A prospective evaluation of endoscopic markers for identifying celiac disease in patients with high and low probability of having the disease

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Summary

Background/Objectives: *the usefulness of duodenoscopic markers for predicting celiac disease (CD) has been questioned. We assessed the diagnostic efficacy of endoscopic markers of mucosal atrophy in individuals with different pretest probability of CD.* ***Methods:*** *we prospectively performed endoscopic intestinal biopsies and CD-related serology tests in 661 individuals, including 143 consecutive patients attending a malabsorption clinic (high pretest probability) and 518 subjects randomly selected from those undergoing routine endoscopy because of upper GI symptoms (low pretest probability). Duodenoscopic markers reported were: mosaic pattern, scalloped folds, and reduction in number or loss of Kerkring´s folds.* ***Results:*** *sixty-three (44.1%) and 18 (3.5%) patients were diagnosed with CD in the high and low risk groups, respectively. Among high pretest subjects, the presence of any marker had very high sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy for the identification of CD (92.1%, 93.8%, 92.1%, 93.8% and 93.0%, respectively). The performance of these parameters for the presence of any marker in the low pretest population were 61.1%, 96.8%, 40.7%, 98.6% and 95.6%, respectively. Sensitivity ($p<0.004$) and positive predictive value ($p<0.0001$) of markers were significantly higher for the high risk patients. The identification of a reduction in number or loss of Kerkring´s folds was not a reliable finding unless other signs were also present.* ***Conclusions:*** *we confirm that endoscopic markers are useful in predicting CD in different clinical scenarios. The high negative predictive value in the low probability group suggests that intestinal biopsy is not required if endoscopic markers are absent.*

Key words: *celiac disease, endoscopic markers, Malabsorption, diagnostic efficacy.*

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Evaluación prospectiva de signos endoscópicos duodenales para identificar enfermedad celíaca en pacientes con alta y baja probabilidad de tener la enfermedad

Resumen

Introducción/Objetivos: *la utilidad de los signos duodenoscópicos para predecir el hallazgo de enfermedad celíaca (EC) ha sido cuestionada. Nosotros evaluamos la eficacia diagnóstica de los signos endoscópicos de atrofia mucosa intestinal en individuos con diferente riesgo de padecer EC.* ***Métodos:*** *en forma prospectiva realizamos biopsias duodenales endoscópicas y serología específica de EC en 661 individuos, incluyendo 143 pacientes consecutivos que consultaron por sospecha de enfermedad intestinal (alto riesgo) y 518 sujetos selec-*

cionados al azar entre los derivados para endoscopía digestiva superior por la presencia de síntomas digestivos altos (bajo riesgo). Los signos duodenoscópicos evaluados fueron: la patente de mosaico, pliegues peinados y reducción en el número o pérdida de pliegues de Kerkring. ***Resultados:*** *sesenta y tres (44.1%) y 18 (3.5%) pacientes, respectivamente, presentaron EC en los grupos de alto y bajo riesgo. En la población de alto riesgo, la presencia de cualquier signo (al menos uno de ellos) tuvo muy alta sensibilidad, especificidad, valores predictivos positivo y negativo, y seguridad diagnóstica para la identificación de EC (92.1%, 93.8%, 92.1%, 93.8% y 93.0%, respectivamente). En el grupo de bajo riesgo el valor estadístico para la visión de al menos un marcador fue 61.1%, 96.8%, 40.7%, 98.6% y 95.6%, respectivamente. La sensibilidad ($p<0.004$) y el valor predictivo positivo ($p<0.0001$) fueron significativamente mayores para la población de alto riesgo. La identificación de una reducción en el número o la pérdida de los pliegues de Kerkring no fue un rasgo confiable para identificar pacientes con EC a menos que otros signos estuvieran presentes.* ***Conclusiones:*** *confirmamos que la presencia de las marcas duodenoscópicas características de la atrofia mucosa son muy útiles para predecir la presencia de EC en diferentes escenarios clínicos. El alto valor predictivo negativo de los marcadores observado en la población de bajo riesgo sugiere fuertemente que no es necesario realizar biopsia duodenal cuando ellos se encuentran ausentes.*

Palabras claves: *enfermedad celíaca, marcadores endoscópicos, malabsorción, eficacia diagnóstica.*

Celiac disease (CD) is a chronic, inflammatory, immune-mediated disorder of the small intestine due to gluten intolerance in genetically susceptible individuals that affects 1% of the population.[1-3] Our knowledge of the clinical diversity of the disorder has grown considerably in the past few decades, and epidemiological studies have shown that only a minority of patients have the classic signs and symptoms caused by overt malabsorption. In contrast, most patients with active disease experience symptoms outside GI system (atypical CD) but minimal gastrointestinal (GI) complains, or no symptoms at all.[4] It is interesting to note that CD is frequently diagnosed in patients undergoing upper endoscopy as part of the work-up due to nonspecific upper GI symptoms.

