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Novel Endoscopic Techniques in Celiac Disease

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Additional information is available at the end of the chapter

Abstract

Celiac disease (CD) is a systemic, immune-mediated illness that primarily affects the small bowel. A few decades ago, in the era of Watson and Crosby capsules, we used to sample the small bowel without even looking at it. Nowadays, with the continuous developing field of digestive endoscopy, we can even see the duodenal villi up closely, allowing for an optical, real-time diagnosis of villous atrophy. Advanced endoscopic techniques such as magnification, chromoendoscopy (dye-based and digital), water immersion, confocal endomicroscopy, endocytoscopy, and optical coherence tomography (OCT) have been evaluated in CD with good results: good agreement with histology, allowing for targeted biopsies and a reduction in the number of biopsies needed for diagnosis. Moreover, with the growing use of open-access endoscopy in many parts of the world, endoscopy is now contributing to increasing the diagnostic rate of CD, by recognition of endoscopic markers in patients without clinical suspicion of this disease. This is however an observer-dependent method; to overcome the endoscopists subjectiveness in assessing villous atrophy, in the last years, many papers have looked at means of computerized analysis of endoscopic images. Currently available data show that these automated, quantitative methods hold very promising for the future.

Keywords: celiac disease, advanced endoscopy, capsule endoscopy, computer-aided, diagnosis, endoscopic marker

1. Introduction

Celiac disease (CD) is a systemic autoimmune disease triggered by ingestion of gluten in genetically susceptible individuals. Although so much is known about this disease (its trigger, autoantigen, genetic predisposition, target organ damage, and diet treatment), it remains heavily underdiagnosed. In this setting, new diagnostic strategies are being searched for, and

great attention has been pointed toward the role of endoscopy in increasing the diagnostic rate of celiac disease. Some have even proposed systematic biopsies for patients with abdominal pain or reflux symptoms undergoing upper digestive endoscopy, but this has proven to have a low yield for diagnosing celiac disease, at a high cost [1–4]. However, with the growing use of open-access endoscopy in many parts of the world, endoscopy can be a great opportunity to identify new celiacs, by recognizing suggestive endoscopic markers in previously unsuspected patients. The premises for this window of opportunity are a thorough examination of the duodenum and appropriate training for the endoscopists to recognize endoscopic markers of villous atrophy.

Moreover, endoscopy with tissue sampling is mandatory to establish a correct diagnosis, at least in adults [5]. In children, the 2012 ESPGHAN guideline proposed a triple diagnostic criteria to avoid biopsy (tissue transglutaminase antibodies over 10 times the upper limit of normal, confirmed with positive anti-endomysial antibodies in a separate blood sample; characteristic symptoms of celiac disease; positive HLA-DQ2/DQ8) [6]. Some studies have validated this rule, while others have questioned it [7–10].

But, endoscopy is more than just a mean to get the duodenal mucosal samples. If we think back a few decades, in the era of Watson and Crosby capsules, we used to sample the small bowel mucosa without even looking at it. Nowadays, with the continuous development of technology, endoscopy has turned into a very powerful tool as we can even see the duodenal villi up closely, allowing for an optical, real-time diagnosis of villous atrophy. Advanced endoscopic techniques such as magnification, chromoendoscopy (dye-based and digital), water immersion, confocal endomicroscopy, and optical coherence tomography (OCT) have been evaluated in CD with promising results: good agreement with histology, allowing for targeted biopsies and a reduction in the number of biopsies needed for diagnosis.

Even more, computer processing of images captured during endoscopy or capsule examination have been studied in diagnosing villous atrophy in celiac disease patients. These novel computerized methods are based on texture analysis or other image features and offer a quantitative assessment of mucosal atrophy, so that someday maybe they will replace the biopsy.

2. Advanced endoscopic techniques in celiac disease

Diseased small bowel mucosa is often difficult to recognize in standard, white light endoscopy. In order to enhance the subtle mucosal abnormalities of celiac disease patients, a special focus has been given to advanced endoscopic techniques: from water immersion and dye-based chromoendoscopy to digital (dyeless) chromoendoscopy, magnification, confocal endomicroscopy, endocytoscopy and optical coherence tomography [11, 12]—these have all improved the way we macroscopically evaluate the duodenal villous pattern and increased the diagnostic accuracy of endoscopy for celiac disease.

Besides better delineation of the subtle mucosal changes compared to standard white light endoscopy, these techniques help in accurately characterizing these changes and driving

targeted biopsies. By targeting the most diseased area of the mucosa, use of advanced endo-scopic techniques has the potential to reduce the number of biopsies needed for diagnosis, or even making a real-time, in vivo diagnosis of atrophy (the so-called concept of "virtual" biopsy). In vivo histology could be very useful, especially in patients who refuse biopsy and keeping in mind the frequent low quality of duodenal biopsy samples. However, most of the advanced endoscopy techniques available in daily practice can only assess villous atrophy and not the other features of celiac-type enteropathy (intraepithelial lymphocytosis and crypt hyperplasia) and this is considered an issue as villous atrophy can have a wide differential diagnosis. Not least, mucosal changes in celiac disease can be patchy and the use of advanced endoscopy could be of great help to identify the patchiness and orient biopsy sampling in these areas.

The **water immersion technique** is a simple, quick, and safe method, which can be used rou-tinely to enhance the duodenal villous pattern during upper digestive endoscopy (**Figures 1** and **2**). Developed by the Italians [13], it consists of two steps: first, suction of the air from the duodenal lumen and second, rapid instilling of up to 150 ml water through the channel of the scope (either manually by connecting a syringe to the biopsy channel port or by using an external water-pump) [14]. This adds only about 30 sec to a standard examination and has very good diagnostic accuracy for villous atrophy (100% sensitivity, 99.7% specificity, 85.7% posi-tive predictive value, and 100% negative predictive value for total villous atrophy, and 75, 99.5, 60, and 99.7%, respectively for partial villous atrophy) [14]. It has a favorable profile regarding the tolerability and examiner's learning curve [15]. In a scenario of a biopsy-avoiding approach,
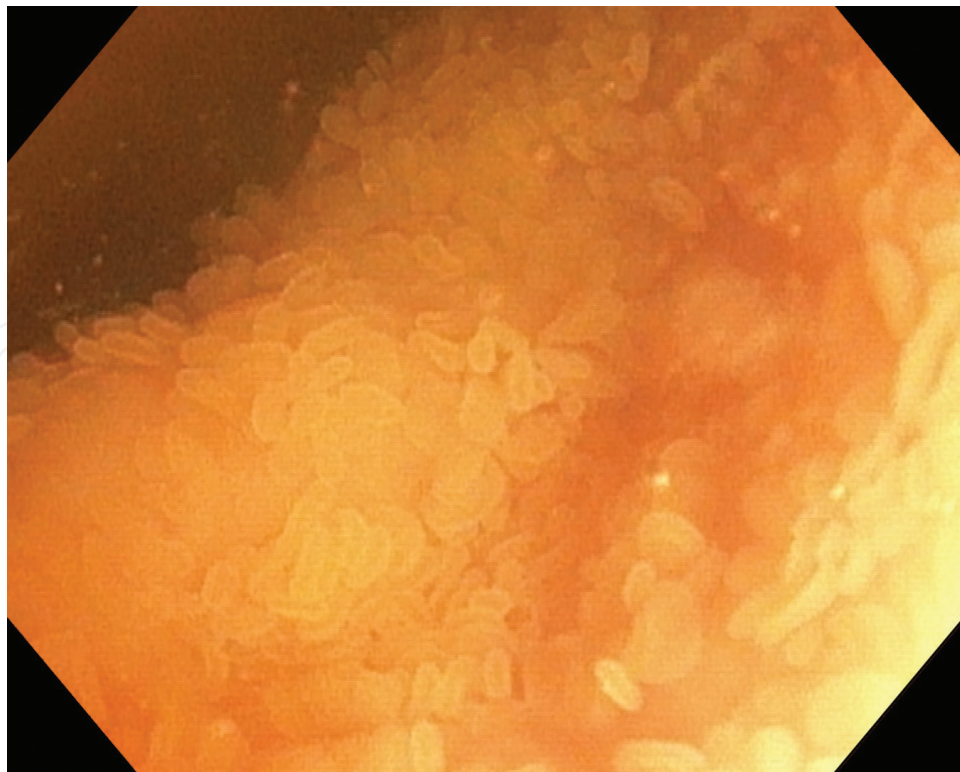
Figure 1. Water-immersion examination of the duodenum showing normal villous pattern.

