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What is the role of small bowel capsule endoscopy in established coeliac disease?

Running title: Capsule endoscopy in coeliac disease.

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Highlights:

- SBCE has a high sensitivity in delineating macroscopic changes of CD.
- Severity of malabsorption on blood parameters (vitamin B12 and folate levels) correlate with extent of CD.
- Patients with CD with a normal SBCE, are unlikely to have significant active disease as an explanation for their symptoms.

Abstract:

Introduction:

Patients with established coeliac disease (CD) can present with signs and symptoms requiring small bowel capsule endoscopy (SBCE) to assess for persistent disease beyond the duodenum and to rule out complications. There is paucity of data on extent of disease on SBCE in relation to histology, clinical and serological parameters.

The aim of this study was to assess the relationship between symptoms, CD serology and Marsh classification of disease and extent of disease on SBCE in patients with established CD.

Methods:

Hundred patients with established CD and 200 controls underwent a SBCE. SBCEs were reviewed by expert reviewers. Extent of disease on SBCE, CD findings and small bowel transit were recorded.

Results:

Considering duodenal histology (D2; Marsh 3a or above) as the gold standard for diagnosing CD activity, the sensitivity of SBCE to delineate active disease was 87.2%. The specificity was 89.0%.

Age at SBCE (p=0.006), albumin (p=0.004) and haemoglobin (p=0.0001), Marsh score of histology from the duodenal bulb (D1) (p=0.0001) and the second part of the duodenum (p=0.0001), refractory CD (p=0.007) on histology correlated with extent of affected small bowel (SB) mucosa on univariate analysis. On multiple regression analysis, albumin (p=0.036) and Marsh score of histology (D1) (p=0.019), vitamin B12 (p=0.001) and folate levels (p=0.008) were statistically significant.

Extent of affected SB mucosa (11.0% vs 1.35%) was greater in patients with complications including those with refractory CD (p=0.008).

Conclusions:

This is the first study showing correlation between extent of disease and severity of duodenal histology, markers of malabsorption such as folate levels and vitamin B12 and complications of CD.

Keyword: coeliac disease, small bowel transit, extent of disease, small bowel capsule endoscopy;

Conflicts of interest: none;

Introduction:

A proportion (7 – 30%) of patients with established coeliac disease (CD) present with recurrent or persisting signs and symptoms despite being on a gluten free diet (GFD) for at least 12 months [1-3]. This can be secondary to non-adherence to a GFD, refractory coeliac disease (RCD) or other causes unrelated to CD such as irritable bowel syndrome [4, 5]. Repeat duodenal histology can provide objective evidence of ongoing disease activity. However, this can only provide information on active disease in the duodenum. Also, not all patients are willing to undergo a repeat gastroduodenoscopy in view of the invasive nature of this procedure. There is evidence to show that symptoms[6-8] and CD serology (sensitivity less than 50%)[9] are not reliable predictors of ongoing villous atrophy. A non-invasive small bowel capsule endoscopy (SBCE) can instead be carried out to assess for macroscopic evidence of CD. The sensitivity of SBCE in the delineation of features of CD in patients with established CD varies between 56 – 95% [10-13] (table 1).

Patients with CD suffer from disordered gut motility [14]. This has been demonstrated in several parts of the gastrointestinal tract [15-17] using manometric studies [14]. Damage to the small bowel (SB) mucosa results in a disruption of hormones regulating gut motility [18] and dysfunction of the autonomic nervous system [19]. Literature on small bowel transit (SBT) in patients with CD using SBCE is very limited [20, 21]. SBT is of relevance in CD as its alteration can have an impact on the pharmacokinetics of medications and on predisposition to other conditions such as small intestinal bacterial overgrowth (SIBO).

The main aim of this study was to assess the relationship between symptoms, CD serology and Marsh classification of disease and extent of disease on SBCE in established CD. Secondary aims were to establish sensitivity and specificity of SBCE in delineating CD features on SBCE and to assess how SBT varied in patients with CD when compared to controls. Confounders that could influence SBT were also examined.