Serologic tests and endoscopic duodenal biopsy are the mainstay of diagnosing CD.[1,5,6] Although serology is a valuable tool, a diagnosis should be confirmed by the recognition of villous flattening in the duodenojejunal mucosa in endoscopic biopsy.[1,6] The severity of the damage may range from mild, i.e., increased intraepithelial lymphocytes and crypt hyperplasia, to severe. The degree of villous atrophy is closely associated to the presence of characteristic duodenal and/or intestinal mucosa findings upon endoscopy.[7] Duodenoscopy performed either for obtaining duodenal biopsies or routine endoscopies due to upper GI symptoms may reveal characteristics of enteropathy (e.g., mosaic pattern, scalloped folds, diminution of height or reduction in the number of Kerkring´s folds, nodularity and the view of underlying blood vessels).[7-12] The finding of these classical endoscopic features makes mandatory to procure intestinal biopsy to confirm and categorize the enteropathy.[7]

Recent studies have attempted to establish the role of endoscopic markers in predicting CD.[8-12] While cohort studies have suggested that these markers are reliable predictors of enteropathy, others have shown less satisfactory results.[13-18] The difference may be related to factors including different study design, potential selection bias in disease and control populations, the pretest probability for CD in the study population, the likelihood of other small bowel disorders with mucosal atrophy (Crohn´s disease, giardiasis, eosinophilic enteritis, tropical sprue, and HIV enteritis, etc.),[18] and the degree of histological damage in CD patients. Endoscopic markers may be less common in patients with partial villous atrophy than those with subtotal or total villous atrophy.[7,19] Although no data are available, it is unlikely that these markers are observed in patients with minor enteropathy.

The usefulness of endoscopic markers as a diagnostic tool needs additional evaluation with consideration of population characteristics. Thus, while there is a general consensus in that intestinal biopsy is essential in high risk patients, the proposed recommendation of systematic biopsy for all low risk subjects undergoing upper endoscopy is debatable.[20,21] We suggest that patients with a low likelihood of CD may be selected for duodenal biopsy based on endoscopy and other indicators, which might reduce patient inconvenience and save time and cost.

The aim of this study was to evaluate the efficacy of endoscopic markers of mucosal atrophy in diagnosing CD in two populations with different pretest probability of CD undergoing upper GI endoscopy.

Materials

Subjects

Between December 2004 and December 2006, we performed intestinal biopsies in 661 adult subjects undergoing upper GI endoscopy at two tertiary referral centers. Patients were categorized into two groups based on their pretest probability of having CD.

High pretest probability: One hundred-forty three consecutive adult patients with suspected but undiagnosed intestinal disorders were enrolled in this study at the first visit to the Small Bowel Diseases Clinic at "Dr. Carlos Bonorino Udaondo" Gastroenterology Hospital. Inclusion criteria required that patients (1) were referred for an endoscopic biopsy because of suspected small bowel disorder, (2) had no previously known diagnosis of a GI disorder, (3) signed the informed consent. Patients with CD serology performed before the endoscopy, a previous diagnosis of CD, prior treatment with a gluten-free diet, or a diagnosis of dermatitis herpetiformis were excluded from the study. Patients considered for study inclusion underwent an upper GI endoscopy and intestinal biopsy at the endoscopy unit of the same institution.

Low pretest probability: This part of the study was performed at the endoscopy units of two tertiary institutions: the "Dr. Carlos Bonorino Udaondo" Gastroenterology Hospital in Buenos Aires and the HIGA "San Martín" Hospital of La Plata, Buenos Aires Province, Argentina. Three experienced endoscopists performed the procedures in each site. We randomly selected 518 subjects from patients who had been referred to routine upper GI endoscopy because of symptoms not primarily related to CD. The main inclusion criterion for enrolment was that patients were referred for endoscopy because of nonspecific GI symptoms and suspected for dyspepsia, acid reflux disorder, or malignancies. Exclusion criteria were similar to those used for the high probability group.