Figure 2. Water-immersion examination in a patient with partial villous atrophy.

using water immersion to diagnose celiac disease has proven to be cost effective [16]. It has also been evaluated with good results in cases of villous atrophy limited to the duodenal bulb only [17] and in the follow-up of celiac disease patients to assess histological recovery after gluten-free diet [18]. As we will see in the following paragraphs, water immersion can also be used in combination with other techniques (digital chromoendoscopy and magnification) in evaluating the duodenal villous pattern.

Dye-based chromoendoscopy is, as the water-immersion technique, a simple, inexpensive method, which can be used to better delineate changes in the mucosal surface of the gastrointestinal tract. It consists in topically administering a colorant (methylene blue, indigo carmine) over the digestive mucosa, by using a spray catheter. The principle of chromoendoscopy is based on the fact that the human eye can better discriminate the contrast given by methylene blue or indigo carmine (which colors the depressed areas of the mucosa and highlights the surface pattern) than the red-pink hue of standard white light endoscopy. Its use in examining the mucosa of celiac disease patients dates back in 1976, as reported by Stevens [19]. Others have followed with small number of patients [20–25], some using combination of chromoendoscopy with magnification, but the most recent study on topic comes from the British; 300 patients with no previous history of CD were evaluated, with 89/300 (30%) being newly diagnosed celiac disease patients; the authors reported an increase of 12% in the identification of endoscopic markers of celiac disease with chromoendoscopy vs. white light endoscopy (48/89 meaning 54% vs. 37/89 meaning 42%, p = 0.001), but the overall diagnostic accuracy was poor compared to serology (**Table 1**) [26].

|	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Standard endoscopy	42	98	90	80
Chromoendoscopy	54	97	89	83

Table 1. Diagnostic accuracy of chromoendoscopy in celiac disease [26].

Virtual chromoendoscopy is even simpler than dye-based chromoendoscopy as it only requires the press of a button on the scope during the examination to get the desired enhancement of the digestive mucosa. Therefore, it saves the additional costs needed for dye spraying and avoids the prolonged procedure time that comes with conventional chromoendoscopy. To get the maximum from a chromoendoscopy examination, the recommendation is to use premedication with an antispasmodic and antifoaming agent and to record images during the examination (for later analysis). Some of the currently available technologies (see **Table 2**) are based on using electronically activated filters to select certain wavelengths, others use post-processing of images.

Most studies have used narrow band imaging (NBI) (**Figure 3**) and i-Scan to better visualize the duodenal mucosa. In the study of Singh et al. [27], NBI performed very good in identifying villous atrophy—93.3% sensitivity and 97.8% specificity (with k values for interobserver and intraobserver agreement of 0.82 and 0.86, respectively) and also in discriminating partial from total villous atrophy (83.3% sensitivity and 100% specificity, k at 0.73 and 0.68, respectively). Even better results have been reported with the combination of NBI and magnification in the study of De Luca [28], with 100% sensitivity, 92.6% specificity, 95% accuracy, and kappa 0.9 when compared to histology (detecting partial villous atrophy in 12 patients which was missed by standard endoscopy). In the paper of Valitutti et al., when combined with water immersion, NBI showed a diagnostic sensitivity of 87.5% with high interobserver agreement (k 0.884) [29]. The Indian experience of Dutta and Goswami has also shown good diagnostic performance for NBI with sensitivity of 87.5 and 95% and specificity of 95.2 and 90.2%, respectively [30, 31]. Goswami even proposed a NBI classification of villous pattern—NBI type I for normal finger-like villi, type II for short and stubby villi (cerebriform pattern), type III for patchy villous atrophy, and type IV for flat mucosa, without villi.

Scope company	Chromoendoscopy technology
Olympus (Tokyo, Japan)	Narrow band imaging (NBI)
	Autofluorescence imaging (AFI)
Pentax (Tokyo, Japan)	i-Scan (surface enhancement/SE, contrast enhancement/CE, tone enhancement/TE)
Fujifilm (Tokyo, Japan)	Flexible spectral imaging color enhancement (FICE)
Fujifilm (Kanagwa, Japan)	Blue laser imaging (BLI)
Karl Storz (Tuttlingen, Germany)	Storz professional image enhancement system (SPIES)

Table 2. Currently available digital chromoendoscopy technologies.
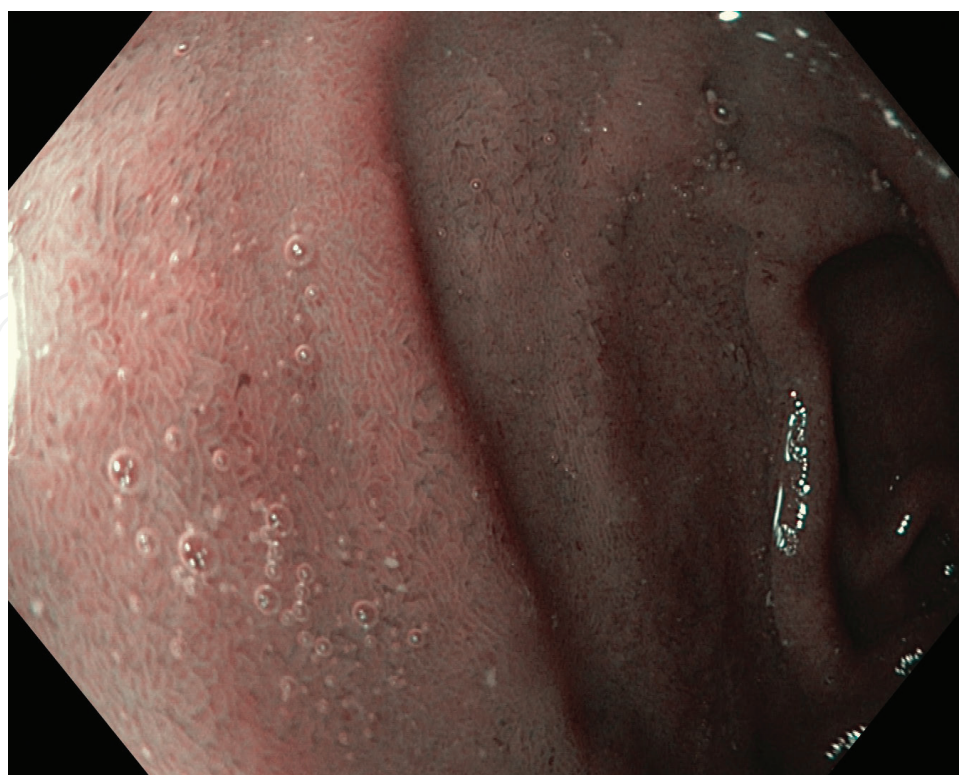
Figure 3. Normal villous pattern, endoscopy with narrow band imaging (Olympus, Tokyo, Japan).

