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ORIGINAL ARTICLE

Retrospective Cohort Study

# Coeliac disease in the modern era: Severity of small bowel mucosal injury at diagnosis with analysis of clinical correlates and rate of improvement on a gluten free diet

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## Abstract

***AIM***

To analyze the relationships between pre-diagnosis coeliac serology, duodenal histopathology, primary presenting symptoms, coeliac-related comorbidity and response to treatment in a modern cohort with new diagnosis of coeliac disease (CD).

***METHODS***

A retrospective cohort study including 99 participants diagnosed with CD between 1999 and 2013. All patients had the following data recorded: baseline characteristics, coeliac serology, small bowel histopathology. A subset of this cohort underwent a repeat small bowel biopsy. Independent associations were assessed with logistic regression.

***RESULTS***

The mean age at diagnosis was 43 years (Interquartile range 30-53 years) and 68% of the cohort was female. At diagnosis 49 (49%) patients had total villous blunting (MS 3c), 12 (12%) had subtotal villous blunting (MS 3b), and 29 (29%) had partial villous blunting (MS 3a). The prevalence of symptoms pre diagnosis was not related to the severity of villous blunting ($P$ = 0.490). 87 (88%) of the cohort underwent repeat small bowel biopsy after a median of 7 mo (IQR 6-11 mo). 34 (39%) patients had biopsy results $\geqslant$ MS 3a which

compared to 90 (90%) at the initial biopsy. 24 (71%) of this group reported adherence to a gluten free diet (GFD). Persistent MS ⩾ 3a at repeat biopsy was not associated with symptoms ($P$ = 0.358) or persistent positive coeliac serology ($P$ = 0.485).

***CONCLUSION***

Neither symptoms nor serology predict the severity of the small bowel mucosal lesion at CD diagnosis. Whilst a GFD was associated with histological improvement many patients with newly diagnosed CD had persistent mucosal damage despite many months of gluten restriction. Negative CD serology did not exclude ongoing mucosal injury.

**Key words:** Coeliac disease; Gluten-free diet



**Core tip:** Coeliac disease (CD) is a common, under-recognized gastrointestinal disorder. The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD. Thyroid related autoimmune co-morbidities were common ($n$ = 17, 17%). Symptoms at presentation were not associated with the degree of villous blunting on biopsy. Similarly, persistent villous blunting at repeat biopsy was not associated with symptoms or positive coeliac serology. Negative coeliac serology did not exclude ongoing mucosal injury.

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## INTRODUCTION

Coeliac disease (CD) is estimated to affect 1.2% of Australians[1]. It is a gastrointestinal disorder that involves an immune response to dietary gluten, resulting in small bowel mucosal damage[2]. Most common presentation of CD in adults is diarrhea although this presentation occurs in less than 50% of cases. Silent or atypical presentations of CD are becoming more common[3,4]. The diagnosis of CD is dependent on correlation between history, serological markers and characteristic histological features on duodenal biopsy[1]. It is currently unclear whether the presenting symptoms of CD have any relationship to the severity of small bowel injury at diagnosis. It also remains unclear whether the severity of small bowel mucosal injury is related to complications of CD such as osteoporosis.

The only known treatment for CD is adherence to a gluten free diet (GFD) which may reduce the risk of long-term complications such as osteoporosis and malignancy[5]. Whilst small bowel mucosal injury is known to improve on a GFD, the rate and completeness of such improvement has been a subject of limited study.

In the current study we analysed the relationship between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a GFD.