Diagnosis of CD and baseline clinical characterization: CD was diagnosed based on the presence of a Marsh´s type II or greater enteropathy at duodenal biopsy (Marsh´s modified classification) and concomitant positive CD serology.[1,6] If the serologic test was negative, clinical and/or histological response to a gluten-free diet was required. Patients with CD were categorized by clinical status as classically symptomatic disease (mostly GI symptoms), with atypical CD (oligosymptomatic patients e.g., chronic anemia, hypertransaminasemia, autoimmune diseases), or with a silent clinical course (asymptomatic CD).

Methods

Study Design

This was a prospective, cross-sectional study on whether endoscopic examination of the distal duodenum is an effective tool for diagnosing CD. Endoscopies, laboratory tests and histological analyses were performed by separate researchers who were blinded to results of other tests. After giving informed consent, all study patients underwent upper endoscopy and intestinal biopsy irrespective of the clinical and endoscopic findings. Serum samples were obtained from study subjects before the endoscopic procedure. The protocol was approved by the Research and Ethical Committees of the Gastroenterology Hospital.

Endoscopic procedure and small bowel histology

Endoscopic examination of the second duodenal portion was performed by experienced endoscopists after topical oropharyngeal anesthesia and without premedication that might affect GI motility. The endoscope was placed beyond the main duodenal papilla and report of findings was performed in dycotomic form (presence or absence) prior to and after air insufflation. The endoscopic markers evaluated were: scalloped duodenal folds (clefts on the dome of folds in the tangential view), mosaic pattern (geometric reticular pattern), reduction in the number or absence of Kerkring´s folds and visualization of underlying blood vessels.[7,11,22] After reporting endoscopic findings, the endoscopist obtained at least three biopsy samples from the descendent duodenum at different levels distal to the papilla using conventional endoscopic forceps (open cup: 8 mm). Samples were oriented carefully on paper, fixed in 10% formalin, embedded in paraffin wax and conventionally stained with H&E.

Morphology and quantitative assessments (intraepithelial lymphocyte –IEL- density) were performed by one of two experienced pathologists from one

center (A.C. and Z.K.) who were blinded to the clinical and laboratory findings. Morphology was categorized according to the modified Marsh classification.[6] Briefly, type 0 is normal mucosa, type I is an infiltrative stage marked by a normal mucosal architecture in which the villous epithelium has intraepithelial lymphocytosis (greater than 30 IEL per 100 epithelial cells). Type II involves the addition of enlarged crypts (hyperplasic stage) and type III comprises a large spectrum of changes ranging from minor villous atrophy to complete villous atrophy (subcategorized as Marsh IIIa, IIIb and IIIc).

Celiac disease-specific serology

Although the endoscopy for patients with low probability of having CD was performed at two endoscopic units, we used one laboratory for serology to avoid variability. Routine hematological and CD-related serologic tests were performed at the time of endoscopy. For serologic testing, serum samples were kept frozen at -30ºC until the assay was performed in a central laboratory. The CD-related tests included: 1) a-tTG IgA (QUANTA Lite ™, h-tTG IgA, INOVA Diagnostic Inc.; San Diego, CA) by ELISA (cut-off at 20 units as recommended by the manufacturer:); 2) IgA and IgG reacting against a deamidated gliadin-derived polypeptides (IgA and IgG a-DGP) using a kit provided by the manufacturer (QUANTA Lite Gliadin IgA and IgG II– Inova Diagnostic Inc.; San Diego, CA) (cut-off at 20 units as recommended by the manufacturer:);[23,25] 3) IgA endomysial antibody (IgA EmA) by immunofluorescence on primate esophagus substrates (INOVA Diagnostics Inc.; San Diego; CA; USA), which was used only in cases with discrepancies between histology and serology; 4) total serum IgA (radial immunodiffusion test; Diffu-Plate, Biocientífica S.A.; BA, Argentina) in atrophic cases with negative IgA serology. Characteristics of tests have been reported in previous studies.[23-25]

Statistical Analyses

Data were analyzed using MedCalc® version 9.3.8.0 (MedCalc Software; Broekstraat, Mariakerke, Belgium). According to data distribution, descriptive data are reported as mean (SD), or median and range, and statistical analyses were used as appropriate. The diagnostic performance of endoscopic markers was determined comparing sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and positive and negative likelihood ratios calculated using conventional formulas. Corresponding 95% confidence intervals (95% CI) were also determined. Results were compared based on individual markers or in the combination of all markers categorized considering a positive result when, at least, one sign is present.