Methodology

Study design and patients:

Patients with established CD (100; group 1) who were on a GFD and control patients (200; group 2) were prospectively recruited from a tertiary CD referral centre during a 2 year period. Patients with CD in group 1 underwent a SBCE to assess for complications in view of persistent symptoms or features of RCD on histology. They all had a gastroduodenoscopy within 2 months prior to SBCE for duodenal histology and contemporary CD serology was checked. CD serology measured included endomysial antibodies (EMA) and anti-tissue transglutaminase antibodies (IgA) (ttg-IgA) (range 0 – 7 U/mL). Consecutive patients with CD were included in group 1. Other features such as signs and symptoms at presentation, serological markers, and human leukocyte antigen (HLA) were noted.

Patients in group 2 had negative CD serology, normal bidirectional endoscopies and duodenal histology with no evidence of CD within 2 months prior to SBCE. These patients had been referred for SBCE for investigations of gastrointestinal signs and symptoms as a secondary investigation into their symptoms. These included: change in bowel habits, iron deficiency anaemia, vitamin B12, folate levels, vitamin D deficiency, persistent nausea and vomiting, bloating, weight loss, fatigue, high inflammatory markers and bleeding per rectum. They also had no significant underlying co-morbidities. Patients in group 2 were age and gender matched to those in group 1.

Duodenal histology:

At least 2 biopsies from the duodenal bulb (D1) and 4 biopsies from the second part of the duodenum (D2) were taken during gastroduodenoscopy in both groups of patients. Histology was then classified according to the Marsh score [22]. Histology from D1 and D2 was regarded separately. All histological samples were reviewed by 2 expert histopathologists. In the case of discrepancy, a third histopathologist was involved in the adjudication process.

Small bowel capsule endoscopy:

Each patient was asked to stay on clear fluids for 24 hours before the SBCE and to drink 2 litres of Klean-Prep® the day before the SBCE. All patients underwent SBCE using Pillcam SB3 (Medtronic, Minneapolis, USA) [23]. Details on gastric and SB passage time, extent of abnormal SB and villous atrophy on SBCE were determined by two expert SBCE reviewers (>300 capsules each/ year). CD findings such as fissuring of mucosa, scalloping of folds, mosaic pattern, nodularity, villous atrophy and ulcers were recorded. Expert reviewers were blinded to the results of duodenal histology and each other's findings. Use of prokinetics such as metoclopramide (after 30 minutes) or erythromycin (after 60 minutes) if the capsule was in the stomach after ingestion was recorded. Features of CD including: mosaic pattern of mucosa, scalloping and fissuring of folds, nodularity of mucosa, atrophic and hypotrophic mucosa (intermediate) [13] and ulcers, and distribution (proximal, mid or distal SB) were recorded. Where there was a discrepancy in results, a third expert reviewer was involved in the adjudication process. In addition, expert reviewers were asked to grade overall severity of disease as mild, moderate or severe according to their subjective expert opinion.

In this study, extent of abnormal SB mucosa refers to SB mucosa with macroscopic features of CD. Villous atrophy refers to SB mucosa with absent villi. Since prokinetics can affect gastrointestinal motility, patients who received prokinetics were left out of the analysis of gastric transit and SBT.

Statistical analysis:

Statistical analysis was carried out using SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp.). Frequencies, medians and ranges were calculated to characterise group 1 and 2. Non-parametric statistical tests were used namely, Fisher's exact test to assess statistical significance between categorical variables and Spearman's correlation co-efficient to assess the correlation between continuous variables. The Mann-Whitney U test was used to compare two independent, continuous variables and the Kruskal–Wallis test

was used to compare multiple independent, continuous variables. Binary logistic regression analysis was carried out to analyse the effect of multiple factors on the positive result of a SBCE. Multinomial logistic regression analysis was carried out to assess the effect of multiple factors on extent of abnormal SB mucosa and SBT. Results were considered to be statistically significant if the p value was less than 0.05.