## MATERIALS AND METHODS

This retrospective cohort study included 99 participants who presented to a single Gastroenterology practice in Victoria (Australia) from 1999-2013. Patients were referred to this practice either by General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data collected at baseline included: Gender, age at diagnosis, primary presenting symptom as assessed by a Gastroenterologist, duration of symptoms prior to diagnosis, family history of CD, complications of CD, associated autoimmune condition. Serological and histology data included the presence of anti- tissue transglutaminase (tTG) antibodies or endomysial (EM) antibodies; small bowel histopathology at the time of diagnosis and at least six months after commencing a GFD, quantified by Marsh-Oberhuber Score (MS). Data were recorded in a Microsoft Excel (2011) spreadsheet and then transferred to SPSS Version 25.0 (IBM SPSS Inc., Chicago, IL, United States) for statistical analysis. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

## RESULTS

### *Presentation*

Among the cohort of 99 patients the mean age at diagnosis was 43 years (IQR 30-53 years) and 68% of the cohort was female (Table 1). Over half of the patients ($n$ = 51, 52%) were asymptomatic at presentation, some of whom for example had been referred by their General Practitioner after having positive CD serology as part of a work-up to investigate iron deficiency. The most common presenting symptom was diarrhoea ($n$ = 31, 31%). Of symptomatic patients, the majority ($n$ = 34, 71%) described symptoms for over 1 year prior to diagnosis (Table 2).

At diagnosis, 17 (17%) patients had an associated autoimmune condition including thyroid pathology ($n$ = 10), Type 1 Diabetes ($n$ = 8), Rheumatoid Arthritis ($n$ = 1) and Pernicious anaemia ($n$ = 1) (Table 3).

### *Diagnosis*

88 (89%) patients had positive CD serology at the time of diagnosis. Small bowel histopathology at diagnosis revealed total villous blunting (MS 3c) in 49 (49%), subtotal villous blunting (MS 3b) in 12 (12%) and partial

**Table 1 Comparison of 99 patients with coeliac disease n (%)**

| | *n* (%) |
|---|---|
| Age, yr | 43 (30-53) |
| Male gender | 32 (32) |
| Family history | 24 (24) |
| Main symptom at presentation | |
| Abdominal pain | 5 (5) |
| Bloating | 6 (6) |
| Bone disease | 6 (6) |
| Diarrhoea | 31 (31) |
| Fatigue | 6 (6) |
| Iron deficiency | 21 (21) |
| Incidental[1] | 6 (6) |
| Screening | 14 (14) |
| Other[2] | 4 (4) |

[1]Gastroscopy performed to investigate dyspepsia; [2]Vitamin B12 deficiency ($n$ = 3), hypoalbuminaemia ($n$ = 1). Continuous variables are presented as median (inter-quartile range).

**Table 2 Comparison of duration of 48 patients with symptoms at diagnosis**

| Duration of symptoms prior to diagnosis | *n* (%) |
|---|---|
| < 1 yr | 14 (29) |
| 1-3 h | 12 (25) |
| > 3 yr | 22 (46) |

villous blunting (MS 3a) in 29 (29%) patients, while 9 (9%) patients had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis (Table 4). Of the patients with MS 3b or 3c, 10 (83%) and 44 (90%) had positive serology respectively (Table 4). The majority of patients with MS ⩾ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c ($P$ = 0.490) (Table 5). Of the 9 patients who had lesser degrees of injury with crypt hyperplasia or only intra-epithelial lymphocytosis, 2 (22%) patients had presented with fatigue, 4 (44%) patients had been detected on screening by a General Practiotioner, 2 (22%) had been investigated for iron deficiency and 1 (11%) patient had been investigated for dyspepsia. Concomitant autoimmune conditions were present in 4 (10%) patients with MS 3a/b and 9 (18%) patients with MS 3c ($P$ = 0.298). 2 (5%) of patients with Marsh 3a/b had osteoporosis or osteopenia at diagnosis compared to 4 (8%) of patients with Marsh 3c ($P$ = 0.534).

### *Follow-up*

87 (88%) of the cohort underwent repeat small bowel biopsy after a minimum of six months (Table 6). Of this group 76 (87%) reported adherence to a GFD at the time of repeat biopsy.

Of the 76 patients reporting adherence to a GFD at the time of the second biopsy 48 (63%) had negative serology, 14 (18%) had positive serology and 14 (18%) did not have serology results available. 37 (49%) were asymptomatic, 7 (9%) reported symptoms and 32 (42%) did not have data recorded. All 7 patients with a concomitant autoimmune disorder who reported compliance with a GFD and had negative serology had persistent MS ⩾ 3a.