For the i-Scan technology, Cammarota reported accuracy of 100% for detection of marked villous atrophy and 90% for partial villous atrophy and normal villous pattern [32]. Strong correlation with histology (r = 0.732) and high sensitivity (96%) was obtained by Iacucci by combining i-Scan with water immersion [33]. In a comparative study with or without i-Scan, Penny et al. concluded that it is the high definition endoscopy that increases the detection of celiac disease during routine endoscopy, irrespective of the use or not of i-Scan [34].

Good results have also been reported with flexible spectral imaging color enhancement (FICE), on small numbers of patients—100% accuracy in evaluation of villous patterns (marked villous atrophy, partial villous atrophy, and normal villi) [35].

Not least, digital chromoendoscopy techniques such as NBI can be used to detect patchy villous atrophy (**Figure 4**) [36].

Magnification or zoom endoscopy allows the endoscopist to get high-resolution, magnified images (up to 135×) in real time (**Figure 5**), which undoubtedly outperforms the standard endoscopy in assessing the villous pattern [15, 37]. It has been studied in combination with other techniques—water immersion, chromoendoscopy, and acetic acid instillation ("acetowhitening"' or enhanced magnification endoscopy), with very good results (see **Table 3**) [37–42]. It is also been shown to be useful in detecting patchy celiac disease [43]. However, contrasting these supporting results, the study by Kiesslich et al. [21], on assessing duodenal abnormalities (not necessarily focusing on villous atrophy) by dye staining and magnification, the latter did not further increase the diagnostic yield of chromoendoscopy.
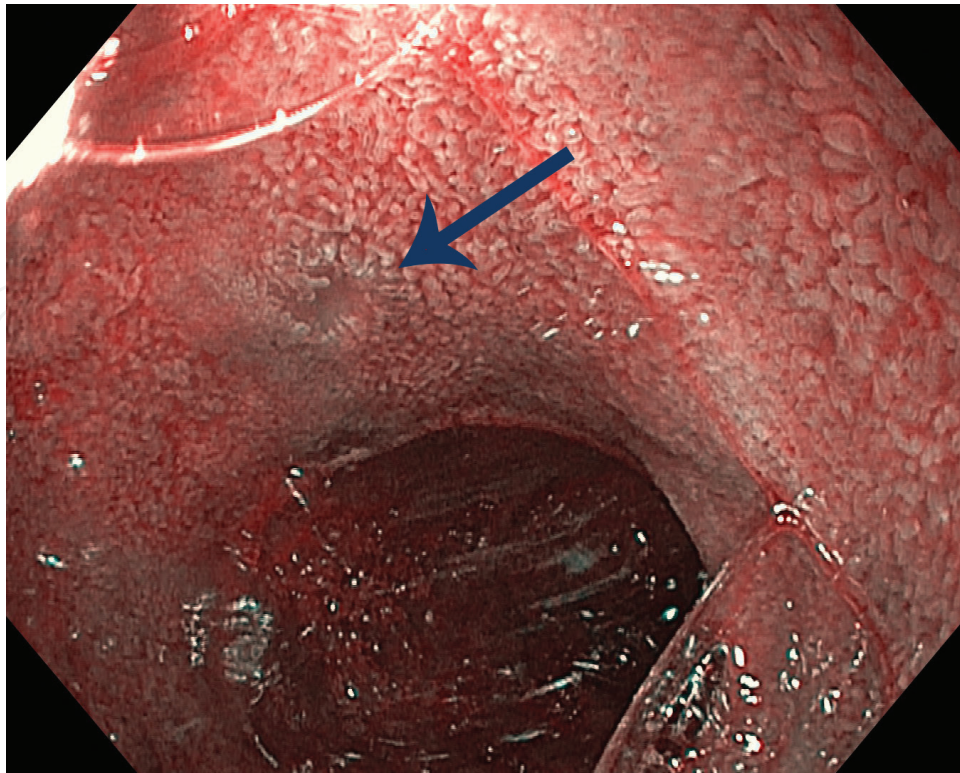
Figure 4. Patchy loss of villi pattern, endoscopy with narrow band imaging (Olympus, Tokyo, Japan).

By using a multimodal approach (standard esogastroduodenoscopy combined with zoom and chromoendoscopy), some authors have even proposed an endoscopic classification of celiac disease (types 0, I, II, and III), with good correlation between the endoscopic changes and the histologic findings (reported as Marsh grade) [44].

Confocal laser endomicroscopy (CLE) was first introduced in practice in 2004 by the team of Ralf Kiesslich (Mainz, Germany). CLE is based on integrating a confocal microscope in the distal tip of a conventional scope, which illuminates the mucosa with a 488 nm wave, allowing for cellular-level imaging (1000× magnification) up to 250 μm in depth. By offering mucosal architectural and cellular details, CLE is considered a method of in vivo histology, thus offering so-called virtual or optical biopsies. Currently, CLE can be done either with a dedicated scope, which has the confocal scanner integrated into the tip of the scope (integrated or endoscope-based CLE, eCLE, or iCLE—available from Pentax, Tokyo, Japan) or by using miniprobes which fit into the working channel of the scope (probe-based CLE, pCLE—available from Cellvizio Endomicroscopy System; Mauna Kea Technologies, Paris, France) [45]. Irrespective of the method used, CLE requires contrast agents, the most commonly used being intravenous fluorescein and topical acriflavine. Because image acquisition during CLE examination is greatly artefacted by peristalsis, respiratory, and circulatory movements (especially in the upper GI tract), the procedure usually consists in capturing the images and analyzing them after.