Ethical considerations:

The study protocol was approved by the Yorkshire and the Humber Research Ethics committee (IRAS 232382) and registered with the local research and development department of Sheffield Teaching Hospital NHS Foundation Trust under the registration number STH 19998. All images used in this study were deidentified. No additional consent was required for the study with the use of deidentified videos as assessed and approved formally by the Research Ethics Committee.

Results:

100 patients with histologically established CD and 200 age (mean age 53.2 SD±15.7 vs 50.0 SD±15.6 years, p=0.088) and gender (females n=70, 70.0% vs n=119, 59.8%, p=0.099) matched controls were included. There were 7 (7.0%) incomplete procedures in the CD group and no incomplete procedures in the controls. All incomplete SBCEs did not reach the caecum but their delayed passage was eventually confirmed on abdominal x-ray. Only 2 patients with incomplete SBCE were administered prokinetics during the procedure. There was no statistical difference in the number of patients given prokinetics between the 2 groups (p=0.558). Prokinetics were administered to 12 patients (12%) within the CD group and to 20 patients (10%) within the control group. There was also no statistical difference in patients on opioids in both groups of patients (p=0.227). More CD patients (n=9, 9%) were on beta blockers than controls (n=1; 0.5%, p=0.0001). BMI was higher in patients in group 2 than in group 1 (median 27.5 range 17.3 – 159.8 kg/m^2 vs median 23.7; range 15.1 – 43.4 kg/m^2, p=0.008).

Patients with CD had a median duration of disease of 7 years (1 – 59 years). All patients were started on a GFD immediately or when they were seen by a dietician within 2 months from their diagnosis of CD. Anti-endomysial antibody (EMA) was positive in 23 patients (23.0%) and the median ttg-IgA was 2.9 (0.3 – 300) U/mL at the time of SBCE. Twenty-nine (29.0%) had a positive ttg-IgA (higher than 7 U/mL). Patients had the following Marsh score on histology in the D1: Marsh 0: 13.9%, Marsh 1: 19.0%, Marsh 2: 7.6%, Marsh 3a 24.1%, Marsh 3b: 21.5%, Marsh 3c 13.9% and D2: Marsh 0: 13.4%, Marsh 1: 28.0%, Marsh 2: 11.0%, Marsh 3a 14.6%, Marsh 3b: 13.4%, Marsh 3c 19.5%. Control patients had normal duodenal histology.

Sixty-four patients (64.0%) in group 1 had symptoms at the time of presentation. Controls had similar presenting symptoms to patients with CD.

Findings on small bowel capsule endoscopy:

Considering duodenal histology (D2) (Marsh score of 1 or above) as the gold standard for diagnosing CD activity, the sensitivity of SBCE to delineate active disease was 76.4% (true positive 55). The specificity was 97.2% (true negative 209). Considering only a Marsh histology of 3 or above, the sensitivity of SBCE to delineate CD changes was 87.2% (true positive 34). The specificity was 89.0% (true negative 219).

Considering histology from the D1 (Marsh score of 1 or above), the sensitivity of SBCE to delineate active disease was 73.5% (true positive 50). The specificity was 98.1% (true negative 207). Considering only a Marsh histology of 3 or above, the sensitivity of SBCE to delineate CD changes was 82.6% (true positive 38). The specificity was 93.1% (true negative 217).

The positive and negative predicative values of SBCE in relation to duodenal histology (D2) were 90.2% and 92.5% respectively.

In CD patients, 30 patients (30.0%) had a normal SBCE, 56 patients (56.0%) had proximal SB involvement, 7 patients (7.0%) had proximal and mid SB involvement and another 7 patients (7.0%) had diffuse disease. Features of CD on SBCE included: mosaic pattern of mucosa, fissuring and scalloping of folds, villous atrophy, nodularity, hypotrophic folds and the presence of ulcers (table 2). CD patients with a normal SBCE (30) had a median ttg-IgA of 2.0 (0.5 – 78.0) U/mL.

