

# High definition i-SCAN endoscopy with water immersion technique accurately reflects histological severity of celiac disease

## Authors

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**Background and aims:** Severe villous atrophy can be revealed with conventional white light endoscopy (WLE), however, milder grades or patchy villous atrophy are more difficult to detect. Novel endoscopic techniques such as high definition i-SCAN endoscopy with the water immersion technique (i-SCAN-HDWI) may provide the ability to visualize duodenal villi more accurately. We aimed to determine the performance of i-SCAN-HDWI in evaluating the severity of histological damage in the duodenum of patients with celiac disease.

**Patients and methods:** A retrospective cohort study was performed in a single tertiary academic endoscopic center. We studied 58 patients (46 women; median age 36.5 years, range 18–72 years) with positive anti-TTG IgA antibody. The villous pattern of the second part of the duodenum was assessed by WLE and i-SCAN-HDWI. The endoscopic grades in both techniques were correlated using Marsh histologic grades by

Spearman correlation coefficient. The diagnostic accuracy of i-SCAN-HDWI for detection of patchy or complete atrophy of the villi was evaluated.

**Results:** A significant correlation was demonstrated between endoscopic grade using i-SCAN-HDWI and Marsh histologic grade ( $r=0.732$ ;  $P<0.00001$ ). The correlation between WLE grade and Marsh histologic grade was inferior to i-SCAN-HDWI ( $r=0.31$ ;  $P=0.01$ ). The sensitivity of i-SCAN-HDWI was 96% (95%CI: 85–99%) and the specificity was 63% (95%CI: 26–90%) in diagnosing abnormal biopsy consistent with celiac disease.

**Conclusion:** i-SCAN-HDWI endoscopy can reflect the histological severity of celiac disease more accurately than conventional WLE alone. This novel endoscopic imaging can improve the diagnostic yield of duodenal biopsies in celiac patients, especially for those with a patchy distribution of villous damage.

## Background

Celiac disease is an autoimmune reaction to dietary gluten that affects the small intestine in those with a genetic predisposition. The prevalence of celiac disease has seen a significant increase over the last 10 years [1–3]. Unfortunately, some of these patients may be difficult to diagnose despite positive serology due to the irregular and patchy histological distribution of abnormalities in the small bowel affected by celiac disease, whose biopsies may be negative, unless targeted biopsies are taken. Patients who partially avoid gluten before biopsies may also have a patchy distribution of abnormalities. In addition, despite gluten avoidance, it may make patients with persistent gastrointestinal symptoms difficult to assess if they only have patchy recovery of the villi [4–7]. Several endoscopic features are well characterized with standard white light endoscopy

(WLE) such as reduction in the folds, mosaic or nodular pattern, scalloping and atrophy of the villi with visible vessels [8, 9]. However, controversial results have been reported concerning the accuracy of these endoscopic markers to predict partial or patchy villous atrophy. The overall sensitivity and specificity of these endoscopic findings in celiac disease vary from 6% to 94% and from 83% to 100%, respectively [10–13]. Novel endoscopic techniques such as water immersion, dye and virtual chromoendoscopy, high definition-zoom magnification, narrow-band imaging (NBI), Fujinon intelligent chromoendoscopy (FICE), optical coherence tomography, probe confocal laser endomicroscopy, and video capsule endoscopy have been developed to provide the ability to visualize the architecture of the villi directly and more accurately [14–27]. The water immersion technique during normal endoscopy is very accurate for detection of total villi atrophy

## License terms



but less accurate in detecting partial villous atrophy (PVA) [17, 19]. Recently, an Italian group has shown that chromoendoscopy with Indigo carmine and endoscopic zoom magnification is also very accurate in difficult diagnoses of celiac disease [25]. However, dye chromoendoscopy can be expensive and time consuming.

