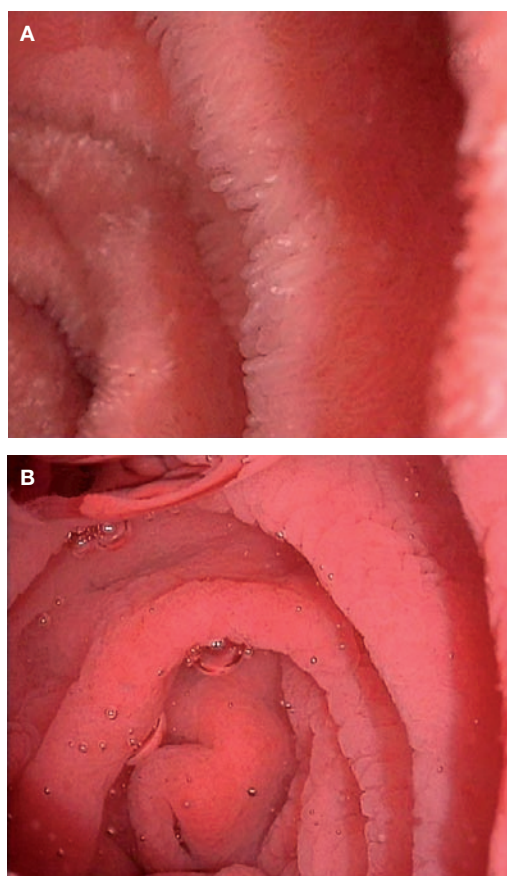


Figure 2 Visualization of duodenal mucosa by high-resolution magnification endoscopy in combination with the water-immersion technique. (A) Normal villous pattern. (B) Total villous atrophy.

and the magnitude of back-scattered light waves from different microstructural features within tissue. The basic principle of OCT is analogous to that of B-mode ultrasound. OCT uses interferometry to measure back-scattered light since the echo time delays of reflected light are too short for direct electronic detection.^{61–63} The images generated by OCT are similar to those generated by B-mode ultrasound and endoscopic ultrasound, but because light is used instead of sound waves the resolution of OCT is far better (5–10 μm) and is closer to the resolution achieved by histopathological analysis of biopsy specimens.^{61,62}

OCT enables the detailed study of the microstructure of the first layers of the gastrointestinal wall and might, therefore, be useful for the early detection of benign and malignant lesions of the layers of the mucosa, lamina propria, muscularis mucosae and submucosa, which would allow prompt treatment to be instigated.⁶³ Hsiung

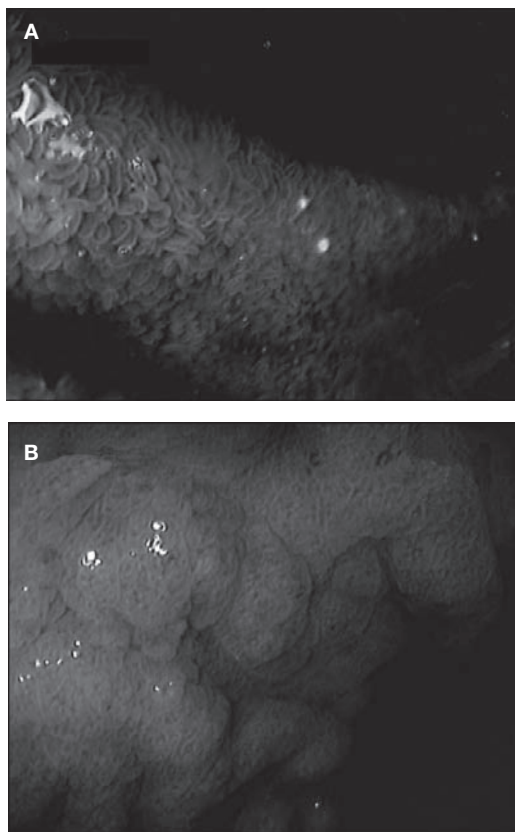


Figure 3 Visualization of duodenal mucosa by optimal band imaging magnification endoscopy. (A) Normal villous pattern. (B) Total villous atrophy. A selected red/green/blue wavelength combination of 500/480/420 nm was used for imaging.