There was a discrepancy between SBCE findings and histology in 21 CD patients (21%). Seventeen patients had a normal SBCE but abnormal D2 histology (Marsh 1: 11, Marsh 2: 1, Marsh 3a: 3, Marsh 3b: 2). In 4 patients, D2 histology was normal but SBCE was positive (proximal changes: 3, mid, distal changes: 1) In these patients where there was a discrepancy between the histopathology result and findings on SBCE, a third expert capsule reviewer and a histopathologist were asked to review the SBCE and the duodenal biopsies respectively. The original findings on SBCE and histopathology were confirmed in all these cases.

In patients with CD, on univariate analysis, age at the time of SBCE (p=0.021), EMA result (p=0.015), haemoglobin level (0.016), Marsh score of disease in the D1 (p=0.003) and D2 (p=0.001), presence of RCD on histology (p=0.006) all correlated significantly with a positive SBCE (macroscopic evidence of CD on SBCE) (supplementary material table 1). On multiple regression analysis, only histology in D1 (p=0.043) maintained statistical significance in being correlated to a positive SBCE.

Age at time of SBCE (p=0.006), serum albumin (p=0.004) and haemoglobin (p=0.001), Marsh score of D1 (p=0.001) and D2 (p=0.001), the presence of RCD features (p=0.007) on histology all statistically correlated with the percentage of affected mucosa on univariate analysis in CD. Histological features diagnostic of RCD on duodenal mucosa included: persistent villous atrophy in patients on a GFD who had been formally assessed by a dietician (RCD I and II), loss of surface CD 3 and CD8 from intraepithelial lymphocytes (RCD II) and monoclonal T cell receptor rearrangement in

patients with RCD II." A multiple regression analysis was run to predict percentage of affected SB mucosa. Serum albumin level (p=0.036) and Marsh score on histology taken from D1 (p=0.019) maintained statistical significance. Serum vitamin B12 (p=0.001) and folate levels (p=0.008) gained statistical significance on multiple regression analysis and correlated inversely with extent of disease (supplementary material table 2). Nine patients had a low b12 level (< 197 ng/L) and 5 patients had a low folate level (< 3.9 ug/L) at the time of SBCE."

Duration of disease did not correlate with percentage length of abnormal SB mucosa (Spearman's rho -0.019, p=0.863). There was no correlation between duration of disease / GFD and ttg-IgA at the time of SBCE (Spearman's rho -0.091, p=0.422) and there was no difference in duration of disease / GFD between patients with positive and negative EMAs (p=0.365).

There was no correlation between ttg-IgA and percentage of abnormal SB mucosa (p=0.194) and no difference in percentage length of abnormal SB mucosa (p=0.087) in patients with positive and negative EMAs.

Extent of abnormal SB mucosa and of villous atrophy correlated with the overall severity of disease on SBCE (mild / moderate / severe) as graded by the expert reviewers (table 3) (p=0.0001).

There was no statistical significant difference in affected SB mucosa according to symptoms at the time of SBCE both when symptoms were considered separately and when the presence or absence of symptoms were considered in group 1.

Extent of affected SB mucosa (11.0% (0 – 100%) vs 1.35% (0 – 100%)) was greater in patients with complications including those with RCD (p=0.008). Thirty-three (33%) patients had RCD (23% type I, 9% type 2) confirmed on duodenal histology. One patient who had an incomplete

SBCE due to an ulcerated stricture which was eventually diagnosed with adenocarcinoma. Another patient had diffuse ulcers throughout the SB and was diagnosed with ulcerative jejunoileitis.

Small bowel transit:

In view of the possibility of prokinetics having an impact on gastric transit and SBT, patients who received prokinetics were left out of the following analyses.

Gastric passage time (21.0; range 0.01 – 163.0 group 1 vs 17.0; range 0.01 - 273 minutes group 2 p=0.737) did not vary significantly between the 2 groups. Patients with CD had a longer SBT than controls (277.0; range 60.0 – 981.0 group 1 vs 235.0; range 38.0 – 544.0 minutes group 2, p=0.0001).

Median SBT was shortest in controls (235 minutes; range 38 – 544), followed by those with established CD but a normal SBCE (256 minutes; range 104 – 427), SBT was longest in those with established CD and macroscopic evidence of CD on SBCE (260 minutes; range 104 – 427) (p=0.001).