The newly developed i-SCAN technology is a post-processing imaging technology that analyzes endoscopic images in real time without the use of dye. It can be performed by simply pressing a button on the endoscope thereby allowing the endoscopist to alternate between different setting modalities in real time [26]. One of the recent studies was performed by Cammarota et al. on the use of i-SCAN in patients with celiac disease and it seems to be a potentially useful tool to anticipate *in vivo* the presence of severe duodenal villi abnormality but it had lower accuracy to detect and predict partial villous atrophy (PVA) or normal villi [27]. Hence, there is a need to study the combination of i-SCAN imaging at endoscopy with the water immersion technique, which should be convenient to perform.

This study aimed to determine the performance of i-SCAN high definition endoscopy in combination with the water immersion technique (i-SCAN-HDWI) in evaluating the severity of histological damage in the duodenum in patients with celiac disease, especially for those with a patchy distribution of villous damage.

## Patients and methods



### Study design

This was a retrospective cohort study performed at a single tertiary referral center. The Conjoint Health Research Ethics Board of the University of Calgary and Calgary Central Laboratory Services approved the study.

### Patients

We studied 58 consecutive patients (46 women; median age 36.5 years, range 18–72 years) with positive anti-TTG IgA antibody who underwent i-SCAN-HDWI endoscopy (Pentax EG-2985K) during the period from September 2011 to December 2013. These patients were referred for upper endoscopy and biopsies. The patients were not on a gluten free diet (GFD).

### Endoscopic procedure – i-SCAN-HDWI

All endoscopic examinations were performed by a single gastroenterologist (MI) experienced in using the i-SCAN technique. All procedures were performed under sedation. Retrospective assessment of the i-SCAN images was performed by two endoscopists (MI and SG). All esophagogastroduodenoscopy (EGD) procedures were performed with a Pentax EPK-I processor, using HD-i-SCAN virtual chromoendoscopy in combination with the water immersion technique (Pentax EC 2985K; Tokyo, Japan). The i-SCAN system is a new and emerging digital virtual chromoendoscopy technique. It is a post-processing imaging technology that analyzes the endoscopic image in real time. This consists of three types of algorithm: surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE) and can provide detailed analysis based on vessel (i-SCAN v), mucosal pattern (i-SCAN p), or surface architecture (i-SCAN SE), and each of these algorithms can be selected by pressing a pre-assigned button on the scope [26].

All patients underwent EGD with an initial careful endoscopic inspection of the duodenum with WLE. Then i-SCAN-HDWI was performed in three steps, first i-SCAN-HDWI with i-SCAN 1 (i.e. high definition water immersion) and then with i-SCAN 2–3 (i-SCAN-HDWI). The latter is considered to be i-SCAN-HDWI together (Fig. 1, Fig. 2, Fig. 3).

The water immersion endoscopic technique was performed during the examination of the bulb and the second part of the duodenum. After removal of air from the lumen of the duodenum by suction, about 100–150 mL of water was rapidly introduced with a pump jet and all three i-SCAN sets were used in sequence, from set 1 to set 3, spending an average time of 15–20 seconds for each single i-SCAN set. The different mucosal patterns of the villi in the duodenum were assessed and graded first with the WLE (standard definition) technique as normal (1), reduction in folds (2), mosaic pattern (3), scalloping (4) and atrophy with visible vessels (5), and then with the i-SCAN-HDWI endoscopic technique (Table 1). The i-SCAN-HDWI was graded as normal, mild, moderate, patchy atrophy of villi, or severe atrophy of villi (Table 2).

The retrospective assessment of six high quality i-SCAN-WDWI endoscopic images in the duodenum was performed by two endoscopists (MI, SG) and the inter-observer agreement was calculated (Kappa agreement statistics).