et al. studied *ex vivo* OCT images of fresh surgical specimens taken from the small intestine and compared them with the results of histological analysis—there was 100% concordance between the pathologists' and gastroenterologists' evaluations.⁶⁴ In a preliminary report from Masci *et al.*, the use of OCT *in vivo* during real-time endoscopic imaging generated promising results for the evaluation of duodenal villous morphology.⁶⁵ These authors, in fact, found total concordance between OCT and histology results for the detection of villous morphology in both patients with celiac disease and healthy individuals. In particular, in patients with celiac disease, OCT correctly identified different stages of villous atrophy.

CONFOCAL ENDOMICROSCOPY

Technological advances in miniaturization of probes have enabled a confocal scanning microscope to be integrated into a conventional flexible endoscope, resulting in so-called confocal

endomicroscopy (CEM) or confocal laser endomicroscopy. This diagnostic tool enables real-time *in vivo* histological images or 'virtual biopsies' of the gastrointestinal mucosa to be obtained during endoscopy.^{66–70} Confocal images are generated simultaneously with the endoscopic images and the endoscope working channel can still be used. The use of intravenous and/or topical fluorescent agents is a requirement. This set-up is the main CEM system used in clinical gastroenterology at present. Current published data suggest that there is good correlation between the confocal *in vivo* images generated and conventional histology of the normal mucosa from the esophagus, stomach, small intestinal and colon.^{66,71–75}

Zambelli *et al.* compared the CEM and histological findings from the duodenal mucosa of two patients with suspected celiac disease and of four patients with dyspepsia.⁷⁶ The images obtained by CEM and histology were similar, both for patients with normal duodenal mucosa and for those with celiac disease. In patients with celiac disease, CEM enabled the identification of moderate-to-severe villous atrophy, whereas the imaging was poorer for visualization of the crypt and inflammatory infiltrate. Another group has since reported the case of a patient diagnosed with celiac disease on the basis of CEM findings; complete duodenal villous atrophy plus the presence of an increased number of intra-epithelial lymphocytes was visualized by use of the technique.⁷⁷

DISCUSSION AND FUTURE PROSPECTS

The classic endoscopic markers of celiac disease are based on endoscopy findings from 20 years ago and have low sensitivity values for the detection of villous atrophy.^{17,26,28,30,36,53} The time has perhaps come for large, multicenter studies to assess the optimal role of endoscopic procedures and technologies developed in the past decade in the diagnosis and follow-up of celiac disease. The main area of disagreement between these new technologies and histological findings seems to be in making the distinction between normal tall villi and morphologically normal but shortened villi (i.e. those corresponding to the Marsh IIIa lesions).^{8,10} By contrast, similarly excellent accuracy values are obtained by the use of these techniques and histology when assessing a severe degree of villous atrophy (Marsh IIIb and IIIc lesions; Table 3). The major advantage of endoscopic identification of villous atrophy would, therefore, be in detecting celiac disease in

patients with severe degrees of mucosal alteration in whom the disease was not suspected.

The ideal diagnostic approach for celiac disease should increase accuracy and sensitivity, be easy to perform, cost-saving, repeatable, and not time consuming. Many of these parameters can potentially be achieved by using modern video endoscopy technology. Although the endoscopic approaches now available need further testing before their use can be recommended, they could increase the accuracy of celiac disease diagnosis in patients with patchy villous atrophy and achieve optimal accuracy for the recognition of severe degrees of villous atrophy. The water-immersion technique can accurately enhance villous atrophy patterns and adds less than 30 s to the time needed to perform a standard upper endoscopy. Furthermore, the technique can easily be performed during routine endoscopy with a standard video endoscope.

