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Alimentary Tract

What are the clinical consequences of 'potential' coeliac disease?

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ABSTRACT

Background: There is limited data on the clinical consequences of potential coeliac disease (PCD).
Aim: To compare the presentation of PCD with coeliac disease (CD).
Methods: A retrospective study of adult PCD patients (>18 years) was performed. Presenting manifestations, serology and HLA-DQ genotyping were compared to an age-at-diagnosis and sex-matched CD cohort.
Results: The PCD cohort comprised 84 patients (median age 37 years, 63% female). The majority of PCD patients were symptomatic at presentation (PCD 91.7% versus CD cohort 94.0%, $p = 0.55$). In total, 79.8% and 76.2% of the PCD and CD cohorts respectively reported ≥1 gastrointestinal symptoms at presentation ($p = 0.58$). Extraintestinal presentation was less common in PCD than CD (65.5% versus 79.8% respectively, $p = 0.038$). PCD patients had fewer haematinic deficiencies than those with CD (iron 21.4% versus 41.7%, $p = 0.005$, vitamin D 14.3% versus 27.4%, $p = 0.037$ and folate deficiency 7.1% versus 28.6%, $p = <0.001$.) Post-diagnosis, 67.5% of the PCD patients chose a GFD. One-third of the patients who continued to eat gluten developed villous atrophy.
Conclusion: The presentation of PCD and CD differ; however, mild enteropathy does not necessarily equate to mild symptoms. The GFD appears to be advantageous in symptomatic PCD.

1. Introduction

Coeliac disease (CD) is a chronic autoimmune disorder precipitated by dietary exposure to gluten in genetically predisposed individuals [1]. Given the underlying pathophysiology, it is unsurprising that the vast majority of patients with CD are serologically positive for coeliac autoantibodies, IgA-tTG-2 and IgA-EMA [2]. However, histological confirmation of villous atrophy (VA) via duodenal biopsy samples taken while a patient is on a gluten-containing diet (GCD) remains essential for diagnosis [2].

The histological features of CD occur on a continuum, with normal villous architecture at one end of the spectrum and flat, atrophied lesions at the other [3]. Symptoms may or may not be present at any point along this histological continuum; therefore, CD-related symptoms can precede VA, the hallmark histological feature of CD [4]. Furthermore, when developing VA due to continued gluten exposure, a patient must first progress through the earlier stages of the spectrum [5]. Conversely, studies show that patients will regress through the earlier lesions when healing [6,7]. The term potential coeliac disease (PCD) describes a patient who, despite having normal (Marsh 0) or only mildly enteropathic (Marsh 1) duodenal biopsies, is at risk of developing CD, as shown by their serological positivity and human leucocyte antigen (HLA) compatibility [1,8]. Biagi et al. demonstrate that whereabouts on the CD spectrum may be influenced by genetic makeup [9].

Clinical diagnosis of PCD can be complex. In 'true' PCD, when multiple biopsies are taken, an individual will demonstrate either normal or mildly enteropathic mucosa despite an adequate GCD prior to oesophago-gastro-duodenoscopy (OGD) [2]. Should a patient reduce gluten prior to endoscopy, or the clinician fail to follow biopsy guidelines (four biopsies including at least one from the duodenal bulb, while the patient is on a GCD), [2] a patient with CD may be misdiagnosed with PCD. Fig. 1 suggests a diagnostic algorithm for diagnosing PCD.

Over recent years, the prevalence of PCD has been increasing, perhaps as a result of guidelines that recommend active screening for CD in at-risk groups [10]. Current estimates indicate that PCD comprises between 10.5 and 18.3% of adult CD diagnoses [4,10–13]. Volta et al. suggest PCD patients are younger at diagnosis than their CD counterparts, thus supporting the hypothesis that PCD is a prodrome of CD [10]. Conversely, Biagi et al. reported no difference in age-at-diagnosis [12]. Thus, this matter needs elucidation.

