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REVIEW

Endoscopic tools for the diagnosis and evaluation of celiac disease

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Abstract

Celiac disease (CD) is an autoimmune disease of the small bowel induced by ingestion of wheat, rye and barley. Current guidelines indicate histological analysis on at least four duodenal biopsies as the only way to diagnose CD. These indications are based on the conception of the inability of standard endoscopy to make diagnosis of CD and/or to drive biopsy sampling. Over the last years, technology development of endoscopic devices has greatly ameliorated the accuracy of macroscopic evaluation of duodenal villous pattern, increasing the diagnostic power of endoscopy of CD. The aim of this paper is to review the new endoscopic tools and procedures proved to be useful in the diagnosis of CD, such as chromoendoscopy, Fujinon Intelligent Chromo Endoscopy, Narrow Band Imaging, Optical Coherence Tomography, Water-Immersion Technique, confocal laser endomicroscopy, high-resolution magnification endoscopy, capsule endoscopy and I-Scan technology.

Key words: Celiac disease; Malabsorption syndrome; Duodenum; Diagnostic techniques and procedures; Endoscopy; Chromoendoscopy; Fujinon intelligent chromo endoscopy; Narrow band imaging; Optical coherence tomography; Water-immersion technique; Confocal laser endomicroscopy; High-resolution magnification endoscopy; Capsule endoscopy; I-scan technology

Core tip: Celiac disease (CD) is an autoimmune disorder induced, in genetically predisposed people, by the ingestion of proteins rich in proline and glutamine. The aim of this review is to focus on the new endoscopic tools and techniques developed over the last years which can be useful in the diagnosis and the follow-up of CD.

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder induced, in genetically predisposed people, by the ingestion of proteins rich in proline and glutamine. It occurs in adults and children with an average prevalence of about 1% of the population. CD is characterized by an inflammatory reaction, primarily in the upper small intestine, with features of infiltration of the lamina propria and the epithelium with chronic inflammatory cells and progressive villous atrophy[1,2]. At the state of the art the role of serology is becoming more and more important, so that, according to the European Society for Paediatric Gastroenterology, Hepatology, and nutrition guidelines, diagnosis of celiac disease can be performed without histology in some selected situations-such as the presence, in children, of human leukocyte antigen-DQ2, high titers of

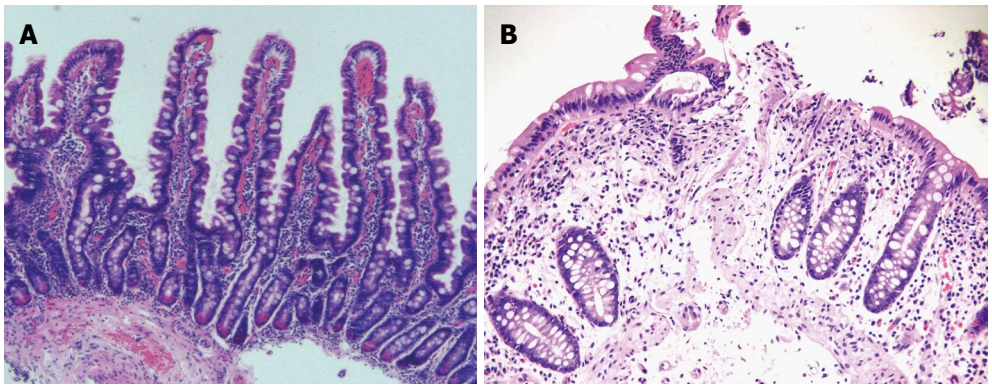

Figure 1 Histological appearance respectively. A: Normal duodenal pattern; B: Celiac disease.

anti-tissue transglutaminase antibodies and the positivity of anti-endomysial antibodies[3]. However, current guidelines indicate histological analysis as the gold standard for the diagnosis of CD: specific pathological features are infiltration of the lamina propria, crypt hyperplasia and villous atrophy, classified according to the Marsh classification and its modifications[4-8] (Figure 1). To perform a correct diagnosis, biopsy specimens have to be well oriented, and of good quality. From 4 to 6 duodenal biopsies, including a bulb biopsy, are required to make diagnosis of CD, even because villous atrophy can be unequally distributed -that is the so-called "patchy atrophy"[7,9-13].

Anyway, the diagnosis of CD can also be missed if the disease is not suspected and biopsy sampling not performed. So, in such situations, the role of the endoscopist becomes crucial, because of the strong importance of the macroscopic appearance of the duodenum[14-16].