Similar results to those achieved with the water-immersion technique can be achieved with high-resolution magnifying video endoscopy or with enhanced magnification endoscopy using acetic acid.^{41,50,53} Every endoscopy unit could, therefore, choose a method to be used in routine upper endoscopy that makes the best use of locally available equipment and expertise.

On the basis of the high accuracy of all the new technologies for the diagnosis of celiac disease and the particularly high accuracy of these technologies for the detection of Marsh IIIb and IIIc villous atrophy (Table 3), we propose that a new endoscopy-based diagnostic approach could be designed for patients at high risk of celiac disease (Figure 4). Although controversial, this approach could potentially avoid (or reduce) the necessity for duodenal biopsy sampling in patients with marked villous atrophy (flat mucosa). In addition, this strategy could provide time and cost savings by avoiding the need for multiple biopsy sampling and multiple histological examinations. On the basis of the findings of our published charge analysis, we predict that the practice of avoiding duodenal biopsy in high-risk patients with celiac-disease-related antibodies and marked villous atrophy would save our hospital €84 per patient.³⁵ As the prevalence of individuals with marked villous atrophy and anti-endomysial and/or anti-transglutaminase antibodies has been estimated at 4.3% per year in our center, the above strategy would result in a calculated charge-saving of €5,647 per year with no detriment to the clinical result.

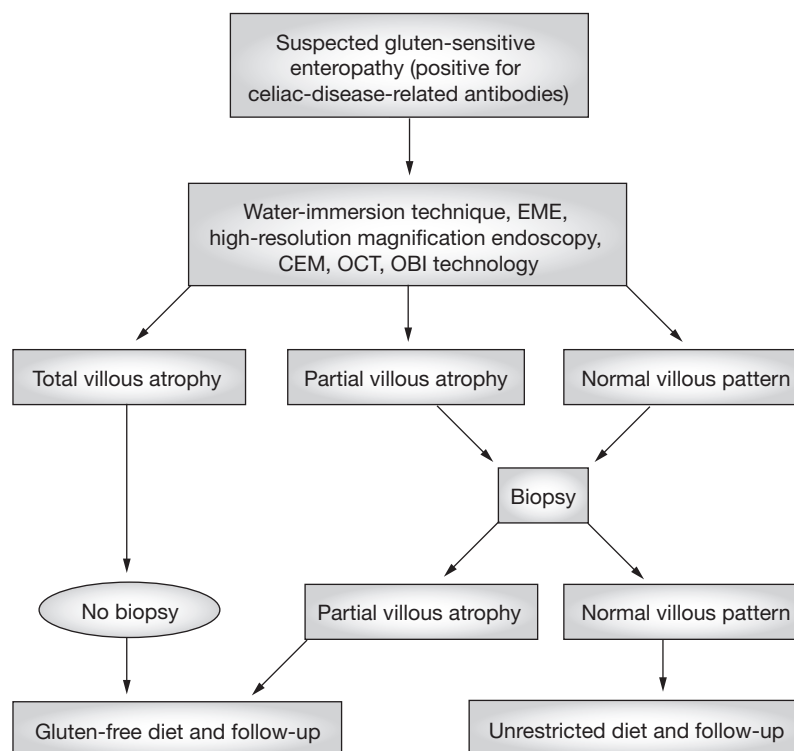


Figure 4 Proposed algorithm to minimize the need for duodenal biopsy in patients with suspected celiac disease. Abbreviations: CEM, confocal endomicroscopy; EME, enhanced magnification endoscopy; OBI, optical band imaging; OCT, optical coherence tomography.

According to the diagnostic algorithm we propose, the need to take duodenal biopsies in patients with celiac disease and marked villous atrophy could be reserved for those who do not improve or who have villous atrophy despite being on a gluten-free diet. A proportion of gluten-sensitive patients are recognized as having Marsh IIIa (which includes partial villous atrophy) and also Marsh I-II lesions (including normal villi), especially those patients who have an atypical clinical spectrum of symptoms; therefore, duodenal biopsies should always be taken in those patients with suspected celiac disease and in whom villi are evaluated as being present (with a partial or a normal villous structure) by endoscopy (Figure 4).^{8,10} To avoid missing a diagnosis of celiac-disease-associated intestinal lymphoma, biopsy samples should always be taken when a macroscopic duodenal wall abnormality is present that the endoscopist feels needs histological analysis.