Results

Subject characteristics and diagnosis of celiac disease

The demographic information and some clinical and histological features of the subjects are presented in Table 1. Compared with those with high pretest probability of CD, subjects with low probability of the disease had a significantly higher mean body mass index (BMI) ($p<0.0001$) (Table 1). Demographic characteristics, indications for endoscopy, histological classification of duodenal biopsies, and clinical and serological findings of low probability patients were comparable between the two centers that performed endoscopy (Table 1).

The prevalence of CD was directly associated with the pretest probability of the disease. Sixty-three (44.1%) of the 143 patients enrolled at the Small Intestine Clinic (high pretest probability group) were diagnosed of CD. In comparison, 18 (3.5%) of the 518 subjects undergoing routine upper GI endoscopy (low pretest probability group) had a diagnosis of CD. No differences were detected in the prevalence of CD between both centers performing the study in low risk populations (3.5% in Buenos Aires and 3.4% for La Plata).

As expected, patients diagnosed with CD in the high probability group had more severe clinical and histological compromise than those from the low probability group. Most patients in the high probability group had classical GI symptoms (82.5%), a significantly lower BMI ($p<0.0001$) (Table 2), and a significantly greater prevalence of type IIIc enteropathy ($p<0.05$) (Table 1) than the CD patients in the low probability group. By contrast, 94.4% of patients diagnosed with CD among low risk subjects had atypical or silent disease ($p<0.0001$). Five patients, all from the low probability group, had an infiltrative type I lesion (Marsh´s classification) but, according to our gold standard, they were classified as non-CD cases.

Table 1. *Demographic, clinical, and histological characteristics of subjects categorized according to the pretest probability of having CD and by site.*

Characteristic	Overall population	High pretest	Low pretest		
			Overall	La Plata	Buenos Aires
N of subjects enrolled	661	143	518	198	320
Mean age (Range). yr	44 (16-87)	40 (16-80)	46 (16-87)		
N of CD patients (prevalence)	78 (11.5)	63 (44.1)	18 (3.5)	7 (3.5)	11 (3.4)
Body mass Index					
Mean ± SEM (Kg/m2)		20.6±3.9	25.2±5.0*		
Histological characteristics					
at the duodenal biopsy					
(Marsh´s modified)					
Type 0 (n of patients)	570	80	495	189	306
Type I	5	0	5	2	3
Type II	2	1	1	0	1
Type IIIa	9	3	6	4	2
Type IIIb	14	10	4	0	4
Type IIIc	56	49**	7	3	4
Serology					
N of positive subjects					
IgA a-tTG		59	24		
IgA a-DGP		64	33		
IgG a-DGP		58	17		
N of subjects with all assays					
Negative		77	470		

*p<0.0001; ** p<0.05

Table 2. *Selected clinical features of newly diagnosed celiac disease in patients with high and low pretest probability for the disease.*

Characteristic	CD patients from populations with		
	High pretest	Low pretest	*p* value
N of patients	63	18	
Mean age (range). Yr	37 (24-74)	37 (19-72)	
Body mass Index			
Mean ± SEM (Kg/m2)	19.6±3.1	23.6±5.0	0.0001
Clinical categorization at diagnosis			
N of patients (%)			
Classical CD	52	1	0.0001
Atypical CD	11	11	0.001
Silent CD	0	6	0.0001
Serology			
N of positive patients (sensitivity %)			
IgA a-tTG	57 (90.5)	13 (72.2)	NS
IgA a-DGP	60 (95.2)	14 (77.8)	=0.61
IgG a-DGP	58 (92.1)	12 (62.7)	0.02

Performance of endoscopic markers

The analysis of the group with high pretest probability showed that the sensitivity, specificity, PPV, NPV, likelihood ratios, and diagnostic accuracy of having any endoscopic marker present were very high, especially the presence of mosaic pattern and/or scalloped folds (Table 3). The loss of folds and the view of subepithelial blood vessels had very high specificity when they were present along with other signs, but were not particularly useful on their own. Five CD patients had negative duodenoscopic findings (false negative cases). Two of these cases had positive specific serology and most of them had minor histological damage (type II, IIIa and IIIc histology in one patient each and type IIIb in two). On the other hand, five of 80 non-CD cases had endoscopic findings suggesting enteropathy (false positive). Scalloped folds were observed in four and loss of folds in one patient, but the CD serology was negative in all of them.