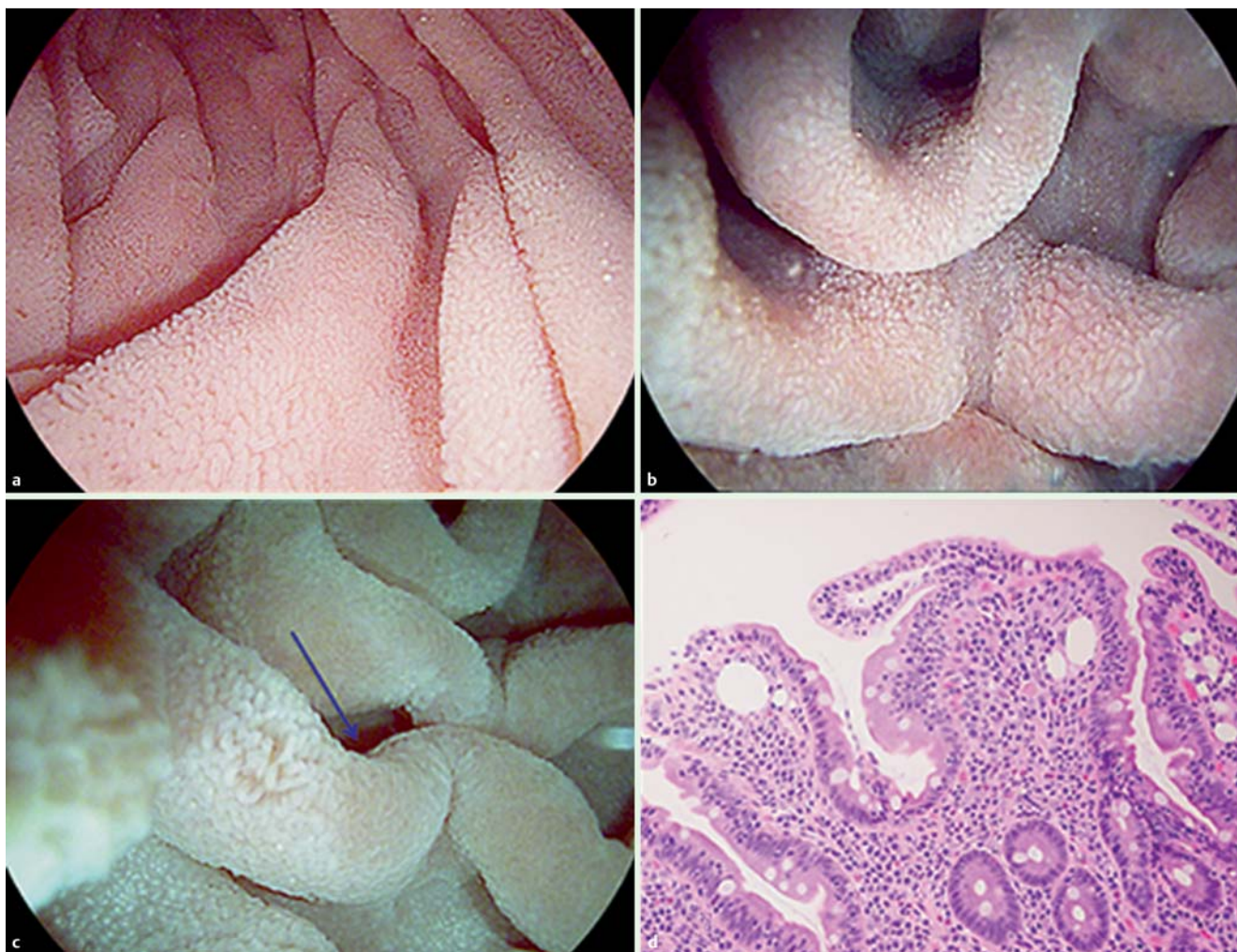
### Histological assessment

A comprehensive histological assessment was performed by one gastrointestinal histopathologist (XG) who was unaware of the endoscopic findings or grading. Four i-SCAN-targeted biopsies were taken from the second part of the duodenum and two from the bulb of the duodenum. The histologic changes in the duodenal biopsies taken from the corresponding duodenal regions were graded using Marsh's classification as revised by Oberhuber et al. [28] (Table 3). The histological score categorized the severity of celiac disease as Marsh 1, Marsh 2, or Marsh 3A–C based on the degree of villous blunting, number of intraepithelial lymphocytes, and volume of deep crypts of duodenal mucosa. The key for Marsh's score for analysis was defined as 1–normal, 2–Marsh 1, 3–Marsh 2, 4–Marsh 3A, 5–Marsh 3B, 6–Marsh 3C.