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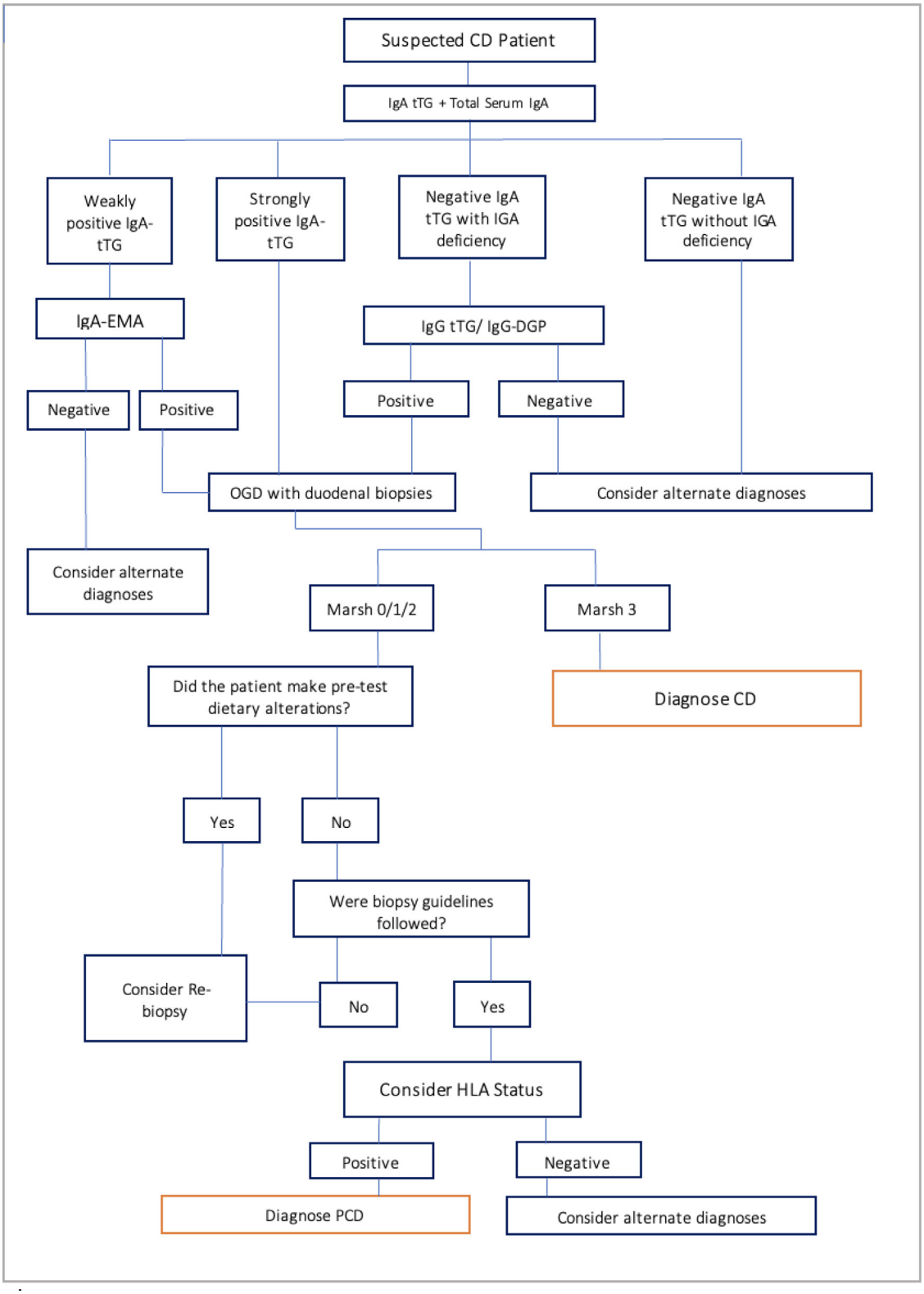

Fig. 1. Proposed algorithm for the diagnosis of 'true' potential coeliac disease (PCD) adapted from current British Society of Gastroenterology guidelines [2]
CD: Coeliac disease, TtG: Tissue transglutaminase, DGP: Deaminated gluten peptide, OGD: oesophago-gastro-duodenoscopy, HLA: Human-leucocyte antigen, PCD: Potential coeliac disease.