The study in low probability subjects was performed in two different centers employing expert endoscopists in order to enroll a higher number of patients and to evaluate possible differences between sites (Table 4). Overall, 11 of 18 diagnosed patients (6/11 and 5/7 in Buenos Aires and La Plata units, respectively) were predicted by any marker present in the duodenoscopic observation. Among the seven patients with CD who had a normal endoscopic appearance, five had a positive specific serology and most of them had a partial or subtotal atrophy (Marsh´s type IIIa in four cases and types II, IIIb and IIIc one patient each). Compared with the La Plata unit, the presence of any marker at the Buenos Aires site had a lower sensitivity (71.4%; 95% CI 35.9-91.8 vs. 54.5%; 95% CI 28.0-78.7, respectively). For the overall analysis, the presence of scalloped folds was the single sign with the best predictive performance, followed by the mosaic pattern. Reduction in the number or absence of Kerkring´s folds as an individual sign did not predict any patient at both centers; when present it was associated to other markers. The PPV for different signs was variable ranging from acceptable values for the mosaic pattern (80.0%) to low for the presence of any marker (40.7%). In contrast, the specificity and NPV for any markers present were extremely high (96.8% to 100% for specificity and 96.7% to 98.6% for NPV). Compared with the performance of endoscopic markers in the high pretest group, sensitivity ($p<0.004$) and PPV ($p<0.0001$) for the presence of any marker was significantly lower in the low risk population.

According to our gold standard, 16 of 500 subjects without CD had endoscopic features interpreted as enteropathy (false positive). One of the false positive cases was observed in the Buenos Aires unit (presence of scalloped folds), 15 other cases ($p<0.0001$) were misdiagnosed at the La Plata site, where 11 of them had reduction in the number or absence of Kerkring´s folds (in eight as a single sign), five scalloping and two mosaic. It results remarkable that no subject in the Buenos Aires unit (patient or control) was identified only by this marker.

Our histological assessment detected five subjects with a type I enteropathy. As expected, all had a normal duodenoscopy but three were detected by a positive serology. While two cases had borderline values (IgA AAA 28 U/mL and IgA a-tTG 23 U/mL for each case), the third patient had very high concentrations of IgA a-tTG (331 U/mL) and IgA a-DGP (170 U/mL).

Table 3. *Statistical performance of endoscopic markers in the high pretest probability group.*

Characteristic	Sensitivity	Specificity	PPV	NPV	PLR	NLR	ACC
Any marker	92.1	93.8	92.1	93.8	14.7	0.08	93.0
95% CI	82.7-96.6	86.2-97.3	82.7-97.3	86.3-97.3			87.6-96.2
Mosaic	88.9	98.8	98.2	91.9	71.1	0.11	94.4
95% CI	78.8-94.5	93.3-99.8	90.7-99.7	84.1-96.0			89.3-97.1
Scalloped folds	90.5	90.5	93.4	92.7	18.1	0.10	93.0
95% CI	80.7-95.6	87.8-98.0	84.3-97.4	84.9-96.6			87.6-96.2
Loss folds	31.7	97.5	90.9	64.5	12.7	0.70	68.5
95% CI	21.6-44.0	91.3-99.3	72.2-97.5	55.6-72.4			60.5-75.6

PPV: Positive predicted value; NPV: Negative predicted value; + LR: Positive likelihood ratio, - LR: Negative Likelihood ratio; ACC: diagnostic accuracy. 95% CI: 95% confidence interval.

Table 4. *Statistical performance of endoscopic markers in the low pretest probability group.*

Characteristic	Sensitivity	Specificity	PPV	NPV	PLR	NLR	ACC
Any marker	61.1	96.8	40.7	98.6	19.1	0.4	95.6
95% CI	39.6-79.7	94.4-98.0	24.5-59.3	97.1-99.3			93.4-97.0
Mosaic	44.4	99.6	80.0	98.0	111.1	0.6	97.7
95% CI	21.6-66.3	98.6-99.9	49.0-94.3	86.9-99.2			96.0-98.7
Scalloped folds	55.6	99.0	66.7	98.4	55.6	0.4	97.5
95% CI	33.7-75.4	97.0-99.6	41.784.8	96.9-99.2			95.8-98.5
Loss folds	16.7	97.8	21.4	97.0	7.6	0.8	95.0
95% CI	5.8-39.2	96.1-98.8	7.6-47.6	95.1-98.2			92.7-96.6