**Table 3 Comparison of 17 patients with an associated autoimmune condition at diagnosis**

| Thyroid pathology | |
|---|---|
| Graves' disease | 4 |
| Autoimmune thyroiditis | 1 |
| Hypothyroidism[1] | 5 |
| Type 1 diabetes | 5 |
| Rheumatoid arthritis | 1 |
| Pernicious anaemia | 1 |

[1]Includes 1 patient with Hashimoto's thyroiditis.

30 (34%) patients had biopsy results revealing a normalization of histology (MS0), 18 (60%) of whom had negative repeat serology, 6 (20%) had positive serology and 6 (20%) did not have serology results available. All 30 patients with MS0 reported adherence to a GFD.

34 (39%) patients had biopsy results ⩾ MS 3a which compared to 90 (90%) at the initial biopsy. Of the 34 patients with persistent ⩾ MS 3a, 18 (53%) had negative repeat serology, 8 (24%) had positive serology and 8 (24%) did not have serology results available. 24 (71%) of this group reported adherence to a GFD.

47 patients reported compliance with a GFD and had negative serology consistent with absent dietary gluten exposure. Among this cohort the repeat biopsy was undertaken at a median of 7 mo (IQR 6-11 mo) and the incidence of persistent villous blunting was 62%. Among the 29 patients with persistent villous blunting, in 16 (55%) the change was ⩾ MS 3a.

Multivariate analysis did not reveal an association between MS ⩾ 3a at diagnosis of CD and positive serology or symptoms at diagnosis (Table 7). Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy (Tables 8 and 9).

## DISCUSSION

The findings in this study support other larger studies which have reported a trend toward an asymptomatic or silent presentation of CD rather than the traditional presentation of diarrhea[4,6-8]. The "coeliac iceberg" is often used to describe the large proportion of undiagnosed asymptomatic or subclinical coeliac disease[9,10]. Nenna *et al*[10] reported that the traditional presentation of CD accounted for 28% of cases, whereas the majority of cases presented as silent forms or non-classical presentations of CD. A third group termed latent CD is also described comprising individuals who are considered at risk due to having a coeliac related HLA type and positive coeliac serology in the absence of current villous blunting. Genetic composition plays a pivotal role in determining the predisposition to CD, with

**Table 4 Symptoms, serology and histology results for 99 patients divided by severity of duodenal histology at initial biopsy**

| Biopsy score[1] | *n* (%) | Positive serology[2] | Symptoms at diagnosis (%) |
|---|---|---|---|
| 0 | 0 (0) | - | - |
| 1 | 7 (7) | Positive = 7 (100)<br>Negative = 0 (0)<br>Unknown = 0 (0) | 0 (0) |
| 2 | 2 (2) | Positive = 2 (100)<br>Negative = 0 (0)<br>Unknown = 0 (0) | 2 (100) |
| 3a | 29 (29) | Positive = 25 (86)<br>Negative = 4 (14)<br>Unknown = 0 (0) | 14 (48) |
| 3b | 12 (12) | Positive = 10 (83)<br>Negative = 1 (8)<br>Unknown = 1 (8) | 7 (58) |
| 3c | 49 (49) | Positive = 44 (90)<br>Negative = 2 (4)<br>Unknown = 3 (6) | 25 (51) |

[1]Marsh-Oberhuber score at diagnosis; [2]tissue Transglutaminase antibodies or endomysial antibodies.

**Table 5 Presenting symptom of Marsh-Oberhuber score 3c compared to Marsh-Oberhuber score 3a/b *n* (%)**

| Presentation | Marsh-Oberhuber score 3a/b[1] | Marsh-Oberhuber score 3c[2] | Odds ratio | 95%CI | *P* value |
|---|---|---|---|---|---|
| Diarrhoea | 13 (32) | 18 (37) | 1.39 | 0.33-5.79 | 0.66 |
| Iron deficiency | 8 (20) | 11 (22) | 1.38 | 0.30-6.40 | 0.69 |
| Bone disease | 2 (5) | 4 (8) | 2.00 | 0.24-16.36 | 0.52 |
| Bloating | 4 (10) | 2 (4) | 0.50 | 0.06-4.09 | 0.52 |
| Fatigue | 1 (2) | 3 (6) | 3.00 | 0.23-39.60 | 0.40 |
| Abdominal pain | 3 (7) | 2 (4) | 0.67 | 0.76-5.88 | 0.72 |
| Incidental | 2 (5) | 3 (6) | 1.50 | 0.17-13.23 | 0.72 |
| Screening | 5 (12) | 5 (10) | 0.33 | 0.25-4.40 | 0.40 |
| Other | 3 (7) | 1 (2) | 1.38 | | 0.89 |