### Statistical analysis

The correlation between histology scores and endoscopy scores used in the study was calculated using the non-parametric Spearman's correlation approach. The sensitivity, specificity, and accuracy values for the endoscopic i-SCAN-based investigation in predicting histological findings were estimated. Confidence intervals at 95% were calculated.

Two endoscopists (MI, SG) analyzed six high quality anonymized i-SCAN images. These images represented the bulb and the second portion of the duodenum of the same patient. The images were anonymous and while MI had performed the procedures, the anonymous nature of the images and the fact that the second rater SG was blinded ensured robustness of agreement. The inter-observer and intraobserver agreement was calculated using Cohen Kappa statistics. Interpretation of Kappa values was done according to evaluation of Cohen's Kappa with >0.75 indicating good agreement, 0.4–0.75 indicating fair to good agreement, and <0.4 indicating poor agreement. The statistical analyses were carried out using the SPSS statistical software package v.22 (IBM, Armonk, New York, United States).



**Fig. 1 a–c** i-SCAN-HDWI using high definition alone or virtual chromoendoscopy in combination with water immersion technique showed this transitional area of normal and patchy atrophic villi. **d** Hematoxylin and eosin staining with magnification  $\times 200$  showed patchy atrophy of the villi; Marsh modified 3b

## Results



### Patient characteristics

In total, 58 consecutive patient (46 women; median age 36.5 years, range 18–72 years) with positive anti-endomysial antibodies or anti-transglutaminase antibodies and with a clinical history consistent with celiac disease were enrolled in the study when they were referred for EGD. Clinical history included symptoms and signs of diarrhea, abdominal pain, bloating and distension, iron deficiency anemia, and weight loss.

### Endoscopic findings on i-SCAN-HDWI

Of the 58 patients, Marsh grades were as follows: normal ( $n=1$ ), Marsh 1 ( $n=7$ ), Marsh 2 ( $n=7$ ), Marsh 3A ( $n=14$ ), Marsh 3B ( $n=12$ ), Marsh 3C ( $n=17$ ) (Table 3).

The seven patients with Marsh grade 1 were not included in the statistical analysis to determine the correlation with WLE and with i-SCAN-HDWI, as the mucosa appeared normal.

