

ORIGINAL ARTICLE

Value of routine duodenal mucosal biopsies in the evaluation of anemia in a large Australian referral centre

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Abstract

Background and Aim: Small bowel mucosal biopsies (SBBx) are routinely performed to investigate unexplained anemia; however, previous studies have demonstrated a low yield in diagnosing celiac disease. Our aim was to determine the yield of routine SBBx in a large cohort of patients who underwent gastroscopy for the investigation of anemia.

Methods: Data from consecutive patients who underwent gastroscopy for the investigation of anemia in a tertiary hospital, from January 2008–December 2011, were prospectively collected. Measured outcomes were the prevalence of celiac disease, the yield of duodenal biopsies, and the correlation between celiac serology and diagnosis.

Results: Over 4 years, 987 patients (385 M:602 F; 48.27 ± 15.89 years) underwent endoscopy for anemia, of which 534 (54.1%) had proven iron deficiency anemia (IDA). Abnormal SBBx consistent with celiac disease were found in 2% (22/987), with a higher prevalence in females (3.2%, *n* = 19 vs 0.8%, *n* = 3 in males) and in those with IDA (3.6%, *n* = 19 vs 0.7%, *n* = 3 in non-IDA). Macroscopic endoscopic abnormalities were present in 86% (19/22) of patients with celiac disease. Of the 178 patients who had celiac serology, tissue transglutaminase antibody had the highest sensitivity (80%) and specificity (99%). Combined serology had a sensitivity of 85.7%.

Conclusion: Only 2% of patients with unexplained anemia had abnormal SBBx consistent with celiac disease and even fewer patients in non-IDA. Given the availability and high sensitivity of celiac serology and macroscopic changes on endoscopy, SBBx should not be routine during endoscopy but should be limited to those with positive celiac serology, abnormal endoscopic appearance, or females with IDA.

Introduction

The prevalence of celiac disease is increasing and now affects up to 1% of the general population and up to 5% of those with iron deficiency anemia (IDA).^{1,2} It is twice as common in women as in men, with the most significant risk factors being an affected first-degree relative (10–15%), type 1 diabetes (3–16%), Hashimoto’s thyroiditis (5%), and various other autoimmune diseases.¹ While the “classic” presentation of celiac disease is chronic diarrhea, malabsorption, and weight loss, the majority of patients do not have any abdominal symptoms. Instead, the most common presentation of celiac disease is IDA.³ Consequently, routine duodenal or small bowel mucosal biopsies (SBBx) are recommended for patients presenting with anemia. However, previous studies have demonstrated the poor diagnostic yield of routine SBBx, at a significant cost to the health-care system.^{4–7} Whilst SBBx is generally safe, clinically significant bleeding requiring blood transfusion can occur in 0.004–0.14%, and there are case reports of SBBx-associated perforation.^{8–10}

There have also been advances made in serological screening and endoscopic imaging in the evaluation of celiac disease. In particular, with the use of antitissue transglutaminase antibody

(anti-TTG) and the assessment of total IgA levels (to exclude total IgA deficiency), celiac disease can be detected in up to 95% of patients.^{11–16} As a result, many guidelines suggested that negative serology may be sufficient to exclude celiac disease where the pretest probability is low.^{11,17} According to the 2013 American College of Gastroenterology guideline, patients with a pretest probability of less than 5% should be tested for anti-TTG IgA and total IgA levels. SBBx should then only be considered if either of these results is abnormal.¹¹ The development of narrow-band imaging (NBI) with high-resolution imaging of the upper gastrointestinal (GI) tract has further improved macroscopic detection of celiac disease, increasing the ability to accurately detect SBBx.¹⁸ Despite this, it remains a common practice in many institutions to routinely perform random routine SBBx for the investigation of anemia.

We hypothesize that, in a large cohort of patients who are referred for the investigation of anemia, the diagnostic yield of routine SBBx is low. Instead, SBBx should be directed by serological testing or macroscopic endoscopic mucosal abnormalities. The aim of this study is to evaluate the role of routine small bowel biopsy in excluding celiac disease in a large cohort of

Table 1 Comparison of investigations for the diagnosis of celiac disease in terms of sensitivity, specificity, and negative predictive value (NPV)

Factors	Sensitivity (CI)	Specificity (CI)	NPV (CI)
Combined serology	85.7% (64–97)	96% (92–99)	98% (94–99)
Anti-TTG	80% (56–94)	99% (96–100)	97% (93–99)
Anti-gliadin	67% (43–85)	96% (91–99)	95% (90–97)
Anti-endomysial	64% (31–89)	100% (94–100)	94% (86–98)
Macroscopic changes	59% (36–79)	94% (92–95)	99% (98–100)
Combined serology or macroscopic changes	86.4% (65–97)	93% (91–95)	99.7% (99–99.9)
Serology or macroscopic changes or IDA in females	100% (85–100)	60% (57–63)	100% (99.4–100)

anti-TTG, antitissue transglutaminase; CI, confidence interval; IDA, iron deficiency anemia.

patients referred to a tertiary referral center for investigation of anemia.