[1]$n$ = 41; [2]$n$ = 49. CI: Confidence interval.

HLA-DQ2 and DQ8 haplotypes expressed in 90% and 5% of affected patients respectively[11]. Gluten is required to trigger the disease but the transition from tolerance to a gluten related immune response is poorly understood[11]. Possible triggers for this immune transition include intestinal infections, the amount and quality of gluten and the composition of the intestinal microbiota[11]. A gluten related immune response may develop early in life and many silent cases are unrecognized for many years, if ever[12]. It has been suggested that although the majority of CD cases have not been diagnosed, population screening may not be appropriate as evidence is lacking as to whether the majority of silent CD cases actually translate into any significant morbidity. It also remains unclear whether these clinically silent cases would benefit from a GFD[13,14].

Microscopic enteritis is a histopathological inflammatory condition (Marsh 0-Ⅱ) which clinically may present as malabsorption or more subtle micronutrient deficiencies but with a relatively intact villous structure[15]. 9 (9%) patients in this cohort could be classified at initial biopsy with microscopic enteritis secondary to CD. Microscopic enteritis is an important, novel diagnostic category of patients whom were previously diagnosed with a functional enteropathy[15].

The contrary view has also been argued, that population screening may be beneficial given there is a high prevalence of associated autoimmune conditions and nutritional deficiencies could contribute greatly to population morbidity[16]. Owing to the absence of identifiable features predicting risk, targeted screening of at risk populations would be difficult. Whilst most seropositive patients will have villous blunting[17], among those seropositive patients with normal small bowel mucosa there is no reliable means of identifying which subsets will go on to develop villous blunting and potentially long term complications of CD. Further clarification *via* large population studies is needed to resolve issues around cost-benefits of screening, which populations and age groups to screen as well as laboratory reference range cut-offs for screening tests[9].

This study found the majority of patients to be female, most patients to be asymptomatic and a minority to present with diarrhea. The widely reported trend toward silent CD could possibly be partly explained by the increased access to serology and upper gastrointestinal endoscopy which have enabled for easier diagnosis of CD[18]. However the reported decrease in the proportion of patients presenting with symptoms such as diarrhea started before the advent widespread availability of

**Table 6 Symptoms, serology and histology results for 87 patients with repeat biopsy**

| Biopsy score[1] | Repeat biopsy score | Positive serology[2] | Reported gluten free diet adherence | Symptoms at repeat biopsy |
|---|---|---|---|---|
| 0 | 31 (36) | Positive = 6 | Yes = 31 | Yes = 4 |
| | | Negative = 19 | No = 0 | No = 14 |
| | | Unknown = 6 | | Unknown = 13 |
| 1 | 17 (20) | Positive = 4 | Yes = 16 | Yes = 2 |
| | | Negative = 9 | No = 1 | No = 10 |
| | | Unknown = 4 | | Unknown = 5 |
| 2 | 5 (6) | Positive = 1 | Yes = 5 | Yes = 1 |
| | | Negative = 4 | No = 0 | No = 2 |
| | | Unknown = 0 | | Unknown = 2 |
| 3a | 26 (30) | Positive = 4 | Yes = 20 | Yes = 3 |
| | | Negative = 17 | No = 6 | No = 12 |
| | | Unknown = 5 | | Unknown = 11 |
| 3b | 1 (1) | Positive = 0 | Yes = 1 | Yes = 0 |
| | | Negative = 0 | No = 0 | No = 0 |
| | | Unknown = 1 | | Unknown = 1 |
| 3c | 7 (8) | Positive = 4 | Yes = 3 | Yes = 1 |
| | | Negative = 1 | No = 4 | No = 4 |
| | | Unknown = 2 | | Unknown = 2 |

[1]Marsh-Oberhuber score at diagnosis; [2]Anti-transglutaminase antibodies or endomysial antibodies.