In addition to the advanced endoscopic techniques previously discussed, CLE also allows for assessment of crypt hyperplasia and intraepithelial lymphocytosis, which brings it closer
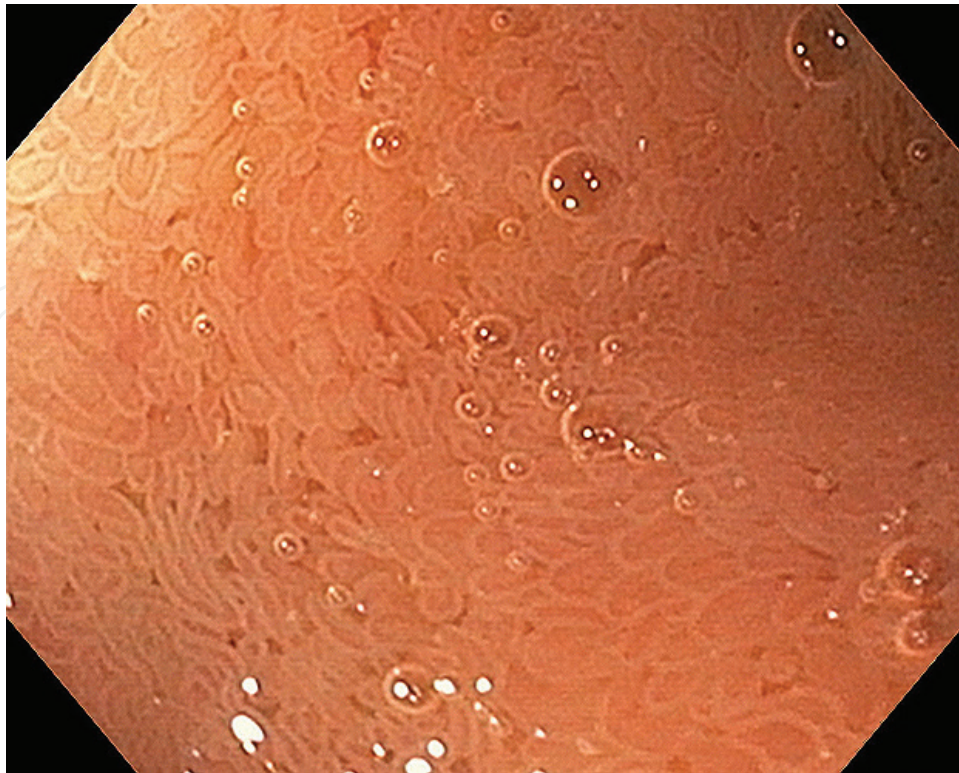
Figure 5. Magnification image of normal, finger-shaped duodenal villi.

to histology when considering all the features of celiac-type enteropathy and not only villous atrophy. Therefore, it can provide a real-time, full diagnosis of celiac disease (avoiding time and cost of processing and difficulty in interpreting biopsy samples), as shown in a case report by Trovato [46]. Furthermore, CLE overcomes the disadvantage of nonrepresentative biopsies of conventional endoscopy by allowing targeted biopsies to relevant mucosal areas [47].

As shown by Zambelli et al., the images acquired by CLE are similar to those obtained by histology, in both normal and celiac disease patients, with best visibility and quality for epithelial architecture and less for inflammatory infiltrate and crypt [48].

Experience of CLE in celiac disease is not very large; three studies have shown good diagnostic performance compared to histopathology—sensitivity of 100, 94, and 73%, specificity of 80, 92 and, 100%, respectively [49–51]. In the study by Leong et al., CLE achieved an excellent AUROC (receiver operator characteristics area under the curve) of 0.946. It is worth mentioning that the CLE has a limited ability to evaluate the crypt depth, as Gunther reported modest agreement with histology for crypt hyperplasia (sensitivity 52%, compared to 74% for villous atrophy and 81% for intraepithelial lymphocytosis). In the same study by Gunther, high interobserver agreement was seen for all three histologic features of celiac disease.

Despite being a very valuable tool, the use of CLE is limited in clinical practice because it is very time consuming, and it is burdened by a high cost of the equipment and need for training.

Author, year	Technique used	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
Banerjee, 2007	Magnification endoscopy	100	91	83	100
Siegel, 1997	Magnification endoscopy + indigo carmine-chromoendoscopy	94	88		
Badreldin, 2005	Zoom endoscopy (115×)	90.7	62.9	83	77.2
Cammarota, 2004	Magnification endoscopy	95	99	95	99
	Magnification endoscopy + water-immersion technique	95	98	92	99
Lo, 2007	Magnification endoscopy + acetic acid instillation (enhanced magnification endoscopy)	100	–	–	–

Table 3. Summary of studies evaluating magnification endoscopy in the detection of villous atrophy [38–42].

Optical coherence tomography (OCT) combines the ultrasound and infrared technologies, and is mostly known for its use in ophthalmology. With OCT, we get 1.5 mm in-depth examination of the digestive mucosa, and the images generated resemble closely the histological architecture. Studies done by Masci et al. have shown 100% concordance with histology in both diseased and normal individuals, also with good discrimination between the various degrees of villous atrophy [52–54].

Endocytoscopy is another novel endoscopic technique that allows in vivo, real-time visualization of mucosa under 450× magnification, by using a high power objective lens. Similar to CLE, it is also available as probe-based and endoscope-based equipment and it requires placing the scope/probe in contact with the mucosa to generate images [55]. The study of Matysiak-Budnik et al. on 16 celiac disease patients and seven non-celiac controls have found good concordance between endocytoscopy imaging and conventional histology [56]. The method is not used in daily practice.

Capsule endoscopy is a non-invasive, but expensive method to examine the small bowel. With 8× magnification lens and the ability to capture images at a rate up to 6 frames/second, capsule endoscopy is an excellent method to evaluate the villous pattern. It is usually reserved for special situations, mainly where there is suspicion of refractory or complicated celiac disease (malignancy and ulcerative jejunitis). However, it can also be used as a diagnostic tool for patients unwilling or unable to undergo upper GI endoscopy or to assess the extent of small bowel involvement [57]. Theoretically, it could be also used to search for villous atrophy in seropositive patients with normal histology on duodenal biopsy, although the study by Lidums et al. does not support this [58]; however, in a small case series, celiac disease was diagnosed on the basis of changes visualized by capsule endoscopy, when upper digestive endoscopy and biopsy were unable to provide a diagnosis [59].

As shown in several studies (**Table 4**), capsule endoscopy has high accuracy in recognizing endoscopic markers of villous atrophy, but its major drawback is the lack of possibility for tissue sampling, which is currently the cornerstone for adult celiac disease diagnosis. Also, another limitation is the need to get training in order to get proficient in this technique. Not least, although it has the highest specificity for detecting total villous atrophy in celiac disease patients (**Table 4**), it performs less well in partial villous atrophy [57].

Author, year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Petroniene, 2005	70	100	100	77
Hopper, 2007	85	100	100	88.9
Rondonot, 2007	87.5	90.9	96.5	71.4
Biagi, 2007	93.6	63.6	100	77
Maiden, 2009	67	100	100	60
Lidums, 2011	93	100	100	89

Table 4. Summary of studies evaluating the diagnostic accuracy of capsule endoscopy in the detection of villous atrophy [60–64].

Enteroscopy has changed the way we think of the small bowel—if a few decades ago, we thought of it as unreachable beyond the limited examination possible during upper and lower GI endoscopy, with the latest technology, we are now confident that we can do an extensive evaluation of the small bowel. The advantage over capsule endoscopy is that enteroscopy allows for tissue sampling and therapy.

Main indications for enteroscopy are patients with positive serology but normal or equivocal findings in duodenal biopsies [65] and patients with suspected refractory or complicated celiac disease [66, 67].

As capsule endoscopy, enteroscopy should be considered as a complementary method in the diagnosis and management of celiac disease.