Method

Study design. We reviewed a prospectively collected database on all consecutive patients who had endoscopies at the Royal Adelaide Hospital between January 2008 and October 2011 for investigation of unexplained anemia. All patients had standard endoscopic examination of the upper GI tract with Olympus gastroscopes (GF 180, Olympus, Japan) and routine SBBx performed, with a minimum of four forceps biopsies taken from the second and third portion of the duodenum. All gastroscopies were performed either by consultant gastroenterologists or supervised gastroenterology registrars/fellows. Patients with a pre-existing diagnosis of celiac disease, however, were excluded from the study. The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital (RAH protocol number 110427). Written consent was obtained from every patient prior to the procedure.

Data collection. In all subjects, clinical, endoscopic, and histological outcomes were prospectively collected. In particular, the variables collected included patients' demographics, the indication for the procedure, comorbidities, preoperative investigations (including complete blood count [CBC], celiac antibody status, and iron studies), endoscopic findings, and histology from the SBBx.

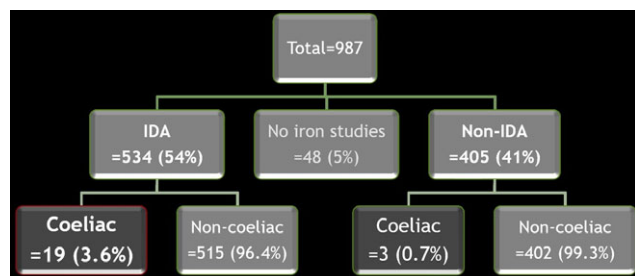


Figure 1 Outline of iron study results in the cohort and its relationship to the presence of celiac disease.

Definitions

- “Iron deficiency” was defined as ferritin of <30 µg/L.
- “Celiac disease” was defined as biopsies consistent with Modified Marsh-Oberhuber classification type 1 or greater¹⁹ combined with either:
 - Positive celiac serology or
 - Documented improvement in villous atrophy with a gluten-free diet (GFD)¹¹
- “Mucosal abnormalities” suggestive of celiac disease were villous atrophy or scalloping of mucosal folds.

“Anemia” was defined as hemoglobin less than:

- 135 g/L in males
- 120 g/L in females

Data analysis. Data were expressed as mean ± standard error or a percentage with 95% confidence interval (CI). Comparison of variables was undertaken using Fisher’s exact test for categorical data and Mann–Whitney test for continuous datasets. Multivariate analysis of factors that independently predicted the presence of celiac disease was performed using the Cox proportional hazard multivariate analysis. Analyses were performed using GraphPad Prism statistical software, version 6 (GraphPad Software Inc., La Jolla, CA, USA). A $P < 0.05$ was considered statistically significant in all analyses.

Results

A total of 987 patients (385 M; 602 F; 48.3 ± 15.9 years) without a known diagnosis of celiac disease had an upper GI endoscopy for the investigation of unexplained anemia. Iron studies were available in 939 (95%) patients and confirmed that IDA was present in 534 (54%) patients (Fig. 1). The overall prevalence of celiac disease was 2.2%, which was significantly higher in patients with IDA than those with non-IDA (19/534 (3.5%) vs 3/405 (0.7%); $P = 0.009$). Females were more likely to have celiac disease than males (19/602 vs 3/385; $P = 0.02$), and females younger than 50 years old with IDA had the highest prevalence of celiac disease (5.1%, CI: 1.9–8.3). No males without iron deficiency were diagnosed with celiac disease. Celiac serology was available in 177 (18%) patients, and 24 had at least one positive celiac antibody. In combination, celiac serology was 85.7% (CI 64–97) sensitive and 96% (CI: 92–99) specific for the diagnosis of celiac disease, with a 98% (CI: 94–99) negative predictive value (NPV). The TTG IgA antibody had a greater sensitivity and specificity than endomysial and anti-gliadin antibodies (Table 1).