Two areas of contention regarding PCD remain within the literature: the nature of its presentation and the use of the gluten-free diet (GFD) in its management. Certain publications suggest that PCD patients present with milder disease than their atrophic CD counterparts [14]. Others consider this to be an oversimplification [4,15]. Recent research indicates that while extraintestinal manifestations are more common in CD than PCD at presentation, there is no difference in gastrointestinal symptoms between groups [4].

Furthermore, despite compelling evidence for the adoption of a GFD in CD with VA [2], the role of eliminating gluten in patients with PCD is unclear. As CD exists on a spectrum, we might expect continued gluten exposure to result in progression to VA and thus CD. However, this progression appears to be spontaneous and cannot be predicted in time [12]. Existing literature suggests a GFD results in symptomatic improvement, thus demonstrating an obvious use for the GFD in symptomatic PCD [10,12,16]. However, adopting a GFD becomes complex when considering asymptomatic PCD. Furthermore, defining asymptomatic can be difficult; patients who present with haematinic deficiencies may perceive themselves as 'asymptomatic' because they assume that coeliac enteropathy requires gastrointestinal symptoms.

This study's aims can be considered in two parts. Primarily, it aimed to compare the presentation of PCD with that of an age-at-diagnosis and sex-matched CD cohort. Secondly, it aimed to observe the follow-up period of the largest PCD cohort to date, placing particular emphasis on the clinical outcomes associated with patients' dietary choice post-diagnosis.

2. Methods

2.1. Identification of the study population

A tertiary centre retrospective cohort study of adult patients diagnosed with or referred for follow-up regarding PCD at Sheffield Teaching Hospitals (STH) NHS Foundation Trust (Sheffield, UK) was conducted. From 1998 to 2021, 2775 adult patients with CD were seen at STH. These patients have been prospectively added to a computerised system, the ArQ Coeliac Database. This population allowed subsequent identification and analysis of both a PCD subpopulation and an age-at-diagnosis and sex-matched CD control group. PCD was defined as serological positivity for IgA-EMA and/or IgA-tTG-2 autoantibodies and normal (Marsh 0) or mildly enteropathic (Marsh 1) duodenal biopsies taken while the patient was on a GCD. Patients with Marsh 2 lesions do not meet the literature definition of PCD and have been excluded for this research. However, clinically, they may be treated as such. Given its specificity, [17] if a patient was IgA-EMA negative, they were only included if they had positive IgA-tTG-2 combined with positive HLA-genotyping. Throughout the study period, IgA-tTG-2 testing was carried out using AEKULISA, EUROSPITAL and Thermo Fisher EliA assays. IgA-EMA antibodies were identified by immunofluorescence techniques using monkey oesophagus substrate. Duodenal biopsies were taken via OGD using a PENTAX or Olympus gastroscope. Samples were fixed in formalin, embedded in paraffin wax, and stained using haematoxylin and eosin before being graded using the Marsh-Oberhuber classification system. This research was approved by the Yorkshire and the Humber-Sheffield Research Ethics Committee (REC reference:14/YH/1216).

2.2. A comparison of presentation

In part one, the presentation of a PCD cohort was compared with an age-at-diagnosis (+/−1 year) and sex-matched CD cohort. This included comparing presenting features, CD-relevant medical history, coeliac serology, HLA-DQ genotyping and bone mineral density (BMD). Presenting features were defined as both gastrointestinal and extraintestinal coeliac-associated symptoms or abnormalities documented on a referral/initial clinic letter or established as part of the initial assessment. Asymptomatic refers to a patient's description of their own health after direct questioning. CD-relevant medical history was defined as the presence of an existing autoimmune disease at diagnosis or knowledge of a first-degree relative with CD. Given that multiple IgA-tTG-2 assays were used over the study period, an IgA-tTG-2 titre ratio was established by dividing the titre by the upper limit of normal for the assay used. LIFECODES (Immucor, USA) polymerase chain reaction sequence-specific oligonucleotides were utilised in the assessment of the HLA-DQ genotype. DEXA scanning was used to establish BMD.