STANDARD ENDOSCOPIC FINDINGS

A number of macroscopic endoscopic markers of CD has been identified over the years, and they include the following: "scalloping" -that is a dented aspect- of the duodenal folds; an absence or a reduction in number of duodenal folds; evidence of submucosal vascular pattern; the so-called "mosaicism", which is a micronodular look of the mucosa; finally, grooves and fissurations of the mucosa[9-10,14,15]. Results about the value of these markers, however, are conflicting: among different studies, the overall specificity and sensitivity sways from 83% to 100%, and from 6% to 94%, respectively[14,15,17-26].

This happens probably because endoscopic markers cannot be present in milder degrees of the disease. (such as partial villous atrophy) and absent in case of patchy disease[12,18,19]. On the other hand, scalloped feature of duodenal folds has a positive predictive value of 69% for celiac disease and 96% for any duodenal mucosal disease[27]. So, the contradictory evidences and the low sensitivity of endoscopic markers implicates that bioptic sampling should always be performed when the disease is suspected, because their absence does not exclude the diagnosis[16].

WATER-IMMERSION TECHNIQUE

The water-immersion technique is a easy, prompt and safe procedure of enhancement of duodenal villous pattern during a conventional upper endoscopy. Our group developed this technique as a method to emphasize the visualization of duodenal villi[28], and then modified it to make it helpful in clinical practice[29]. The mechanism of the water-immersion technique is very simple, comprising, at first, the removal of air from the duodenal lumen by suction, quickly followed by the injection of 90-150 mL of water[29]. The procedure requests about 25-30 s more than a standard upper endoscopy, resulting very fast. Our group proved the high accuracy of the water-immersion technique in highlighting the duodenal villous pattern in patients undergoing upper endoscopy for the investigation of dyspepsia[29]. This procedure was also trialed in the follow-up of celiac patients after gluten-free diet[30], and also in cases with patchy villous atrophy or villous abnormality limited to the duodenal bulb[11,30], and moreover in children with suspected CD, achieving the same optimal diagnostic accuracy for *in vivo* prediction of areas of the duodenum with villous damage[31]. The water-immersion technique has the potential to reduce the number of biopsy specimens, because of his power of enhancing visualization of areas with villous atrophy (Figure 2A, B); moreover, in patients strongly suspected from CD and with total villous atrophy at water-immersion visualization during upper endoscopy, the high specificity of the procedure could allow to avoid biopsy sampling, with a considerable cost saving[32]. Furthermore, water-immersion technique shows excellent results in terms of operator learning curve, safety, tolerability, and diagnostic accuracy[11,29-32]. In conclusion, for its facility and quickness of performance, and because of its high reliability in evaluating the duodenal villous pattern, the water-immersion technique could potentially be used as a routine procedure during conventional upper gastrointestinal endoscopy, potentially pulling down the number of misdiagnosis of CD, especially when not suspected. Trials with the water-immersion technique has not been replicated by other