The role of endoscopic techniques for the screening of patients in whom celiac disease is not suspected also needs to be evaluated. In

our opinion, some endoscopic procedures, for example the water-immersion technique, can easily be performed during routine clinical practice. The simplicity of the water-immersion procedure means that it is highly reproducible; moreover, a relatively small number of cases seem sufficient for endoscopists to become proficient in the technique.⁷⁸ At our tertiary care hospital, our specific teaching role is to initiate residents in the use of digestive endoscopy. Most members of our group (including residents) successfully perform duodenoscopy with water immersion with or without magnification. In the past 4 years, this procedure has been used during routine duodenal examinations to evaluate the *in vivo* duodenal villous patterns of all patients referred for upper endoscopy. For us, this approach has facilitated the diagnosis of celiac disease in individuals who were not suspected of having a malabsorption disease.

In regard to the usefulness of the other endoscopic options available for the screening of patients in whom celiac disease is not suspected (such as OBI-based endoscopy, OCT and CEM), in our opinion their use should be considered on the basis of the local availability of equipment and expertise, and after a careful cost analysis and outcome analysis. Although the costs of OCT and CEM have not yet been assessed, these techniques could provide an accurate means of selecting patients who require duodenal biopsy and be potentially useful in reducing the number of biopsies needed and the time spent by the endoscopist and pathologist.

CEM provides real-time histological information during endoscopy; therefore, unlike other conventional endoscopic techniques, performance of CEM requires a fundamental knowledge of the normal and diseased microarchitecture of the gastrointestinal tract. Although endoscopists performing CEM do not need to be pathologists they must be able to identify areas of abnormal mucosa that can be biopsied during the endoscopy for later examination by a pathologist. On the other hand, a specific background in endoscopic ultrasound could be fundamental for the learning curve of endoscopists who perform OCT.

CONCLUSIONS

Some of the technology developed in the past few years needs to be further refined to become more user-friendly and generate more-informative results; however, we believe that clinicians should

be encouraged to revise their practice for the diagnosis of celiac disease. However, it is also important to recognize that a change in practice is currently only possible in well-equipped endoscopic centers that have the appropriate expertise. In addition, a series of technical, training and medicolegal issues need to be considered and discussed before the technologies described in this Review can have a role in clinical practice. One important issue concerns the interpretation of the virtual *in vivo* 'histological' images obtained with some techniques (i.e. CEM, OCT and OBI) and the possible medicolegal consequences of the histological report being given by a gastroenterologist and not by a pathologist. Basic histological training should, therefore, be integrated as a core part of the training program for dedicated endoscopists who are using the techniques described. Trained endoscopists who use these technologies should not replace but should interact closely with pathologists, as any biopsy specimens taken will still need to be formally examined. Unnecessary biopsy procedures could be avoided in the future by taking this approach. Clearly, positive findings from large, randomized trials that include cost analyses and clinical outcome evaluations are needed to encourage a change in practice for the diagnosis of celiac disease and for the change to be accepted by health authorities and approved by an apposite experts' panel.

KEY POINTS

- The gold standard for the diagnosis of celiac disease is the histological demonstration of characteristic pathological changes of the duodenal mucosa
- The role of endoscopy is at present limited to obtaining a number of duodenal biopsies because of its low accuracy in predicting histological changes
- Newly developed technologies in the field of gastrointestinal endoscopy make possible the real-time recognition of the duodenal villous pattern during upper endoscopy
- Further investigations are needed to confirm encouraging preliminary reports of the use of newly developed endoscopic techniques in the diagnosis of celiac disease
- The water-immersion technique, magnification endoscopy, optical band imaging, optical coherence tomography and confocal endomicroscopy demonstrate potential to have a more incisive role in the diagnosis of celiac disease

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Competing interests

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