Categorical variables were predominantly assessed for significance using the Pearson Chi-squared test of association. In a minority of cases, where the expected cell count was <5, the Fisher's Exact Test of significance was used. Continuous variables were compared using the Independent Samples T-test. The Mann-Whitney U test was used in a minority of cases, where the assumptions of the Independent Samples T-test were not met. A p-value of ≤ 0.05 was considered statistically significant.

2.3. An observation of follow-up

In part two, the follow-up period of the PCD cohort was retrospectively observed by use of the follow-up clinic letters. Upon diagnosis of PCD at STH, patients make an informed decision surrounding treatment. Patients either opt to eliminate dietary gluten by means of a GFD, or they choose to continue their consumption of gluten, either to a lesser extent than prior to diagnosis (a partial GFD) or as normal (GCD). Patients self-report the dietary changes they have made at clinics post-diagnosis. Analysis of the clinic letters allowed for categorisation of the patients into one of three groups: GCD, partial GFD or GFD. Thematic analysis of the data was carried out as per the methodology recommended by Braun and Clarke (2006); clinic letters for each patient were initially reviewed and summarised in aid of familiarisation with the data set, general codes and subsequent themes were generated from the data and reviewed to ensure accuracy. Time to progression was defined as the duration between initial diagnosis and the date VA was demonstrated via biopsy.

3. Results

3.1. A comparison of presentation

In total, 84 patients fulfilled the diagnostic criteria for PCD (63% female, median age 36.5 years, IQR 27) and were matched to 84 CD patients. The majority (91.7%) were symptomatic at presentation, and this proportion did not significantly differ from the matched CD cohort (94.0%, $p = 0.55$). There was no statistically significant difference between the number of patients in the PCD and CD groups with knowledge of a first-degree relative with CD (11.9% versus 15.5% respectively, $p = 0.50$). However, there was a statistically significant difference in the prevalence of pre-existing autoimmune disease between the PCD and CD groups (29.8% versus 15.5% respectively, $p = 0.027$).

3.1.1. Gastrointestinal presentation

In total, 79.8% and 76.2% of the PCD and CD cohorts respectively reported ≥ 1 gastrointestinal symptom at presentation ($p = 0.58$). Abdominal pain, bloating, and diarrhoea were the most common manifestations in both groups (Table 1). Bloating appeared to be significantly more common in those with PCD at presentation (38.1% versus 21.4%, $p = 0.02$), whereas nausea was more common in those with CD (0.0 versus 9.5%, $p = 0.007$).

Table 1
Comparison of gastrointestinal presentation in potential coeliac disease and coeliac disease cohorts.

	PCD, $n = 84$ n (%)	CD, $n = 84$ n (%)	Significance, p
≥1 form of gastrointestinal presentation	67 (79.8)	64 (76.2)	0.576
Abdominal pain	34 (40.5)	34 (40.5)	1.00
Bloating	32 (38.1)	18 (21.4)	**0.018**
Diarrhoea	27 (32.1)	22 (26.2)	0.396
Weight loss	11 (13.1)	14 (16.7)	0.515
Dyspepsia	9 (10.7)	9 (10.7)	1.00
Constipation	6 (7.1)	3 (3.6)	0.304
Urgency†	5 (6.0)	2 (2.4)	0.443
Flatulence†	3 (3.6)	2 (2.4)	1.00
Steatorrhoea†	1 (1.2)	1 (1.2)	1.00
Vomiting†	1 (1.2)	2 (2.4)	1.00
Nausea†	0 (0)	8 (9.5)	**0.007**

PCD: Potential coeliac disease CD: Coeliac disease, NS: Not significant, †: Fisher's Exact test (2-sided) used.

Table 2
Comparison of extraintestinal presentation in potential coeliac disease and coeliac disease cohorts.