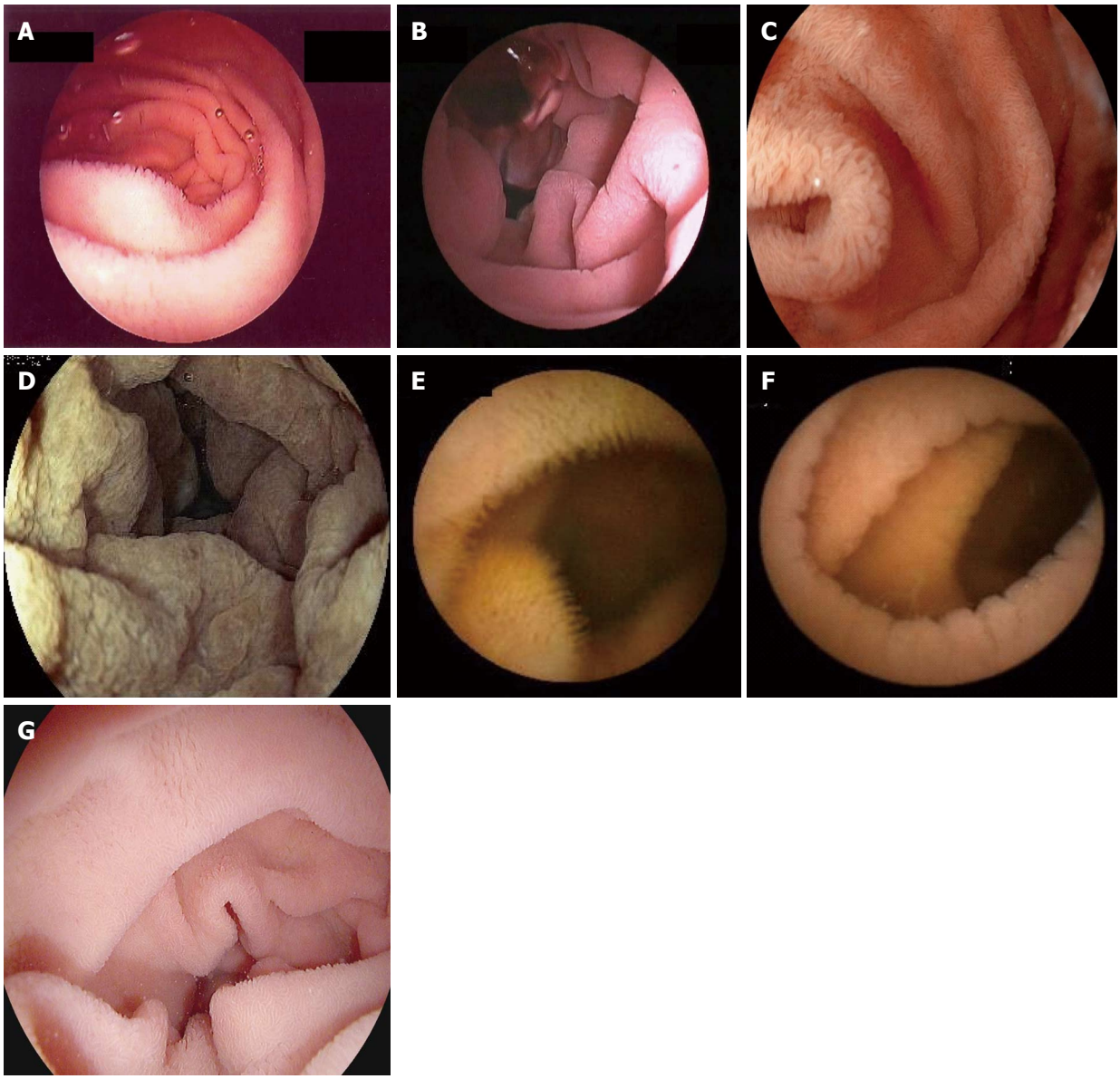

Figure 2 Evaluation of duodenal villous pattern with the water-immersion technique, Fujinon intelligent chromo endoscopy system, capsule endoscopy, I-scan technology. A: Presence of villi with the water-immersion technique; B: Total villous atrophy with the water-immersion technique; C: Presence of villi with Fujinon intelligent chromo endoscopy (FICE) system; D: Total villous atrophy with FICE system; E: Presence of villi with capsule endoscopy; F: Total villous atrophy with capsule endoscopy; G: Duodenal villous pattern with I-scan technology.

groups: therefore, further data, with larger population trials, including large multicenter studies, are required to strengthen this evidence.

CHROMOENDOSCOPY AND HIGH-RESOLUTION MAGNIFICATION ENDOSCOPY

The efficacy of dye-staining chromoendoscopy with indigo carmine or methylene blue in enhancing the visualization of the mucosal surface is nowadays well known[33,34]. The usefulness of chromoendoscopy with indigo carmine for the evaluation of celiac disease was proved yet in 1976[35]. However, this evidence was not confirmed in a latter study[36]. A new generation of endoscopic tools-the "magnification" or "zoom" endoscopes-can produce magnified, high-resolution images (up to 100-135 ×), enhancing details compared to conventional endoscopy[33,37]. They own charged computed device chips with a density of more than 850000 pixels; standard instruments, instead, have charged computer device chips with a density of 100000-300000 pixels. Video endoscopes can provide more and more details about the mucosal surface than conventional ones[38]. The association of indigo carmine-chromoendoscopy and magnification endoscopy in the evaluation of duodenal villous pattern was experienced by Siegel *et al*[39]: this combination showed a sensitivity and specificity of 94% and 88%, respectively for the detection of any villous alteration, and was especially helpful in documenting partial villous atrophy. In a following study, neither this combination technique nor each technology alone showed ad-