All in all, there is strong evidence for the use of advanced endoscopic techniques in the evaluation of the duodenal mucosal pattern (**Table 5**), as it brings several benefits: improving detection of mucosal changes (especially in the setting of partial villous atrophy, where endoscopic markers are not that evident), delineating their extent, identification of patchy disease, and targeting biopsies. This latter aspect allows for a reduction in number of biopsies needed for diagnosis by focusing on relevant mucosal areas and it could be of great significance to optimize the endoscopic evaluation, as several studies have shown low compliance with the currently recommended number of biopsies [68, 69].

As some of these techniques are readily available, being just a press of a button away, endoscopists should be trained to use them routinely. Besides equipment costs and training, another major limitation of these techniques is that while they are very accurate in detecting villous atrophy, most of them cannot establish the full extent of histologic injury, as they cannot asses for intraepithelial lymphocytes and crypt hyperplasia. For techniques that offer in vivo histology, solid expertise and histological knowledge is mandatory.

| Author, year	Endoscopic tool	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Oxentenko, 2002	Standard endoscopy	59	92	–	–
Cammarota, 2004	Water immersion	90.9	99.5	83.3	99.7
Johnson, 2014	Chromoendoscopy	54	97	89	83
Singh, 2010	NBI	93.3	97.8	93.6	96.7
Iaccuci, 2016	i-Scan + immersion	96	63	–	–
Banerjee, 2007	Magnification endoscopy	100	91	83	100
Lo, 2007	Enhanced magnification endoscopy	96	–	–	–

Table 5. Summary of studies evaluating the diagnostic performance of various endoscopic techniques in the detection of villous atrophy [14, 26, 27, 33, 38, 42, 78].

3. Endoscopic markers in celiac disease

Over the time, several endoscopic features suggestive of villous atrophy have been described, and many studies have investigated their diagnostic accuracy for celiac disease. The endoscopic markers described in celiac disease are [70–73]:

- mucosal atrophy, with visible submucosal vascular pattern (**Figure 6**),

- mosaic appearance (**Figure 7**),

- nodular pattern of the mucosa (**Figure 8**),

- presence of mucosal fissures (grooves), leading to a "cracked-mud" appearance (**Figures 9** and **10**),

- reduction or complete loss of folds in the distal duodenum (**Figure 11**), and