BMI correlated with SBT in patients with CD (Spearman's rho -0.375, p=0.026) but not in controls (Spearman's rho 0.013, p=0.927). Other comorbidities and medications that might have affected motility in patients with CD included: microscopic colitis (2), SIBO (1), hypothyroidism (4), ulcerative colitis (1), right hemicolectomy for adenocarcinoma (1), pancreatic insufficiency (1). One patient was on morphine sulphate. Another patient was on bisoprolol.

Age at the time of SBCE (Spearman's rho 0.303, p=0.006) and at the time of diagnosis of CD (Spearman's rho 0.244, p=0.032), haemoglobin level (Spearman's rho -0.272, p=0.024) measured at the time of SBCE correlated with SBT on univariate analysis in patients with CD. However, all factors lost statistical significance on multiple regression analysis. Grade of histology from D1 (p=0.489) and D2 (p=0.827) did not correlate with SBT.

Duration of disease / GFD did not correlate with SBT (Spearman's rho 0.174, p=0.125). There was no difference in SBT in patients with positive and negative SBCEs (p=0.140). There was also no correlation between anti-TTG and SBT (Spearman's rho 0.057, p=0.645) and no difference in SBT (p=0.149) in patients with positive and negative EMAs. There was no statistical difference in SBT for most of the CD features in the SB."

Discussion

In this study, low serum albumin and vitamin deficiencies secondary to malabsorption correlated with extent of disease in the SB. This suggests that more extensive SB disease has a significant impact on malabsorption. Severity of Marsh classification of disease on duodenal histology in the D1 correlated with a positive SBCE and extent of affected SB mucosa. Complicated CD patients (RCD) had more extensive SB disease. We have also confirmed that SBT is prolonged in patients with CD when compared to controls.

Sensitivity and specificity of SBCE in delineating CD changes were similar to those reported in other studies on SBCE in patients with CD (table 1) [6, 10-12, 24-28]. The sensitivity of SBCE in detecting active disease in D1 and D2 were similar. Sensitivity of SBCE was higher, when only histology of marsh 3a or above was considered. This is significant as it is still uncertain if Marsh score of 1 and 2 can be considered as active CD on repeat duodenal histology. It also confirms that SBCE is better at detecting active CD of higher Marsh scores.

Most patients with CD had evidence of active disease in the proximal SB. Only a few patients had disease extending beyond the duodenum and only one patient had a malignant complication secondary to CD. This confirms that persistent disease most commonly affects the proximal SB and that malignant complications are rare and do not usually account for the persistent signs and symptoms in patients with underlying CD. EMA was only positive in 27% of patients and the median ttg-IgA was low confirming that serology is a poor marker of persistent disease [9] There was no correlation between symptoms and extent of disease on SBCE as demonstrated by previous studies [6, 24]. We have therefore confirmed that both CD serology and symptoms at the time of presentation do not correlate with extent of disease in these patients.

Our study confirms the findings of previous studies that correlate serological markers of malabsorption with SBCE findings [29, 30]. However, we have gone a step further and shown that vitamin B12 and folate levels correlate inversely with extent of disease on SBCE. In a study by Efthymakis et al, albumin and haemoglobin correlated inversely with diagnostic yield of SBCE in CD patients [29]. Serum albumin has been shown to correlate inversely with disease extent in another study [30]. Older patients were also found to have more extensive disease on univariate analysis. This is clinically relevant as it confirms that patients with non-responsive CD and abnormal serology are more likely to have extensive disease on SBCE.

Traditionally, severity of CD has been determined by severity of villous atrophy on duodenal histology according to the Marsh classification of CD [22]. Previous studies have failed to confirm a correlation between extent of disease in the SB and severity of duodenal histology [6, 31]. In this study, extent of affected SB mucosa correlated with severity of disease on duodenal histology. This is the first study that shows such a positive correlation and therefore defines the complementary role that SBCE can play to duodenal histology in the follow up of patients with established CD. This can help to overcome the inaccuracies that can occur from an inadequate number and preparation of duodenal histological samples and target those with extensive disease more aggressively by ensuring a strict GFD and a closer follow up with experts in CD and specialized dieticians.”