vantage compared to standard endoscopy in identifying duodenal lesions such as polyps or hyperplastic Brunner's glands, but anyway authors recognized the role of this combination in case of suspected CD[40]. The role of zoom endoscopy, with a total immersion technique (instillation of 10 mL of water), in the diagnosis of CD was analyzed in 2005[41]: 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 diagnosis of any degree of villous atrophy resulted; diagnosis of total villous atrophy was better performed than diagnosis of partial villous atrophy. Cammarota *et al*[42] investigated the combination of magnification endoscopy and water-immersion technique in subjects with suspected duodenal disease, showing a concordance of 100% with histopathology for detecting the absence or the presence of villi. The sensitivity, specificity, positive predictive value and negative predictive value for the detection of total villous atrophy were all 100%, and quite lower for the diagnosis of partial villous atrophy and normal villous patterns. According to other reports, magnification endoscopy could play a role in the detection of patchy villous atrophy[43,44]. In conclusion, enhanced magnification endoscopy, a technique that combines use of acetic acid instillation with magnification endoscopy, has showed a better accuracy in the evaluation of duodenal mucosal pattern than conventional endoscopy[45].

FUJINON INTELLIGENT CHROMO ENDOSCOPY SYSTEM

Fujinon intelligent chromo endoscopy system or optimal band imaging (also known as multiband imaging) is able to assure the same contrast enhancement power of the standard chromoendoscopy, but in a virtual manner. This technology is based on the selection of particular wavelengths from a reflected light signal, resulting in an establishment of digitally created, enhanced images[46]. The usefulness of FICE technology has been successfully proved in Barrett's metaplasia, early gastric cancer, small colorectal tumors[47-49]; moreover, it has showed a great accuracy (100%) for the evaluation of duodenal villi and for the depiction of duodenal villous patterns in CD[50] (Figure 2C, D).

NARROW BAND IMAGING

Narrow-band imaging (NBI) is a new endoscopic technique that allows evaluation of minimal mucosal alterations. NBI uses a narrowed wavelength of light, deriving from the narrowing of the bandwidths of the blue and green filters. This particular wavelength of light is greatly absorbed by hemoglobin, enhancing the visualization of microvascular pattern. It also has a quite deeper superficial penetration than standard white light[51,52]. The efficacy of NBI has been proved in the endoscopic evaluation of a number of diseases, among which also in CD[53,54]. According to Singh *et al*[54], NBI technique is able to detect and grade villous atrophy, with a sensitivity and specificity in detecting villous atrophy of 93.3% and 97.8% respectively, and a sensitivity and specificity in grading villous atrophy of 83.3% and 100%.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) had its debut in medicine in 1991, and nowadays is a cornerstone in ophthalmology, for the usefulness in the evaluation of the retina and atheromasic plaques[55]. The mechanism of OCT is very similar to that of B-mode ultrasonography: OCT detects the echo time delay and the magnitude of back-scattered light waves from various structural tissue features, using interferometry to measure back-scattered light because the delays of reflected light are too little for a direct electronic measurement[55-57]. The images performed by OCT resemble those generated by B-mode ultrasound and endoscopic ultrasonography; however, the resolution of OCT is better (5-10 mm)-because of the use of light instead of sound waves-, closer to the histological images[55,56,58]. So, OCT allows the study of the proximal layers of gastrointestinal (GI) wall, and may be helpful in the early diagnosis of neoplasms[57]. The usefulness of OCT has been proved yet in the study of GI malignancies[59,60], Barrett's esophagus and dysplasia[61-67], pancreatic and biliary ducts[68,69], and other diseases. Preliminary reports from Masci *et al*[70-72], the use of OCT *in vivo* during real-time endoscopic imaging generated promising results for the evaluation of duodenal villous morphology. These authors, in fact, found total concordance between OCT and histology results for the evaluation of villous morphology in both patients with CD and healthy individuals, also in children, exactly identifying, furthermore, different degrees of villous atrophy.

CONFOCAL LASER ENDOMICROSCOPY

Confocal laser endomicroscopy, or confocal endomicroscopy, is a novel technology that allows an *in-vivo* microscopy of the human gastrointestinal mucosa during upper or lower endoscopy[73,74]. Endomicroscopy has been applied in a number of gastrointestinal diseases, and also in CD[73-77]. In particular, in the experience of Zambelli *et al*[76], the images obtained by confocal endomicroscopy and histology were similar, both for negative subjects and for celiac patients; moreover, in celiac patients confocal endomicroscopy was able to identify moderate-to-severe villous atrophy, but quite less to visualize the crypt hyperplasia and flogistic infiltration. In a case report, CD was diagnosed *in vivo* by confocal endomicroscopy on the basis of the presence of complete villous atrophy and a rise of intraepithelial lymphocytes[77].