- scalloping or a dented aspect of the Kerckring folds (**Figure 12**).
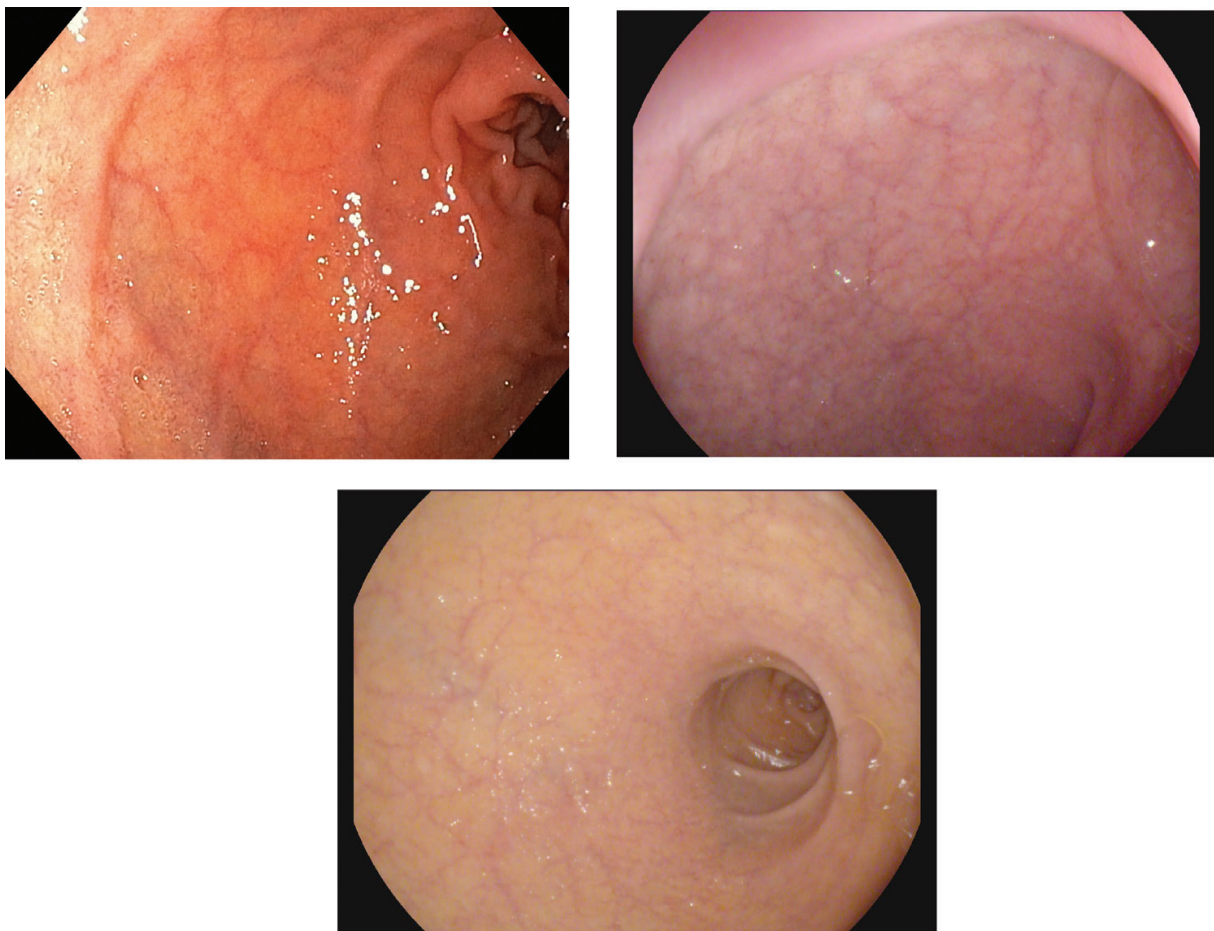
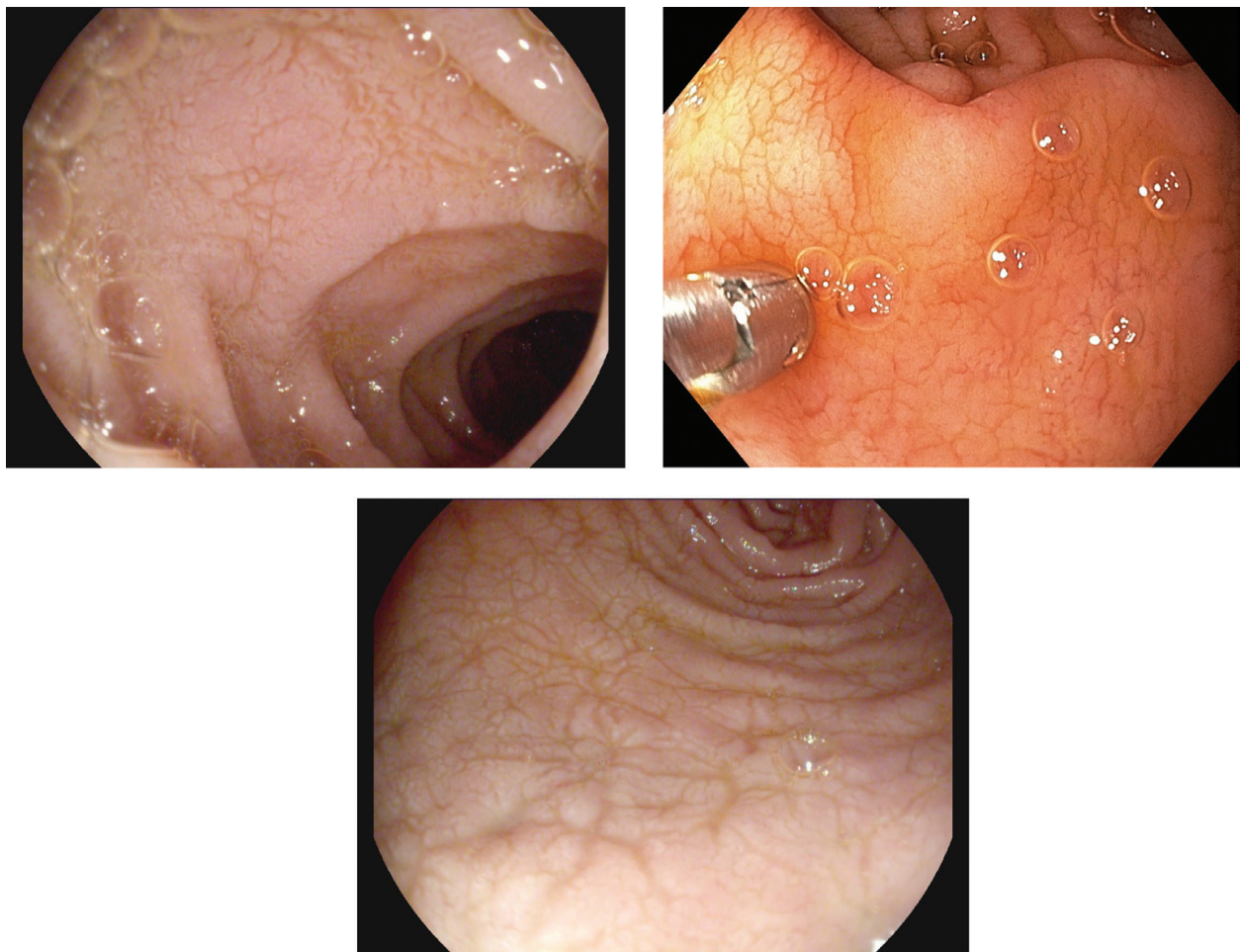**Figure 6.** Standard endoscopy showing atrophic mucosa of the duodenal bulb.
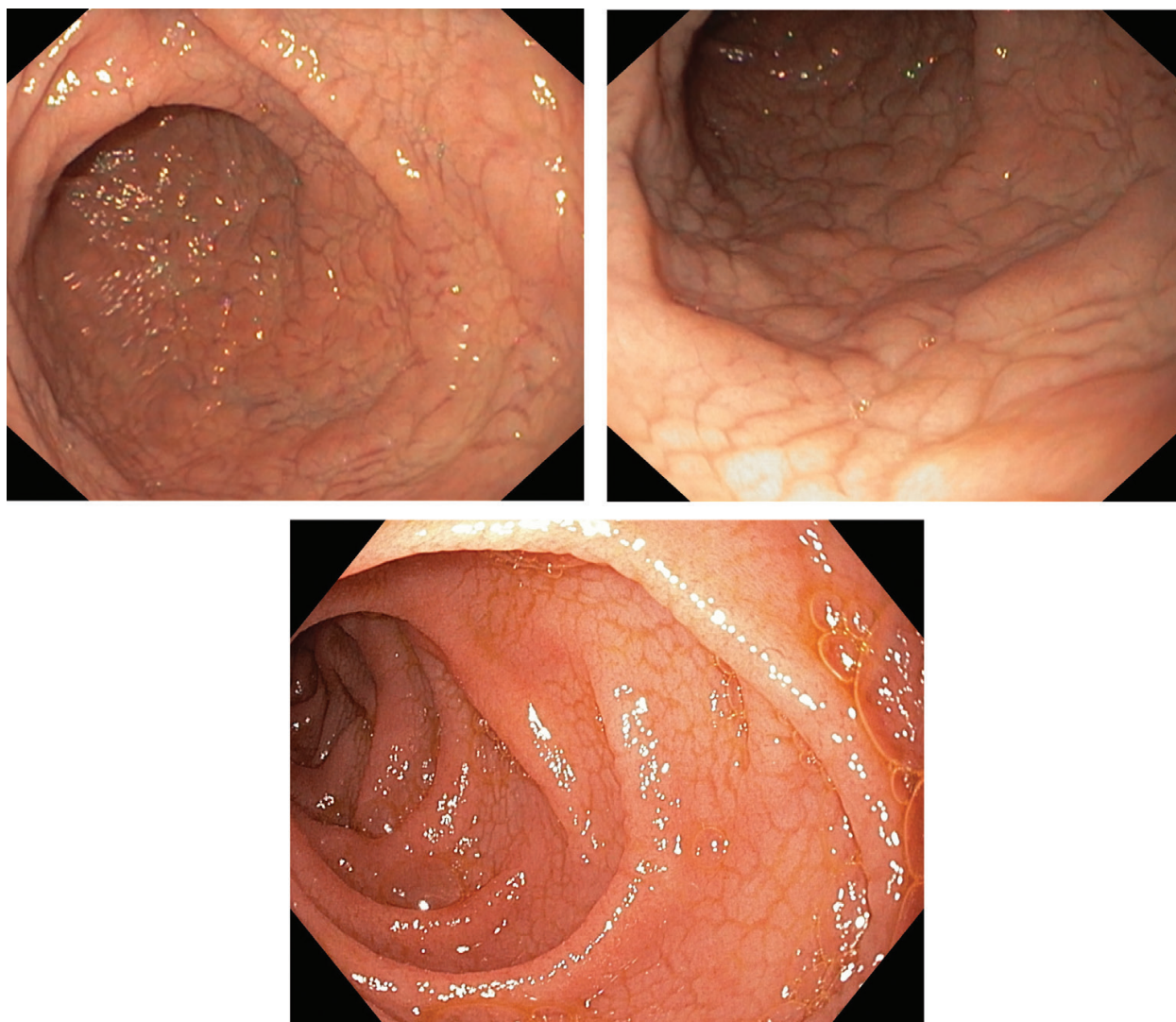
Figure 7. Mosaic pattern of the duodenal mucosa.
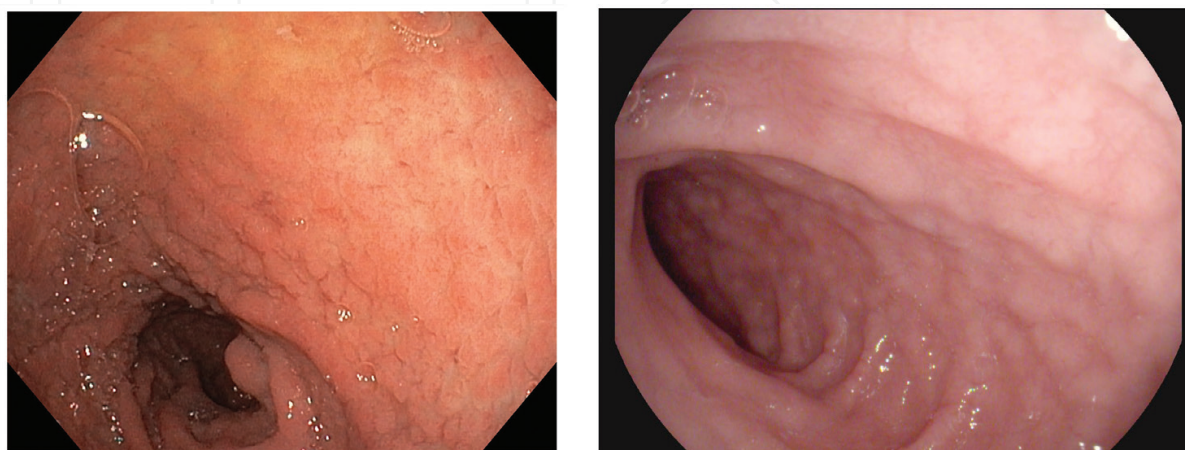
**Figure 8.** Fine nodular pattern of the duodenal mucosa.