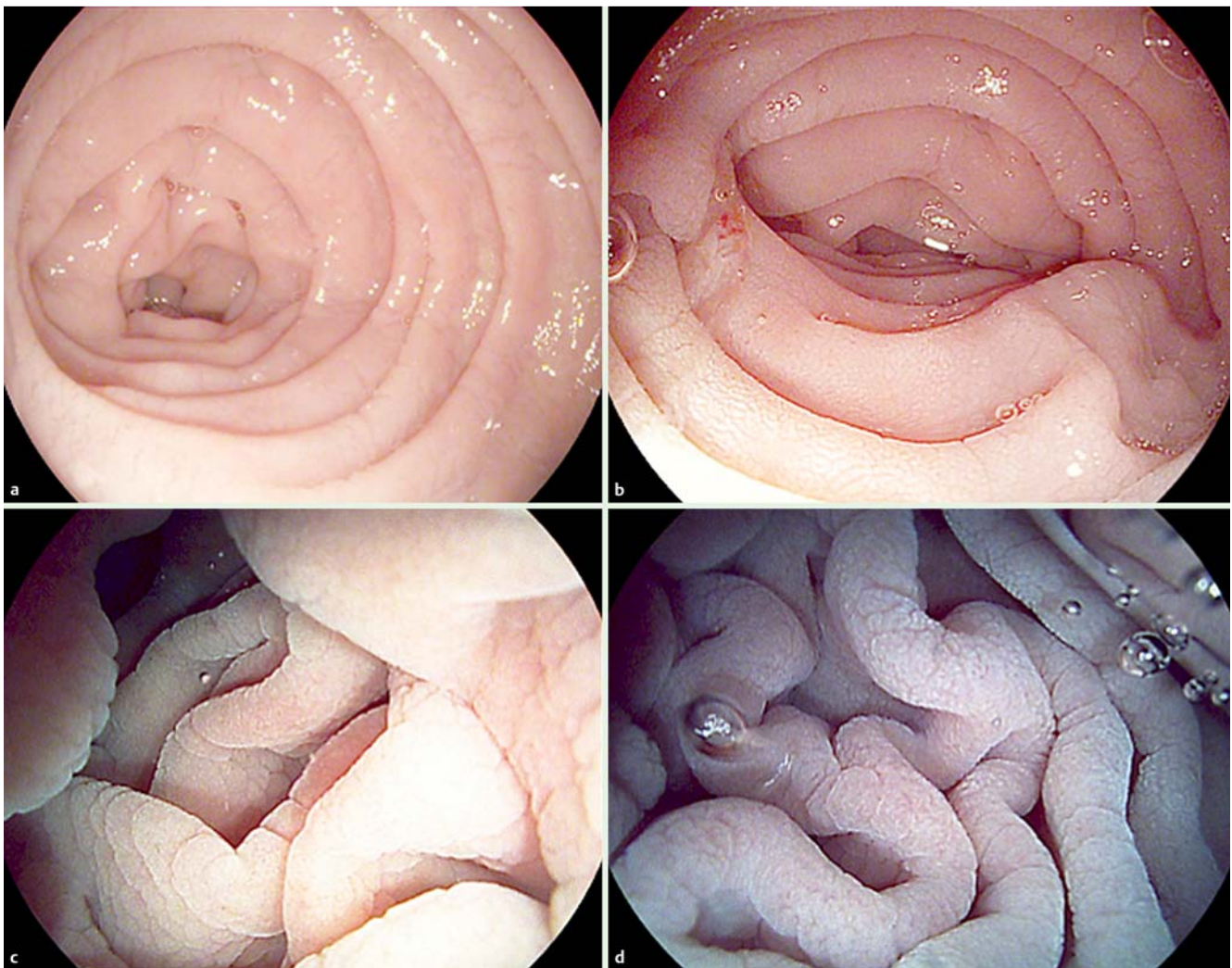
A significant and good correlation was demonstrated between endoscopic grade using i-SCAN-HDWI and modified Marsh histologic grade ( $r=0.732$ ;  $P<0.00001$ ) (Table 4). The correlation between standard WLE grade and Marsh histologic grade was poorer than with i-SCAN-HDWI ( $r=0.31$ ;  $P=0.01$ ).

The sensitivity of i-SCAN-HDWI was 96% (95%CI: 85–99%) and the specificity was 63% (95%CI: 26–90%) in diagnosing abnormal biopsy consistent with celiac disease (Marsh 2, 3a, 3b, 3c). [If Marsh grade 1 was included, the sensitivity was 88% (95%CI 76–95%)]. The accuracy of i-SCAN-HDWI to predict histology was 100% (51 out of 51) if Marsh grade 1 was excluded.

The sensitivity of WLE (standard definition) was 78% (95%CI 64–88%) and specificity was 50% (95%CI 17–83%) in diagnosing abnormal biopsy consistent with celiac disease (Marsh 2, 3a, 3b, 3c). [If Marsh grade 1 was included, the sensitivity was 74% (95%CI 60–84%)]. The accuracy of WLE (standard definition) to predict histology was 72%.

Of the nine patients with patchy atrophy of the villi on i-SCAN-HDWI, five showed normal endoscopic findings on WLE (standard definition) (55.6%). Of the six patients with mild atrophy of the villi on i-SCAN-HDWI, two patients had normal endoscopic findings on WLE (standard definition) (33.3%). Of the 20 patients with moderate atrophy of the villi on i-SCAN-HDWI, only two patients had normal endoscopic finding on WLE (standard definition) (10%).

The interobserver agreement of i-SCAN-HDWI between the two endoscopists was calculated and the Kappa statistic was 0.86 (95%CI 0.72–0.90) and the strength of observation was considered to be 'very good'.