Celiac disease was diagnosed in 22 (2.2%) patients based on abnormal SBBx histology consistent with Modified Marsh-Oberhuber classification type 1 or greater and positive celiac serology or endoscopic improvement with GFD (Fig. 2). A total of 42 patients had duodenal biopsies showing either isolated intraepithelial lymphocytes with intact villous architecture ($n = 27$) or nonspecific duodenitis ($n = 15$), with negative celiac serology and no clinical or endoscopic improvement on GFD. Among patients diagnosed with celiac disease, endoscopic and/or serological abnormalities were noted in 86.4% (19/22) of cases, with an NPV of 99.7% (CI 99–99.9). On multivariate analysis, factors that independently predicted the presence of celiac disease were age < 50, female gender, iron deficiency, presence of macroscopic changes of celiac disease, and positive serology (Table 2). GI symptoms did not correlate with an increased risk of celiac disease.

Discussion

To our knowledge, this is the largest study that evaluates the role of routine SBBx in the investigation of anemia, with 95% of patients having iron studies previously performed. The main findings were as follows: (i) celiac disease was diagnosed in 2.2% of patients with anemia and was significantly more common in patients with IDA (3.6% vs 0.7% in the non-IDA group); (ii) endoscopic and/or serological abnormalities were present in the majority (86.4%) of patients with celiac disease; and (iii) significant predictive factors of celiac disease were age < 50 years, female gender, iron deficiency, presence of macroscopic changes of celiac disease, and positive serology. Given that most patients with celiac disease have endoscopic and/or serological abnormalities, our study suggests that SBBx should not be routinely performed for the investigation of anemia, particularly in males and those who have non-IDA. Thus, the performance of SBBx during endoscopy should be selective based on predictive risk factors and endoscopic findings. Such a practice would not only result in cost saving but also minimize the risk of complications from SBBx.

Previous studies have demonstrated the poor diagnostic yield (0.4–1.6%) of routine SBBx in the evaluation of anemia

without positive serological tests or other strong indications.^{4–7} These studies have established the need for biopsies in only those with “high-risk” features but have not categorized anemia into IDA versus non-IDA, a group in which the incidence of celiac disease is low. Studies have also assessed the role of routine biopsy for IDA, finding a prevalence of celiac disease of around 5–10% in those with documented IDA.^{20–22} In addition, a 2016 cost analysis by Broide et al. found that SBBx, regardless of serological status, is cost-effective in populations in which the prevalence of celiac disease is >5% and, therefore, suggested that all patients with IDA should have SBBx during endoscopy.²² These studies, however, have not combined serological and endoscopic indications for biopsy and have not included demographic features to identify at-risk populations. Given the discrepancy in prevalence between males and females, as well as the improving sensitivity of advanced endoscopic techniques, it would be prudent to further specify the group in which routine SBBx are justified in order to prevent unnecessary SBBx. Furthermore, the large sample size in this study would suggest that the incidence of celiac disease in iron deficiency may be lower than 5%, in which case routine SBBx would not be cost-effective.

This study found an incidence of celiac disease of <1% in men and all patients without IDA. Given that most guidelines only recommend SBBx with a pretest probability of >5%,^{11,22} these patients should not have SBBx during endoscopy unless serological or endoscopic abnormalities are found. In our population this approach would have resulted in a sensitivity of 100% (CI 85–100%) and an NPV of 100% (99.4–100%). Restricting the indications for SBBx further to only those with positive serology or abnormal endoscopic appearance would have resulted in a sensitivity of 86.4% and an NPV of 99.7% (CI 99–99.9). The sensitivity of this approach could be increased further with the use of advanced endoscopic techniques and the incorporation of HLA haplotyping as discussed below.

The large population in this study reflects real-life experience, with nearly half of patients referred for endoscopy not having documented iron deficiency, a group in which the prevalence of celiac disease is extremely low. The study also highlighted the

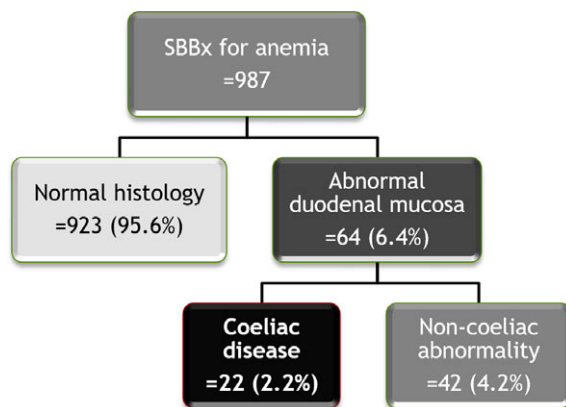


Figure 2 Outline of small bowel biopsies (SBBx) results in the cohort and the prevalence of celiac disease.