**Figure 9.** Standard endoscopy showing fissuring of the mucosa.

Erosions in the duodenum have also been described in celiac disease, but they are more frequently related to peptic injury or non-steroidal anti-inflammatory drug use [74].

Studies assessing the diagnostic performance of aforementioned markers have shown highly variable results, with sensitivity ranging from 6 to 96.7% and specificity from 83 to 100% [75]. This could be explained by the heterogeneity of the studies regarding inclusion criteria, the subjectiveness of the examiners in evaluating the endoscopic markers, and by the different pre-test probability of having celiac disease (as reported in comparative studies with low- and high-risk groups) [76, 77].

Because of the conflicting results of studies investigating the diagnostic accuracy of these endoscopic markers, one cannot rely on their presence or absence to decide whether to do or not to do biopsies in case of suspected celiac disease. Current recommendation is to perform biopsies when there is clinical suspicion of celiac disease, regardless of the presence of endoscopic markers [73], although some proposed that owing to their high negative predictive value, biopsy avoidance could be accepted with a normally appearing duodenum on careful examination in a low-prevalence population [77].
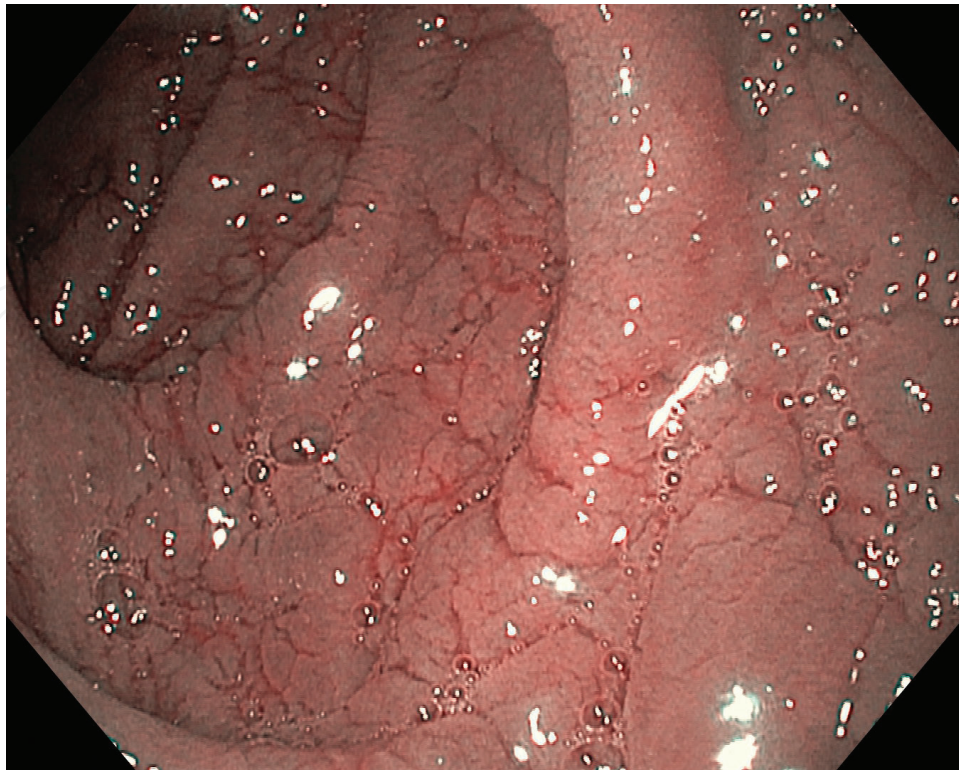
Figure 10. Mucosal fissuring seen with NBI (Olympus, Tokyo, Japan).
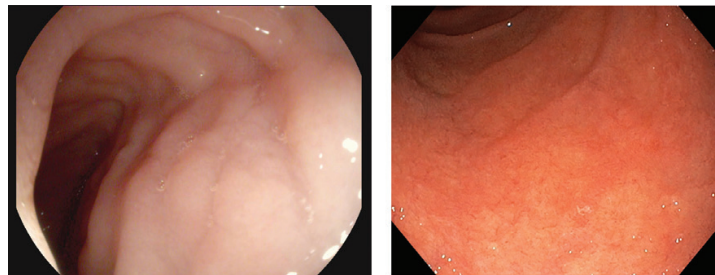
Figure 11. Loss of folds in the distal duodenum.

Another point is that such endoscopic markers are usually described and searched for in the distal duodenum, while bulb changes are frequently neglected [78]—this could be a major pitfall in the practice of endoscopists, especially in light of recent evidence about ultrashort celiac disease (meaning celiac disease with histopathologic changes limited to the duodenal bulb only) [79]. In our paper on this issue [75], we evaluated both the duodenal bulb and the distal duodenum with respect to the presence of endoscopic markers. We have shown high specificity for scalloping, mosaic pattern and fissures, concordant to results of others who even stated that a normal duodenum, with the absence of scallops or grooves, excludes subtotal villous atrophy [80]. Scalloping was reported to be a reliable endoscopic marker for celiac disease from the study of Kasirer also [81].
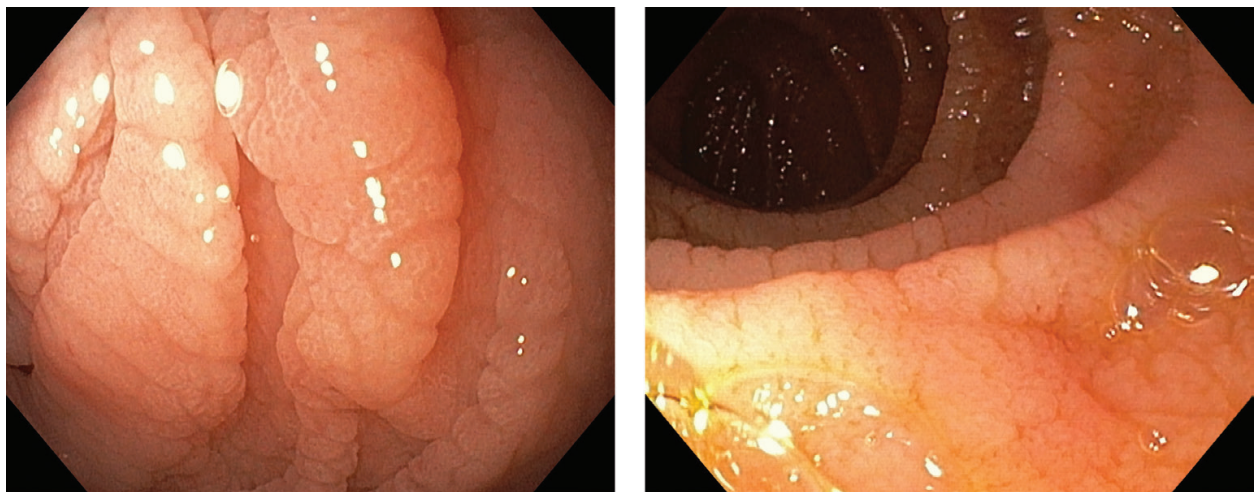
Figure 12. Scalloping of the duodenal mucosa.