**Fig. 2** a WLE (standard definition) showed scalloping in the duodenum. b High definition-i-SCAN technique improved the characterization and the detailed atrophy of the villi. c, d i-SCAN-HD virtual chromoendoscopy in combination with water immersion technique enhanced and magnified the moderate atrophy of the villi

## Discussion

The current study showed that high definition i-SCAN in combination with the water immersion endoscopic technique has a good accuracy in the diagnosis of patchy atrophy of villi in patients with celiac disease. Endoscopy with histological assessment of villous atrophy of the duodenum still represents the gold standard for diagnosis of celiac disease.

However, WLE with random biopsies in the duodenum has not been shown to have great accuracy in the diagnosis of celiac disease [10, 13]. Our study has shown a poorer correlation between WLE grade and Marsh histologic grade in the diagnosis of celiac disease ( $r=0.31$ ;  $P=0.01$ ) compared with the i-SCAN-HDWI endoscopic technique. In addition, a more recent paper by Barada et al. has indicated that standard endoscopic findings were related to a significant rate of underdiagnosis of celiac disease [13].

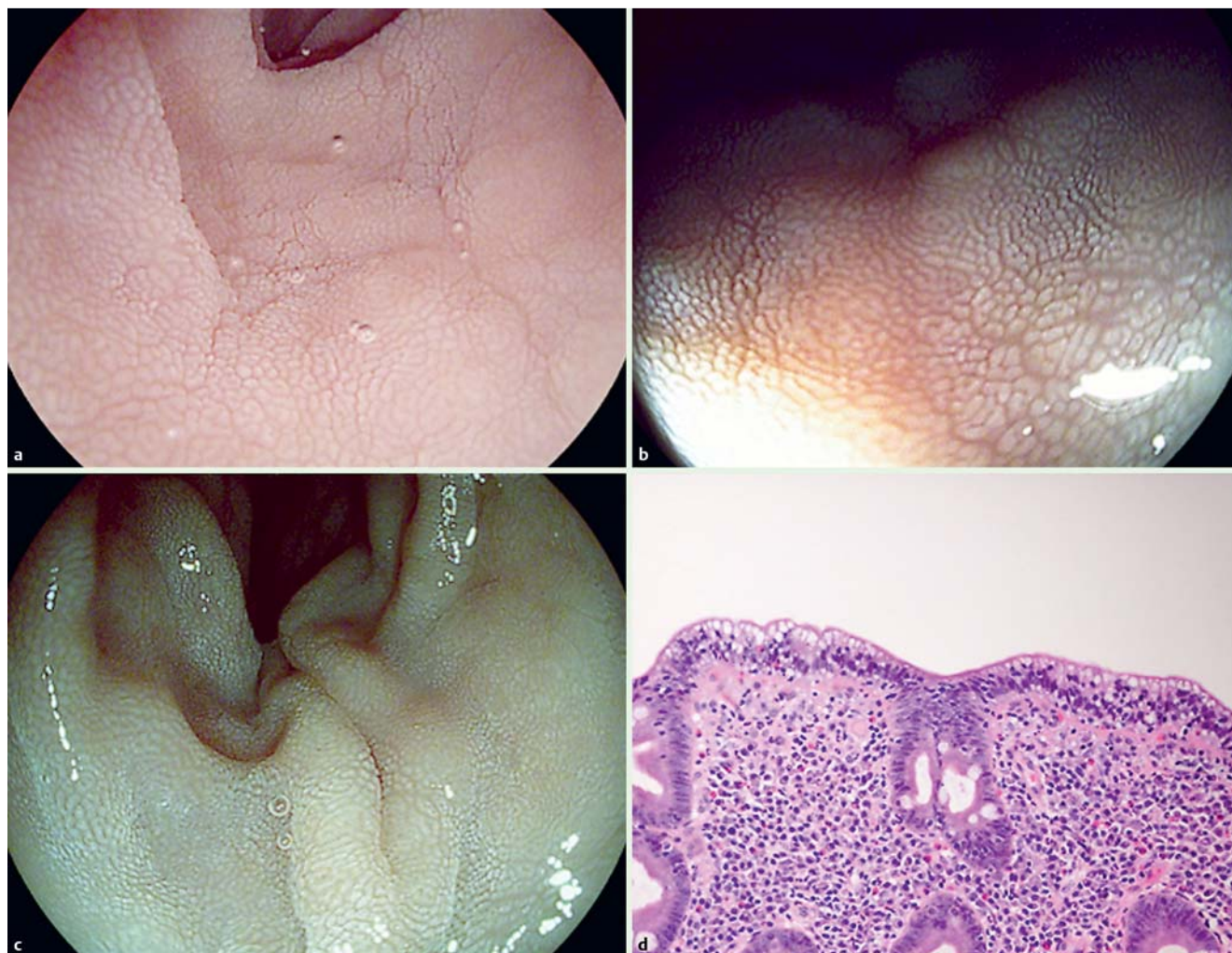
Novel emerging endoscopic techniques such as water immersion techniques, chromoendoscopy, and optical digital enhancement virtual chromoendoscopy have been developed to better characterize in detail the vascular and surface architecture of the gastrointestinal tract. These endoscopic techniques have been found to be a useful adjunctive tool to increase the diagnostic yield of