**Table 7 Independent predictors of a Marsh-Oberhuber score ⩾ 3a at diagnosis of coeliac disease for 99 patients**

| Characteristic | Odds ratio | 95%CI | *P* value |
|---|---|---|---|
| Age below 40 yr | 0.38 | 0.08-1.85 | 0.231 |
| Female gender | 3.20 | 0.35-29.10 | 0.301 |
| Positive serology | 2.06 | 0.17-25.52 | 0.573 |
| Symptoms for over 3 yr | 0.70 | 0.04-11.37 | 0.804 |
| Symptoms at diagnosis | 4.54 | 0.51-40.60 | 0.176 |

CI: Confidence interval.

**Table 8 Independent predictors of a Marsh-Oberhuber score ⩾ 3a after repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients**

| Characteristic | Odds ratio | 95%CI | *P* value |
|---|---|---|---|
| Age below 40 yr | 0.59 | 0.23-1.57 | 0.292 |
| Female gender | 1.13 | 0.40-3.20 | 0.824 |
| Gluten free diet | 0.03 | 0.00-0.34 | 0.004 |
| Symptoms at second biopsy[1] | 0.45 | 0.81-2.48 | 0.358 |
| Positive serology at second biopsy | 0.64 | 0.18-2.27 | 0.485 |

[1]*n* = 51 patients. CI: Confidence interval.

serologic testing[4]. The proportion of atypical or silent presentations of CD is increasing, most often manifesting as bone disease, anaemia or an incidental finding at the time of investigation of dyspepsia *via* endoscopy[8,19]. There is also an increased proportion of diagnoses through screening of first degree relatives[20]. Age at diagnosis has slightly increased since the 1960s, which it is suggested is at least partly related to the later administration of dietary gluten to infants[21].

17 (17%) of cases in this study had autoimmune co-morbidities, mainly thyroid-related. Other studies have reported increased rates of autoimmunity, predominantly thyroid-related although at rates are slightly lower than reported in this study[3,16,22,23]. Ventura *et al*[11] reported a higher prevalence of autoimmune disorders in a CD population relative to healthy controls. While the higher prevalence of autoimmune conditions in CD is often explained by shared HLA antigens, Ventura *et al*[24] reported that the prevalence of autoimmune disorders in CD was associated with the duration of exposure to gluten. They found that the age at diagnosis of CD was the single best predictor of the prevalence of autoimmune disease when corrected for gender and actual age of the patients[24]. It is possible that the increased prevalence of autoimmune comorbidity in the current cohort compared with other cohorts reported in the literature[3,16,22,23], reflect the relatively advanced age at diagnosis which correlated with many years of gluten exposure prior to diagnosis.

We identified 6 (6%) of patients in this study to have osteoporosis or osteopenia. Low BMD is more common in patients with CD[25]. Compared with the current cohort, Kemppainen *et al*[25] have previously reported higher rates bone disease at the time of CD diagnosis (*n* = 20, 26%) although this could perhaps be explained by the relatively older study population in that study (mean 46 years). Kemppainen *et al*[25] has previously reported that low BMD was associated with a new diagnosis of CD, as well as patients not in disease remission. Kemppainen *et al*[25] did not find that mean BMD differed between patients classified by disease severity. Patients with newly diagnosed osteoporosis have higher rates of CD relative to the general population with one study reporting the prevalence of CD in an osteoporotic population to be 3.4%[26]. Patients with CD have significantly decreased bone mineral density (BMD) in the femoral neck and lumbar spine. The pathogenesis of bone mineral loss associated with CD is not well understood. Chronic inflammation of the damaged intestinal mucosa results in release pro-inflammatory cytokines such as tumour