At the opposite, reduction in number or loss of folds had a low diagnostic yield, as Niveloni et al. also reported and explained it by the subjectiveness of the endoscopists in the evaluation of folds (interobserver agreement 0.41 compared to 0.76 for mosaic pattern and 0.83 for scalloping) [82]. This finding is supported by the paper of Reyes et al., who stated that reduction or loss of folds are not reliable unless other endoscopic features are also present [77]. On the other hand, Maurino et al. had previously found the opposite—the changes in folds were both sensitive and specific for celiac disease [83]. Regarding the number of markers detected during endoscopy, we found that the presence of two or more markers performed well in predicting celiac disease, with an AUROC (under the curve receiver operating characteristics) of 0.885 [75].

Another issue of these endoscopic markers is that they are present in case of marked villous atrophy, but are usually absent in milder degrees of atrophy (such as Marsh 3a), nondestructive enteropathy (Marsh 1 or 2, meaning infiltrative and hyperplastic enteropathy) or in patchy disease. It has been shown that prevalence of endoscopic markers is lower in partial villous atrophy than subtotal or total villous atrophy (58 vs. 82%) [84]. This is an additional argument, why a no-biopsy strategy, with an apparently normal duodenum, is not feasible.

Also, endoscopic markers are not always that obvious on a gross examination of the duodenum, so that use of novel endoscopic techniques such as chromoendoscopy may be useful to detect these markers by enhancing the subtle changes in the duodenal mucosal pattern. As shown in the study by Niveloni et al., use of chromoendoscopy better delineated the endoscopic markers but did not provide any additional diagnostic yield; however, dye staining improved the interobserver agreement for some of the endoscopic markers (folds changes—k at 0.41 in standard endoscopy, 0.59 with chromoendoscopy) [82]. Other authors have even proposed a key role for these advanced endoscopic techniques in the decision to perform tissue sampling; according to them, biopsy should be done only in patients with villous atrophy detected by image-enhancing endoscopic techniques; however, they also acknowledge that this would miss Marsh 1 patients [85].

In summary, recognition of endoscopic markers during routine endoscopy could represent a great opportunity to increase the diagnostic rate of celiac disease. In the era of open-access endoscopy, this incidental action to detect unsuspected celiac disease patients could have a significant diagnostic impact [86]. Careful examination of the duodenum is needed to detect endoscopic markers of villous atrophy, which should trigger the endoscopist to do biopsies. As shown by Castro et al., detection of endoscopic markers is associated with a high probability of diagnosing celiac disease (15.6 positive likelihood ratio) [87], so they should be attentively searched for, especially in high-risk patients.

However, absence of endoscopic markers does not rule out celiac disease. Not doing biopsies in a normal-appearing duodenum is associated with a significant miss rate [88]. On the other hand, excessive biopsies without any clinical, laboratory workup or endoscopy-guided selection of patients could represent an unnecessary burden to both endoscopists and pathologists. The best approach to maximize the diagnostic rate with limiting unnecessary biopsies is to use a prediction model that combines pre-endoscopic with endoscopic findings [88].

Not least, one should keep in mind that detection of villous atrophy on endoscopy does not necessarily imply celiac disease, as the differential is very wide (peptic injury, infectious enteropathy, common variable immune deficiency, collagenous sprue, autoimmune enteropathy, drug-induced enteropathy, and eosinophilic enteropathy) [89].

4. Computer-aided diagnosis in celiac disease

During routine examinations, analysis of endoscopy images to detect villous atrophy can be quite difficult because of peristalsis, and presence of luminal foam and bubbles; also, mucosal changes are frequently subtle and are not so easy to spot in the above-mentioned conditions. In the last years, great attention has been paid to processing and analyzing of images captured during endoscopy (especially capsule endoscopy), with regard to several image-related characteristics, in evaluating celiac disease patients. The strong point of using such techniques is that it provides a quantitative, automated evaluation compared to the subjectiveness of assessing the presence of endoscopic markers of villous atrophy—it thus eliminates the interobserver bias reported for other techniques [90].

First studies on this matter looked at the texture, brightness, and motility of the small bowel in videoclips from videocapsule examinations of celiac disease patients and controls [91–94].

Later, Ciaccio et al. converted the original images from capsule endoscopy in grayscale and performed an automated histogram analysis, with good results in discriminating celiac disease patients from controls [95]. An interesting feature was that of using shape-from-shading modeling to assess the architecture of the mucosa, which was validated by the same group of Ciaccio et al. [96]—the number of villous protrusions/image was statistically significant lower in celiacs versus controls (p < 0.0001). Other methods tested for the quantitative, computerized assessment of villous atrophy in celiac disease are the degree of fissuring [97] and spectral analysis [98]. They even proposed that such quantitative, automated analysis of the

structural features of the mucosa could be done in real time and displayed as a score during endoscopy [99].

Other research groups have also studied some advanced image processing techniques (wavelets, feature vectors, and distortion correction) in optimizing the computer-aided diagnosis of celiac disease [100–102]. However, these methods are not yet ready for current practice.

But, although histology is the current gold standard in diagnosing celiac disease, computer-aided diagnosis holds very promising for the future. Such computerized methods have been studied on imaging from non-treated celiacs at endoscopy, capsule, and even confocal laser endomicroscopy [103]. Compared to an endoscopy + histology approach, which is invasive, costly, time-consuming and subject to interobserver variability, a computer-based decision strategy is less invasive, time-sparing, and observer independent. Even in the current biopsy-based diagnostic approach, computer-assisted image analysis could be useful by helping endoscopists to target the areas with significant mucosal alterations, which would be otherwise difficult to detect. Not least, the result of using such computational means is numeric, which makes it more accurate in differentiating pathology from normal and in monitoring patients on a gluten-free diet. They need however to be validated in larger cohorts and in gluten-free–treated celiac disease patients. Also, strong collaboration with image engineering techs should be developed in order to optimize descriptors for image processing in celiac disease [104, 105].

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