	PCD, $n = 84$ n (%)	CD, $n = 84$ n (%)	Significance, p
≥ 1 form of extraintestinal presentation	55 (65.5)	67 (79.8)	**0.038**
Fatigue	30 (35.7)	30 (35.7)	1.00
Iron deficiency	18 (21.4)	35 (41.7)	**0.005**
Vitamin D deficiency	12 (14.3)	23 (27.4)	**0.037**
Osteopenia	9 (23.1)	16 (28.6)	0.550
Folate deficiency	6 (7.1)	24 (28.6)	**<0.001**
Arthralgia†	6 (7.1)	3 (3.6)	0.496
Neurological	5 (6.0)	5 (6.0)	1.00
B12 deficiency	4 (4.8)	11 (13.1)	0.058
Osteoporosis†	2 (5.1)	7 (12.5)	0.300

PCD: Potential coeliac disease, CD: Coeliac disease, NS: Not significant, †Fisher's Exact test (2-sided) used.

3.1.2. Extraintestinal presentation

Presentation with ≥1 extraintestinal manifestation of CD was significantly more common in those who presented with VA than those with PCD (79.8% versus 65.5% respectively, $p = 0.038$). Specifically, iron (41.7% versus 21.4% respectively, $p = 0.005$) vitamin-D (27.4% versus 14.3% respectively, $p = 0.037$) and folate deficiencies (28.6% versus 7.1% respectively, $p=<0.001$) were significantly more common in those with atrophic mucosa (Table 2).

3.1.3. Serology

There was no difference between IgA-EMA positivity at presentation between groups (PCD 86.7% versus CD 95.2%, $p = 0.55$). There was also no significant difference between the proportion of both groups who were serologically positive for IgA-tTG-2 at presentation (PCD 93.8% versus CD 93.4%, $p = 1.0$); however, patients with atrophic mucosa demonstrated significantly higher IgA-tTG-2 titres than those with PCD (8.4 versus 3.9 median titre ratio, $p = 0.008$).

3.1.4. Genotyping

HLA-DQ genotype data was available for 60 and 76 of the 84 patients in each of the CD and PCD cohorts, respectively. The majority of both the CD and PCD cohorts showed HLA DQ2 heterozygosity (61.7% and 63.2%, respectively, $p = 0.86$). Comparison of genotyping did not reach statistical significance.

3.1.5. Bone mineral density

T-score data were available for 56 and 38 of the 84 patients in the CD and PCD cohorts, respectively, as shown in Table 3. Mean hip T-score was significantly lower in the CD group compared to the PCD group (−0.445 versus −0.005 respectively, $p = 0.033$). Comparison of spine BMD did not reach statistical significance.

3.2. An observation of follow-up

The median follow-up time was 20.5 months (IQR 37). During follow-up, 30 patients underwent repeat OGD. Generally, this was either to confirm a PCD diagnosis or for persisting symptoms.

3.2.1. Initial dietary choice

Most patients (67.5%) opted to eliminate dietary exposure to gluten by means of a GFD. The remaining individuals chose to remain exposed to gluten. This was either to a lesser extent than pre-diagnosis, described as a partial GFD (7.5%) or to the same extent as pre-diagnosis, described as a GCD (25.0%) (Fig. 2). The most common reason for continuing gluten was lack of (or minimal) symptoms, followed by the perception that the GFD would be too restrictive.

3.2.2. Outcomes associated with the gluten-free diet

Of the 54 patients who chose to exclude gluten from their diet, follow-up data was available for 41 patients. Clinical improvement was noted in 70.7% (29/41) of these patients. Despite improvement, two patients chose to reintroduce gluten and undergo repeat OGD, both progressed to VA. Ongoing clinical features of CD were noted in 29.3% (12/41) patients. During the investigation for persisting symptoms, a non-CD cause of the symptoms (including IBD, pancreatic insufficiency and IBS) was identified in 50.0% (6/12) of these individuals. Superimposing the low-FODMAP diet onto the GFD entirely resolved symptoms in patients whose

Table 3
Comparison of bone mineral density in potential coeliac disease and coeliac disease cohorts.