A similar correlation was also true for patients with RCD. These patients had a greater extent of affected SB mucosa than patients with uncomplicated disease. The correlation of extent of disease to RCD is also reported in another study [30]. This is of clinical relevance. SBCE in patients with extensive disease, should be followed by a gastroduodenoscopy or device assisted enteroscopy for a histological exclusion of RCD, pre-malignant and malignant complications [32].

The immune mediated reaction to gluten and tissue transglutaminase antibody in patients with CD results in large quantities of undigested gluten [33] remaining in the SB. This heightens the inflammatory response in the intestinal lining, resulting in villous atrophy that in turn slows orocaecal transit. The inflammatory changes in the SB wall can result in decreased contractions, disruption of hormones involved in gut motility [18] and autonomic nervous system dysfunction [19]. Undigested carbohydrates have been shown to delay gastric emptying and prolong orocaecal transit time in patients with CD [34]. Intestinal dysmotility normalises after a GFD [35]. This pathogenesis can explain the distinction in SBT between patients with CD and controls. In a study by Urgesi et al, there was no difference in the SBT between CD patients and controls (252.2±67.4 minutes vs 244.7±88.4 minutes) on SBCE [20]. Ciaccio et al, have estimated SB motility by comparing changes in luminal SB width on SBCE. There was less luminal width variation in CD patients than in controls signifying delayed SBT in CD patients [21]. These are the only 2 studies on SBT utilising SBCE. The former study only included a small number of patients and there was an insignificant difference in SBT. The latter study describes a laborious and unconventional method to estimate SBT. Our study is the first to show a difference in SBT time between patients with CD and controls utilising capsule reviewing software that is routinely used and does not require any extra calculations.

An increase in mucosal permeability in patients with CD and histological remission has been demonstrated in older studies [36]. A significant proportion of patients with CD and an normal SBCE in this cohort of patients, also had normal duodenal histology (60%). Persistent microscopic changes in

the SB mucosa can explain the prolonged SBT in patients with CD in remission. Persistent prolonged SBT can also be unrelated to CD such as irritable bowel syndrome [37] and pancreatic enzyme insufficiency [38].

Several factors have been identified as risk factors for incomplete SBCE including patient mobility, performance of a SBCE in hospitalised patients, prior abdominal surgery or bowel obstruction, elderly patients and poor bowel preparation during SBCE [39]. In a meta-analysis by Elli et al on the use of SBCE and enteroscopy in patients with CD, SBCE completion was reported to range between 62 and 100% [32]. In this study there was an incomplete SBCE rate of 7% which is within the reported range. An incomplete SBCE due to insufficient capsule battery life is one of the possible implications of a slower SBT that can lead to secondary investigations such as SB radiology or a repeat SBCE with prokinetic medications. One suggestion would be to carry out SBCEs with a longer battery life in patients with CD to overcome the potential problem of a slower SBT that can be encountered in patients with CD [40].

A prolonged SBT in patients with CD can also have clinical implications. CD patients frequently have other co-morbidities in particular autoimmune conditions [41] and neurological conditions [42] that require medications. A delayed SBT can have an impact on absorption of medications complicating management. A prolonged SBT can promote SB bacterial overgrowth leading to a rise in serum bile acids due to the action of bacteria in the gut on undigested food leading to a higher risk of gallstones [43].

One of the CD features described in the methodology - hypotrophic folds was not identified in any of the CD patients in this study. This was a feature of intermediate changes in the mucosa identified by Biagi et al [13]. In their study, this feature was associated with any histological pattern. This aspect and the fact that none of our patients had this feature on SBCE, raises the question of its significance in patients with CD.

The inclusion of a control group with similar symptoms to those of CD at the time of SBCE is one of the strengths of the study as this enabled comparison of SBT between a group of patients with CD and controls. Expert SBCE reviewers were blinded to the results of duodenal histology and each other's findings. This resulted in a stronger study to distinguish between patients with CD and controls and helped us determine the sensitivity and specificity in delineating CD changes.