Table 2 Characteristics predictive of celiac disease in patients who presented with anemia for upper gastrointestinal (GI) endoscopy

Characteristics	Celiac disease (n = 22)	Non-celiac disease (n = 965)	P value
GI symptoms	2	68	0.71
Age < 50	10	247	0.04
Age > 50	12	728	
Female	19	583	0.02
Male	3	382	
IDA	19	515	0.01
Non-IDA	3	402	
Macro changes	13	63	<0.0001
Macro normal	9	902	
Serology + ve	18	6	<0.0001
Serology -ve	3	150	

IDA, iron deficiency anemia.

inconsistent assessment of celiac serology in patients with iron deficiency, with less than half having celiac serology prior to endoscopy. This may be due to a lack of awareness in general clinical practice. Given the high sensitivity and specificity of celiac serology, its use in combination with endoscopic findings may avoid a large proportion of SBBx and therefore result in substantial cost saving. According to our study, this approach can successfully exclude celiac disease in >99% of patients. Previous studies have shown that the sensitivity and specificity of anti-TTG are 85–95%.^{11–16} While the sensitivity of anti-TTG was only 80% in our study, this was likely due to a small sample size of patients with celiac disease and, therefore, increased variability of results. In addition, the sensitivities of anti-endomysial and anti-gliadin antibodies in our study were only 64 and 67%, respectively, compared to previous studies that demonstrated sensitivities of >90% and 75–90%.^{12,13,15} Despite the seemingly low sensitivities of antibodies in our cohort, the NPV of combined celiac serology remained high (98%) due to the low pretest probability of celiac disease.

The diagnostic yield of macroscopic changes on endoscopy was low in our study, likely as a result of multiple factors. Olympus 160–180 high-definition (HD) endoscopes were used, which may have missed subtle early changes. It has recently been reported that, with the use of NBI with optical magnification, macroscopic endoscopic appearance is up to 93.3% sensitive for the diagnosis of villous atrophy,¹⁸ which was noted microscopically in 21 of 22 celiac patients in our study. Comparatively, macroscopic changes had a sensitivity of only 59% in our cohort. It was also likely that our endoscopists did not focus on the detection of macroscopic changes when routine biopsies were being performed. Hence, the sensitivity of macroscopic changes consistent with celiac disease on endoscopy may be higher if this was specified as an indication for SBBx. In addition, this study was conducted in a large tertiary teaching hospital, and therefore, variable endoscopist experience may have influenced results. This should, however, reflect real-world experience and thus improve the generalizability of our results. With advanced endoscopic techniques and a focus on detecting macroscopic changes, the sensitivity of abnormal endoscopic appearance would therefore be expected to be higher than in this study.

The study has several potential limitations. First, genetic testing was not performed as part of this study but may have a role in further directing SBBx in order to minimize the number of SBBx performed in nonceliac patients. There is a strong genetic component in celiac disease, with the HLA-DQ2 haplotype present in 90–95% and HLA-DQ8 present in 5–10%.^{11,17,23} The absence of either of these haplotypes virtually excludes the diagnosis of celiac disease (NPV > 99%).^{23,24} The limiting feature of genetic testing is the low specificity, with these HLA subtypes present in 20–30% of the population.^{11,15,25} However, by testing for HLA-DQ2/8 only in a subgroup of female patients with confirmed iron deficiency, biopsies could be limited to only 20–30% of this population. In addition, this was a single-center, nonrandomized study and was noninterventional, with multiple patients undergoing endoscopy with incomplete preoperative investigations. Therefore, further studies are required to validate our findings, which could include randomization to more restrictive indications for biopsy and possibly involve HLA-DQ2/8 haplotyping.

Conclusion

The incidence of celiac disease in the anemic population is low (2.2%), especially in those without iron deficiency (0.7%) and in males (0.8%). Even in patients who have proven IDA, the yield is low (3.5%), and it may not be cost-effective to perform routine SBBx during endoscopic evaluation. Instead, the use of celiac serology and/or enhanced endoscopic imaging as indicators for SBBx would minimize risk and be more cost-effective than routine SBBx. From our study, the strongest indicators for SBBx were females with iron deficiency and anyone with positive celiac serology or macroscopic endoscopic changes consistent with celiac disease.

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