	CD mean (SD)	PCD mean (SD)	Mean difference (CI)	Significance, *p*
Hip T-score	−0.445 (1.15)	−0.005 (0.81)	−0.44 (−0.84 - −0.004)	**0.033**
Spine T-score	−0.55 (1.42)	−0.15 (1.23)	−0.40 (−0.97 – 0.17)	0.17

PCD: Potential coeliac disease, CD: Coeliac disease, NS: Not significant.

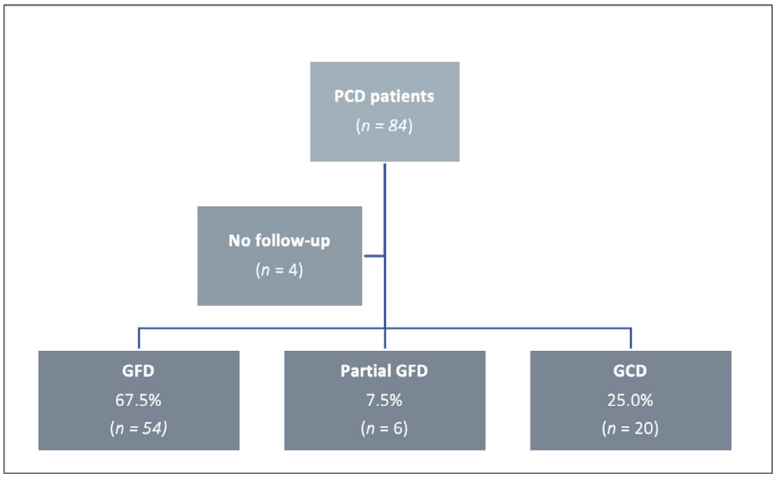

Fig. 2. Initial dietary choices after diagnosis with potential coeliac disease
PCD: Potential coeliac disease, GFD: Gluten-free diet, GCD: Gluten-containing diet.

symptoms were thought to be caused by IBS ($n = 2$). Four of the remaining six patients underwent investigations for persisting symptoms, but no definite cause was identified. The remaining two patients were awaiting investigation at the time of the study.

3.2.3. Outcomes associated with a partially gluten-free diet

Of the six patients who adopted a partially GFD post-diagnosis, 33.3% (2/6) patients had clinical improvement. Of these two patients, one presented with only haematinic deficiency and improved on the diet with ongoing supplementation. The remaining four patients (75.0%) continued with ongoing clinical features of CD. Subsequently, one of the four opted to adopt a GFD before the end of their follow-up period, while three remained on a partial GFD.

3.2.4. Outcomes associated with a gluten-containing diet

Of the 20 patients who continued a GCD, follow-up data was unavailable for $n = 3$. Of the remaining 17 patients, 2/17 (11.8%) had clinical improvement despite continued exposure to gluten. These patients presented asymptomatically with only haematinic deficiency and improved on dietary supplementation alone. To counter this observation, some patients failed to demonstrate improvement on supplementation alone. In fact, one patient who originally presented with asymptomatic IDA progressed to show VA during follow-up. The vast majority, 88.2% (15/17), of patients who had continued exposure to gluten experienced ongoing clinical features of CD. One-third of these patients (5/15) remained on a GCD despite ongoing symptoms, one-third (5/15) opted to go on a GFD during follow-up because of ongoing symptoms, and the final one-third (5/15) demonstrated VA during the follow-up period. The mean time to progression in those who developed VA during the study period was 23.4 months (range <1–72 months). Fig. 3 displays these observations.

4. Discussion

Part one of this study highlighted the significant symptomatic burden of PCD; equal proportions of both groups were symptomatic at presentation, and, for the most part, there was no difference either in the nature or frequency of gastrointestinal symptoms between groups. These findings broadly corroborate the limited existing literature which has compared the gastrointestinal presentation of mild and severe coeliac enteropathy [4]. Comparison of these cohorts did however demonstrate two ways in which the nature of gastrointestinal symptoms significantly differed between groups; bloating appeared to be more common in PCD at presentation while nausea was more common in CD. These findings have not been previously demonstrated, and thus, more research is required to confirm such trends.