VIDEOCAPSULE ENDOSCOPY

Capsule endoscopy is a useful, patient-friendly method for the evaluation of the whole small bowel. Obscure

gastrointestinal bleeding is the strongest indication for capsule endoscopy[78]; however, recent evidences point out new, intriguing purposes and indications: in particular, regarding the object of this review, the role of capsule endoscopy in the diagnosis and follow-up of CD is growing up quickly[79-91]. The optical system of the capsule possesses a 8-folds magnification power, that allows to easily evaluate the duodenal villous pattern (Figure 2E, F). Moreover, it allows an evaluation of the small intestine along its whole length. Capsule endoscopy seems to be able to recognize the endoscopic markers of celiac disease described in the literature, such as scalloping and reduction in number of duodenal plicae, nodularity and mosaic pattern of mucosa[81,82,86,87].

In an initial multicenter trial, capsule endoscopy had an excellent reported sensitivity and specificity of 87.5% and 90.9%, respectively, for the detection of villous atrophy as compared with the criterion standard of duodenal histology[84], but such promising data have not been confirmed in the series presented by the same group[85]. Summarizing the most important studies about the role of capsule endoscopy in CD, it counts a high sensitivity (range, 70%-95.2%), a quite less high specificity (range, 63.6%-100%) and high positive predictive value (96.5%-100%), but a lower negative predictive value (71.4%-88.9%)[82,83,85,88]. These results are cheerful, but the relatively low negative predictive value indicates that CD can't be surely excluded by a negative evaluation at capsule endoscopy.

It should be noted that there is not an overall high degree of agreement between investigators (range 0.41-0.87), and it probably denotes a difficulty in evaluating correctly villous atrophy even if operators are well-experienced in video capsule enteroscopy.

However, the use of capsule endoscopy could be considered in patients with positive tissue transglutaminase or anti-endomysial antibodies who are unable or unwilling to perform an upper endoscopy[89], and also for the evaluation of the whole small bowel in patients with positive antibodies and duodenal histology negative for CD, even if regarding evidences don't confirm this hypothesis[90]. More realistically, capsule endoscopy can be very useful in case of suspected refractory or complicated CD. In particular, capsule endoscopy can detect alterations such as malignancy or ulcerative jejunitis in refractory celiac disease (RCD) type Ⅱ, but evidences are not so bright regarding RCD type Ⅰ [91].

I-SCAN TECHNOLOGY

I-scan technology is an image enhanced endoscopy technology recently developed by Pentax Medical®, Japan[92]. It can be classified among digital contrast methods. It allows three different modalities of image enhancement: surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). SE enhances light-dark contrast by obtaining luminance intensity data for each pixel. CE digitally adds blue color in relatively dark areas, enhancing minute irregularities on the mucosal depressed areas. Both enhancement functions work in real time without impairing the original color of the organ. TE separates and analyzes the individual red, green and blue components of a normal image; the algorithm then alters the color frequencies of each component, recombining the components to a single, new color image. For SE and CE, it is possible to switch among three enhancement levels (low, medium and high). At now, three types of TE are available: TE-e (for esophagus), TE-g (for stomach) and TE-c (for intestine). Switching the levels or modes of enhancements can be done on a real-time basis, without any time lag, by pushing a relevant button.

I-scan technology has been applied to several field of interest in gastrointestinal endoscopy, such as colorectal lesions[93-97], Whipple's disease[98], gastroesophageal reflux disease[99-101], Barrett's esophagus[102]. Recently, our group has experienced I-scan technology for the evaluation of duodenal villous pattern[103], with the following results: I-scan system was demonstrated to have great accuracy (100%) in the detection of marked villous atrophy patterns and quite lower accuracy in determining partial villous atrophy or normal villous patterns (respectively, 90% for both items) (Figure 2G).

Therefore, I-scan technology seems to be a reliable tool also for the diagnosis of CD. Obviously, further, larger studies are needed to confirm this feeling.

CONCLUSION

The recent advances in terms of technology and techniques of endoscopy, reviewed above, can certainly improve our diagnostic possibilities in the evaluation of CD, and should not be ignored, but accepted with wisdom. Surely, it is important to perform these tools in appropriate endoscopic centers, owning good equipment and enough expertise. Moreover, in a hypothetic world without biopsy sampling, but with a virtual histological analysis, a gastroenterologist can not absolutely brush aside a solid histological training. Therefore the most realistic scenario is not a replacement, but an interaction between endoscopic and histological analysis: a similar "joint-venture" might knock down misdiagnoses and reduce overall costs of diagnostic course of CD: large, randomized trials, also with cost analyses and clinical outcome evaluations, are needed to carry out this concept.

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