**Table 9 Independent predictors of a Marsh-Oberhuber score < 3 on repeat duodenal biopsy, at least 6 mo after diagnosis of coeliac disease for 87 patients**

| Characteristic | Odds ratio | 95%CI | *P* value |
|---|---|---|---|
| Age below 40 yr | 1.16 | 0.63-4.31 | 0.313 |
| Female gender | 0.90 | 0.32-2.52 | 0.834 |
| Negative serology at time of repeat biopsy | 0.72 | 0.26-1.99 | 0.524 |
| Asymptomatic at repeat biopsy | 1.07 | 0.41-2.80 | 0.899 |
| Gluten-free diet | 23.57 | 2.61-212.99 | 0.005 |

CI: Confidence interval.

necrosis factor α and Interleukin (IL)-6. Higher levels of these cytokines, which directly trigger osteoclasts, have been found in untreated CD patients[27,28]. At the same time lower levels of IL-18 and IL-12, which play an inhibitory role, have been observed in CD patients[27,28]. Other important contributors of decreased BMD may differ between patients but include: malabsorption of calcium; secondary hyperparathyroidism driven by vitamin D deficiency; inadequate dietary intake; lapses from GFD[29,30]. Treatment of CD with a GFD has been shown to improve axial BMD however loss of peripheral skeletal BMD may persist[29]. While patients with CD have increased bone loss, the overall fracture rate is only slightly increased and therefore it is argued osteoporosis related morbidity does not justify population screening for coeliac disease[31]. It has been suggested that screening for CD should be performed in all patients with osteoporosis[26]. However other studies have not supported screening of this population citing that while the prevalence of CD may be increased in osteoporotic cohorts, it makes up only a small contribution relative to the overall post-menopausal osteoporotic population[32,33].

After diagnosis, the key endpoints for CD management are absence of symptoms and histologic evidence of mucosal healing[34]. As was found in this study, negative serological markers are not reliable surrogates for mucosal healing[17,19,35]. Serum EM antibodies and tTG antibodies are often used as surrogate measures of villous health. However these tests were designed for screening for CD among untreated persons consuming gluten. For monitoring known CD patients on a GFD, both EM and tTG antibodies have a high specificity but a low sensitivity resulting in the majority of patients on a GFD with villous blunting having normal serological levels. This is contrasted with a high specificity and sensitivity in patients with untreated CD. False positive tests for patients on a GFD are less common[36].

39% of patients in the current study had persistent villous blunting at repeat biopsy which is higher than similar studies[37,38]. Hutchinson *et al*[37] reported 80% of cases demonstrated histological improvement while Ciacci *et al*[38] reported severe intestinal damage persisted in only 23.8% of patients. An explanation for the difference could be the longer time to follow-up relative to our study of 1.0 year[37] and 6.9 years[38]. There is no consensus on timing of repeat biopsy; some experts favour repeat biopsy in 1 year and others do not recommend a repeat biopsy in the management of uncomplicated CD cases[39]. Serology often does not reflect the mucosal health in patients on a GFD however there is a paucity of evidence to address whether a repeat biopsy changes clinical outcomes and the cost-benefit analysis is yet to be established. A repeat biopsy may be needed, especially in patients with ongoing symptoms. The optimal timing of any such biopsy is unclear[39]. In a cohort of 39 patients with CD reporting GFD adherence all of whom had responded clinically, 77% had abnormal endoscopic and histopathologic appearances on repeat biopsy performed after a mean of 8.5 years[40]. A strict GFD is associated with improvement of histology which has been supported by previous studies, re-enforcing that diet modification is the only known effective management option for these patients[41,42]. The cause of persistent villous blunting is thought to often be caused by trace amounts of gluten consumed inadvertently by the patient. GFD adherence as assessed by interview has been demonstrated as an effective low-cost, non-invasive surrogate for villous damage[38].

This study has a number of limitations. Firstly, this is a relatively small study from a single specialist centre, thus may not reflect results in the greater community. However, a strength is that all patients were assessed by the same local protocol by a single Gastroenterologist which avoided heterogeneity between observers. Secondly, data were collected retrospectively. A number of patients did not have a repeat biopsy nor had missing data at the time of the repeat biopsy. A strength of this study is that it is the first study to look at the presentation of CD in an Australian population in the modern era. There are no published Australian studies which have recognized the changing nature of CD presentations and a prospective study would further add to this field.