Some limitations to this study exist. This was a single centre study carried out at a tertiary centre where patients with established CD, persistent symptoms and a number of patients with RCD are routinely followed up. This might have introduced bias in the selection of patients with CD. More patients with CD were on beta-blockers than controls. Some CD patients had co-morbidities such as hypothyroidism. Both beta-blockers and co-morbidities might have led to a delayed SBT in CD patients when compared to controls. BMI had a significant impact on SBT in both groups, thus making BMI an unlikely parameter to have contributed to the difference in SBT between both groups of patients.

Conclusions:

This is the first study that links extent of SB disease to severity of duodenal histology suggesting an important role for SBCE as a non-invasive marker in the follow up of patients with CD. Patients with lower albumin, vitamin B12 and folatt levels are most likely to benefit from SBCE as they are more likely to have active SB disease. Ongoing SB disease can be one explanation for persistent signs and symptoms in patients with CD.

Author, year	Suspected CD / newly diagnosed CD / established CD	Study design	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
(Petroniene et al, 2005)[24]	New CD	4 investigators reviewed SBCEs of 10 CD patients and 10 controls; (2 with and 2 without pre-study experience)	70%	100%	100%	77%
(Hopper et al, 2007)[25]	Suspected CD	21 patients (EMA positive) and 23 controls underwent SBCE;	85%	100%	100%	88.9%
(Rondonotti et al, 2007)26	Suspected CD	43 patients were studied (11 normal duodenal histology; 32 CD);	87.5%	90.9%	96.5%	71.4%
(Murray et al, 2008)[6]	New CD	38 patients with untreated CD and age, sex-matched controls; SBCE was repeated after 6 months of gluten withdrawal;	92%	100%		
(Rubio-Tapia et al, 2009)[10]	Established CD	Comparison of clinical characteristics and outcome in 57 patients with RCD: (42 RCD I; 15 RCD II);	87.5%			

(Maiden et al, 2009)[11]	Established CD	19 patients with CD on a GFD for at least 12 months underwent gastroscopy with duodenal biopsies and SBCE;	67%	100%	100%	60%
(Lidums et al, 2011)[27]	Suspected CD	22 patients with positive EMA or anti-ttg-IgA; (8 normal and 14 had duodenal CD histology) underwent SBCE;	93%	100%	100%	89%
(Atlas et al, 2011)[12]	Established CD	SBCEs from 42 consecutive patients with nonresponsive CD and 84 age and sex-matched controls were included;	56%;	85%		
(Lujan-Sanchis et al, 2017)[28]	Suspected CD	Multi-centre study; SBCEs from 163 patients divided into 4 groups were compared;	47.4%, (seronegative CD with atrophy), 64.1% (seropositive CD without atrophy), 50% (contraindication to gastroscopy), 28.3% (seronegative CD without atrophy);			

Table 1: Sensitivity, Specificity, positive and negative predictive value of small bowel capsule endoscopy in patients with suspected, newly diagnosed and established coeliac disease;

Proximal small bowel n (%)		Mid small bowel n (%)		Distal small bowel n (%)	
Mosaic pattern	40 (40.0)	Mosaic pattern	9 (9.0)	Mosaic pattern	1 (1.0)
Fissuring of mucosa	39 (39.0)	Fissuring of mucosa	7 (7.0)	Fissuring of mucosa	1 (1.0)
Scalloping of mucosa	43 (43.0)	Scalloping of mucosa	11 (11.0)	Scalloping of mucosa	3 (3.0)
Villous atrophy	19 (19.0)	Villous atrophy	4 (4.0)	Villous atrophy	2 (2.0)
Nodularity of mucosa	9 (9.0)	Nodularity of mucosa	4 (4.0)	Nodularity of mucosa	1 (1.0)
Ulcers	5 (5.0)	Ulcers	3 (3.0)	Ulcers	2 (2.0)
Hypotrophic folds	0	Hypotrophic folds	0	Hypotrophic folds	0

Table 2: Features of coeliac disease in the proximal, mid and distal small bowel on SBCE;