celiac disease, especially in the presence of patchy villous atrophy [14, 27]. All procedures were performed under sedation, and the instillation of 100–150 mL of water was not associated with any episode of bronchial aspiration. The fluid was rapidly aspirated after detailed inspection.

In our study, we have found a significant correlation between endoscopic grade using i-SCAN-HDWI and modified Marsh histologic grade ( $r=0.732$ ;  $P<0.00001$ ). Correlation coefficients were used to indicate a linear relationship between the different methods but these did not indicate agreement.

The strength of agreement between the two i-SCAN readers (MI and SG) was considered to be very good. The two endoscopists have performed more than a thousand i-SCAN procedures.

Cammarota and colleagues [18], pioneers of the water immersion endoscopic technique, have demonstrated that the sensitivity, specificity, and positive and negative predictive values of the immersion-based duodenal investigation in predicting areas of duodenal villous atrophy were always 100%. In contrast, the water immersion technique alone was less accurate in distinguishing partial villous atrophy (PVA) (72% sensitivity and 97% specificity values) from a normal condition of the villi (97% sensitivity and 85% specificity).



**Fig. 3 a – c** i-SCAN-HD alone or with virtual chromoendoscopy in combination with water immersion technique showed severe atrophy of the villi and could differentiate single villi in detail. **d** Hematoxylin and eosin staining with magnification  $\times 50$  revealed severe atrophy; Marsh modified 3c

**Table 1** White light standard endoscopic classification.

Normal villi
Reduction of the fold
Mosaic pattern
Scalloping
Atrophy with visible vessels

**Table 2** i-SCAN-HDWI endoscopic classification.

Normal villi	Arranged as regular carpet of fingertips
Mild atrophy of villi	Irregular shape and arrangement and shortened villi of villi
Moderate atrophy of villi	Very shortened but still detectable villi
Patchy atrophy of villi	Patchy areas of flattened villi within normal finger-shaped arrangement
Severe atrophy of villi	Completely flat duodenal mucosa with no identifiable villi

**Table 3** Modified Marsh histological classification.

Marsh Type	IEL/100 enterocytes	Crypt hyperplasia	Villi
0	<40	Normal	Normal
1	>40	Normal	Normal
2	>40	Increased	Normal
3a	>40	Increased	Mild atrophy
3b	>40	Increased	Marked atrophy
3c	>40	Increased	Absent

IEL/100 enterocytes, intraepithelial lymphocytes per 100 enterocytes.

**Table 4** Endoscopic findings for HD-i-SCAN with water immersion and agreement with histological Marsh grade (one patient was negative for celiac disease).

i-SCAN-HDWI	Marsh 2	Marsh 3A	Marsh 3b	Marsh 3c
Normal villi	1	–	–	–
Mild atrophy of villi	2	–	1	–
Moderate atrophy of villi	3	9	3	5
Patchy atrophy of villi	3	4	1	1
Severe atrophy of villi	–	–	6	11

Correlation between endoscopic grade and histologic grade was  $r=0.734$  using Spearman correlation.