In this study, the majority of patients were asymptomatic at the time of CD diagnosis. Neither symptoms nor serology predicted the severity of the small bowel mucosal lesion. The majority of patients had histological improvement on repeat biopsy. Whilst a GFD was associated with histological improvement many patients had persistent mucosal damage despite a GFD. Early repeat duodenal biopsy may have limited diagnostic and prognostic value due to delayed mucosal healing. Biopsy after at least 1 year may provide more valuable results rather than an earlier biopsy as was done in this cohort. Negative CD serology did not exclude ongoing mucosal

injury.

## ARTICLE HIGHLIGHTS

### Research background

Coeliac disease (CD) is a common gastrointestinal disorder that involves an immune response to dietary gluten. The condition is under recognised, particularly because silent or atypical presentations are becoming more common. Diagnosis is made with the combination of symptoms, serology and characteristic features seen on duodenal biopsy. It remains unclear whether there is an association between symptoms at diagnosis and the degree of small bowel injury. In addition, it is unclear whether symptoms and serology at the time of repeat duodenal biopsy are associated with the degree of mucosal healing.

### Research objectives

The aim of this study was to analyze the association between both pre-diagnosis coeliac serology and initial duodenal histopathology, and primary presenting symptoms, coeliac related comorbidity and response to a gluten-free diet (GFD). Most patients in this study were asymptomatic at diagnosis. Neither symptoms nor serology were associated with the severity of small bowel injury. Many patients had persistent mucosal damage at the time of repeat duodenal biopsy despite reported adherence to a GFD suggesting that mucosal healing may take longer than previously reported. These findings have revealed the increasing difficulty in recognizing the symptoms of CD. Further research is needed to develop more reliable non-invasive biomarkers to be used as surrogates to assess mucosal healing.

### Research methods

This was a retrospective cohort study which included 99 participants who presented to a single Gastroenterology practice in Victoria, Australia from 1999-2013. Patients were referred from General Practitioners or other specialists. All patients were assessed by a Gastroenterologist. Data recorded included: baseline demographics, co-morbidities, family history, duration of symptoms, complications of CD. Serology and histology results were recorded for each patient. The majority of these patients underwent repeat duodenal biopsy after a period on a GFD to check for mucosal healing. Results were compared to repeat serology and symptoms. Numerical data were presented as median and inter-quartile range (IQR). The association of severity of duodenal blunting to symptoms and serology were examined using logistic regression.

### Research results

The mean age at diagnosis was 43 years (IQR 30-53 years) and the majority was female. Most patients ($n$ = 51, 52%) were asymptomatic at diagnosis. 17 (17%) patients had an associated autoimmune condition, the majority of whom had thyroid pathology ($n$ = 10, 59%). The majority of patients with Marsh-Oberhuber Score (MS) $\geqslant$ 3a were symptomatic at diagnosis. There was no difference in symptoms between patients in a combined group of MS 3a/b compared to MS 3c. There was no difference of concomitant autoimmune conditions between patients with MS 3a/b ($n$ = 4, 10%) and MS 3c ($n$ = 9, 18%). Multivariate analysis did not reveal an association between MS $\geqslant$ 3a at diagnosis of CD and positive serology or symptoms at diagnosis. 87 (88%) patients had repeat biopsy. Lack of improvement in small bowel histology was not associated with persistently positive coeliac serology or ongoing symptoms at the time of repeat biopsy.

### Research conclusions

This study supports larger studies that have reported an increase in asymptomatic presentations of CD. Severity of villous blunting at diagnosis was not associated with symptoms. This study did not find an association between symptoms and serology at the time of repeat duodenal biopsy with persistent villous blunting. Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

### Research perspectives

Duodenal healing whilst on a GFD may persist for longer than previously reported. Discovery of new non-invasive biomarkers is needed to better predict the degree of villous blunting.

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