PPV: Positive predicted value; NPV: Negative predicted value; + LR: Positive likelihood ratio, - LR: Negative Likelihood ratio; ACC: diagnostic accuracy. 95% CI: 95% confidence interval

Discussion

Research exploring the clinical value of duodenoscopic markers for diagnosing CD has yielded conflicting results. These differences may be caused by the diversity in the awareness of CD among endoscopists, selection bias, differences in the pretest probability of populations, and other factors.[18-34] To estimate the diagnostic efficacy of the endoscopic observation of the distal duodenum for predicting mucosal atrophy and diagnosing CD, we investigated the sensitivity and specificity of this method in different clinical scenarios and the causes of misdiagnosis.

Our study results support the clinical usefulness of the duodenoscopic assessment when CD is suspected. First, we confirmed the diagnostic accuracy of characteristic endoscopic markers among patients with high probability for the disorder. The rates of false positive and false negative were very low. Second, the identification of mosaic and scalloping in the distal duodenum was strogly associated with the diagnosis of CD. However, because duodenal biopsy may provide significant insight for diagnosing small bowel disorders other than CD and the fact that almost 8% of new cases from the high risk population can be missed, we agree with others that biopsy should be routinely performed on patients highly suspected for intestinal diseases regardless of duodenoscopic appearance.

Among patients with a low probability for CD, duodenoscopy had relatively limited effectiveness, as the procedure missed almost 40% of the patients with CD. While the presence of mosaic and/or scalloping predicted the diagnosis in 61.1% patients, their specificity was very high. These findings were similar to other recent studies where the sensitivity of endoscopic markers was lower in patients undergoing routine endoscopy.[13,14,16,17,26] We found that the sensitivity of endoscopic markers was directly related to the severity of mucosal damage, as 83% of false negative cases in the overall population had partial or subtotal villous atrophy.[7,13] Finally, endoscopy was not able to detect patients with Marsh I and II enteropathy in our study. Interestingly, while endoscopy missed patients in the low probability group who had mild to moderate histological damage, five of the seven false-negative cases were identified by serologic testing.

Because endoscopic markers are not very effective in patients who undergo the procedure for upper GI symptoms or dyspepsia, some researchers have suggested routine duodenal biopsy in all patients undergoing routine upper endoscopy.[14,20,21] Our findings disagree with this proposed strategy. In our study, specificity and NPV were extremely high, particularly at the Buenos Aires unit. The majority of false positive cases at La Plata were attributable to the identification of the reduction in number or loss of Kerkring´s folds. This sign, which was considered the most sensitive feature more than 10 years ago when fiberendoscopy was the method for procuring duodenal biopsies, has been replaced by the videoendoscopy which gives a very irrelevant place to this sign.[8-11] This marker is highly subjective and directly related to the severity of mucosal damage as well as the grade of air insufflation used. In our study, the sign was present in CD patients with severe enteropathy and always associated with other markers in diagnosis. If we omit this marker in our model, the specificity and NPV for patients at the

La Plata unit and the overall low probability group would increase to nearly 99%. Therefore, our analysis does not support biopsy for all patients undergoing routine upper endoscopy regardless of endoscopic findings.[28,29,31] Furthermore, our data support a recent study that suggested serologic screening and endoscopy should be combined to more accurately identify patients who would be biopsied.[33] Cost effectiveness analysis should be conducted to compare routine biopsies and targeted biopsies based on endoscopic and/or CD serology findings.

Several studies have explored new tools to improve the sensitivity of endoscopy (e.g. dye spraying, water instillation, magnification).[30,37-39] Some of these sophisticated tools are not widely available and may add substantial cost and time with marginal benefits. Our study involved standard endoscopic assessments that were consistent with the procedures frequently used in most academic institutions and endoscopic units, so that our results are widely generalizable.

In conclusion, this study confirmed that endoscopic markers are useful in diagnosing CD in different clinical settings. Our study highlights that the presence of endoscopic markers of villous atrophy makes mandatory of duodenal biopsies. The endoscopic markers correlate with the severity of enteropathy, and mild histological lesions may be missed in the procedure. Systematic endoscopic biopsies are probably not necessary in patients undergoing routine endoscopy because endoscopic markers appeared to have high specificity and NPV for CD diagnosis in these patients. Finally, the marker of reduction in number or lack of Kerkring´s folds should not be used alone for predicting enteropathy unless other markers are also present.

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