	Grading by expert reviewers	Percentage of affected mucosa		
		Median (%)	Minimum (%)	Maximum (%)
Percentage of abnormal small bowel mucosa (with macroscopic features of coeliac disease)	Normal	0	0	0
	Mild	3.6	0	45.5
	Moderate	44.7	37.3	85.3
	Severe	100.0	44.4	100.0
Percentage of small bowel with atrophic mucosa (absent villi)	Normal	0	0	0
	Mild	0.1	0.1	0.2
	Moderate	0	0	0
	Severe	1.0	0.1	1.0

Table 3: Overall severity of affected small bowel mucosa as graded by the expert reviewers;

Supplementary material:

	Univariate analysis			Binary logistic regression analysis	
Factor	SBCE Positive	SBCE Negative	Significance (P value)	Unstandardized Coefficients	Significance (P value)
Age at the time of SBCE (median, years)	55	49	0.021	1.16	0.079
Age at diagnosis of CD (median, years)	48.5	40.5	0.169	0.940	0.334
Presence of symptoms n(%)	44 (64.7)	20 (66.7)	0.521	0.168	0.129
EMA positive at SBCE n(%)	21 (34.4)	2 (8.3)	0.015	1.1	0.955
ttg-IgA at SBCE (U/mL)	3.0	2.7	0.102	1.0	0.783
Albumin at SBCE (g/L)	44	46	0.136	1.12	0.529

Vitamin B12 at SBCE (ng/L)		443	351	0.259	0.997	0.201
Folate level at SBCE (μg/L)		9.9	10.5	0.554	0.871	0.292
Haemoglobin level at SBCE (g/L)		132	139	0.016	1.0	0.989
Marsh score of D1 biopsies	0	4 (7.4%)	7 (28.0%)	0.003	9.04	0.043
	1	7 (13.0%)	8 (32.0%)			
	2	5 (9.3%)	1 (4.0%)			
	3a	12 (22.2%)	7 (28.0%)			
	3b	16 (29.6%)	1 (4.0%)			
	3c	10 (18.5%)	1 (4.0%)			
	0	4 (6.9%)	7 (29.2%)	0.001	0.275	0.169

Marsh score of D2 biopsies	1	12 (20.7%)	11 (45.8%)			
	2	8 (13.8%)	1 (4.2%)			
	3a	9 (15.5%)	3 (12.5%)			
	3b	9 (15.5%)	2 (8.3%)			
	3c	16 (27.6%)	0 (0%)			
Refractory coeliac disease (RCD)		29 (41.4%)	4 (13.3%)	0.006	0.153	0.130

Table 1: Correlation of factors with positive / negative small bowel capsule endoscopy;

	Univariate analysis		Multiple regression analysis	
Factor	Spearman's rho / Mean	Significance (P value)	Unstandardized Coefficients	Significance (P value)
Age at the time of SBCE	Spearman's rho 0.283	0.006	0.057	0.854
Age at diagnosis of CD	Spearman's rho 0.171	0.106	0.018	0.941
Presence of symptoms	No symptoms 19.1% vs symptoms 15.9%	0.613	-3.475	0.543
EMA at SBCE	Spearman's rho 0.0001	0.140	5.645	0.512
ttg-IgA at SBCE	Spearman's rho 0.131	0.245	-0.001	0.986
Albumin at SBCE	Spearman's rho -0.312	0.004	-1.623	0.036
Vitamin B12 at SBCE	Spearman's rho -0.061	0.587	-0.034	0.001

Folate level at SBCE	Spearman's rho 0.001	0.992	-1.475	0.008
Haemoglobin level at SBCE	Spearman's rho -0.382	0.0001	-0.302	0.117
Marsh score of D1 biopsies	Spearman's rho 0.558	0.0001	10.494	0.019
Marsh score of D2 biopsies	Spearman's rho 0.558	0.0001	-5.835	0.174
Refractory coeliac disease (RCD)	No RCD 11.6% vs RCD I 24.5% vs RCD II 41.5%	0.007	5.552	0.212

Table 2: Correlation of factors with percentage of affected small bowel mucosa;

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