The same result has been confirmed by Cammarota et al. using i-SCAN techniques alone with high accuracy (100%) in the detection of marked villous atrophy patterns but has shown lower accuracy in characterizing PVA or normal villous patterns [27].

It is becoming recognized that patients with celiac disease (especially when on a partial gluten free diet) may have endoscopic irregular or patchy distribution of gluten-sensitive enteropathy, which can be difficult to detect by WLE (standard definition). Moreover, some patients with celiac disease, especially those with a patchy distribution of atrophy of the small bowel, may have negative celiac disease-specific serology and positive HLA DQ2-DQ8, but this does not completely exclude the diagnosis of celiac disease. This, unfortunately, could cause underdiagnosis, especially when random specimens of apparently normal mucosa are taken during endoscopy [3, 14].

High magnification endoscopy with virtual or dye chromoendoscopy has been shown to improve the detection and diagnosis of partial villous atrophy of the villi compared with WLE (standard definition) [15, 16]. Iovino et al. have demonstrated that chromoendoscopy with indigo carmine and endoscopic zoom-magnification chromo-zoom endoscopy have high accuracy for cases of difficult diagnosis of celiac disease, but only in untreated patients with celiac disease [25].

In our study, we have combined i-SCAN high definition endoscopy with the water immersion technique (i-SCAN-HDWI) to determine whether both techniques could better magnify the architecture of the villi and improve the accuracy and diagnostic yield of patchy atrophy of the villi in the duodenum (Fig. 1, Fig. 2, Fig. 3). We have also confirmed the good sensitivity of i-SCAN-HDWI—96% (95%CI: 85–99%) in diagnosing abnormal biopsy consistent with celiac disease (Marsh 2, 3a, 3b, 3c) and the good accuracy of i-SCAN-HDWI to predict histology. It was interesting that, of the nine (15.5%) patients with patchy atrophy of the villi, six showed normal endoscopic findings on WLE but all of them had positive endoscopic findings on i-SCAN-HDWI.

In future, analysis of endoscopic images obtained directly or via wireless capsule using computerized image analysis may help to distinguish various degrees of villous atrophy. Ciaccio and colleagues have analyzed endoscopic images and have recently tested a quantitative technique for the evaluation of villous atrophy and of motility in endoscopic images [29, 30]; however, histological diagnosis still represents the gold standard for celiac diagnosis. Limitations of this study include the fact that it is a retrospective study, and that it is a single center study. We did not use the water immersion technique in isolation with WLE, or in isolation with the i-SCAN technique. However, the study is strengthened by the fact that it is the first to assess patients with celiac disease using HD i-SCAN in combination with the water immersion technique, which improved the diagnosis of patchy atrophy of the villi in celiac disease. It will require long-term prospective studies with a larger number of patients to validate these findings. We feel that, in this era, these electronic image enhancement techniques can provide a much clearer characterization of the vascular pattern and surface architecture of the villi and may be an important adjunctive tool, especially to recognize the patchy distribution of villi in patients who were serologically positive or negative for celiac disease. The water immersion and i-SCAN techniques can be easily and regularly performed in the duodenum by endoscopists during routine EGD. This procedure is simple, feasible, and can accurately detect atrophy of the villi. However, the learning curve for this technique was not evaluated as this was not an aim in this study.

## Conclusions

High definition-i-SCAN endoscopy with the water immersion technique (i-SCAN-HDWI) provides the ability to enhance the vascular and mucosal pattern and to visualize duodenal villi directly and more accurately. These endoscopic techniques in combination can improve the characterization of patchy atrophy of the villi and differentiate Marsh histological grades. They can help in directing and targeting duodenal biopsies and improve their diagnostic yield in celiac patients, especially for those with difficult diagnoses and patchy distribution of villous damage. However, large and multinational validation studies are required to confirm the ability of these techniques for widespread use in daily clinical practice and to establish their learning curve. It is important to be aware of the limitations of the usual white-light endoscopy technique in recognizing these subtle abnormalities.

**Competing interests:** None

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