One clear distinction between groups became apparent when comparing extraintestinal presentation; extraintestinal manifestations, specifically iron, folate and vitamin-D deficiencies, were significantly more common in those with atrophic mucosa at presentation. Existing literature corroborates these findings; using a large sample size, Zanini et al. demonstrated that patients with VA had a significantly higher incidence of ferritin and folate deficiency compared to patients with mild enteropathy (51% versus 39% and 75 versus 64%, respectively) [4]. Lewis et al. also reported comparable trends [18]. In contrast to both of these studies however, the present research established that those with VA were also significantly more likely to be deficient in vitamin-D at presentation. While the exact underlying mechanism of extraintestinal manifestations of CD is unknown, theoretically, we can attribute such manifestations to compromised bowel mucosa and migration of the immune response to extraintestinal tissue. Thus, it is plausible to assume that those with VA would more commonly present with extraintestinal manifestations, including vitamin-D deficiency, subsequent to inflammation of increased severity and

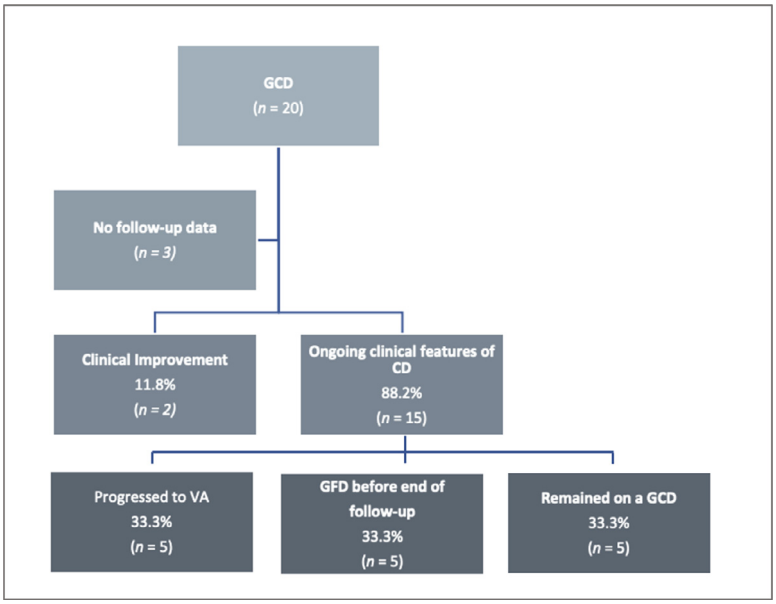

Fig. 3. Outcomes associated with maintaining a gluten-containing diet post-diagnosis
GCD: Gluten-containing diet, CD: Coeliac disease, VA: Villous atrophy, GFD: Gluten-free diet, GCD: Gluten-containing diet.

duration. Nonetheless, further research is required to confirm these findings.

While this study has demonstrated that extraintestinal manifestations are more likely to be present in those with atrophic mucosa, it should not be overlooked that such manifestations can nonetheless be common in those with PCD. For example, 21.4% of the PCD cohort were iron deficient at presentation. Clinically, all individuals on the CD spectrum should have the same baseline investigations.

This paper also demonstrated a statistical difference between the hip BMD of patients with PCD and CD, however, no statistically significant difference was found in spine BMD between groups. Kurppa et al. found no difference between the BMD of patients with CD versus mild enteropathy [15]. On the contrary, Zanini et al. reported that patients with atrophic mucosa have a significantly lower BMD than those with mild enteropathy [4]. This matter needs clarification in future work.

The serological profile of PCD appears to differ from CD; those with PCD appear to yield lower IgA-TtG-2 titres compared to their atrophic CD counterparts. The notion that higher IgA-tTG-2 titres are predictive of VA is well described within both paediatric [19–21] and adult [15,18,22] literature. From a clinical perspective, these findings suggest that positive but low titres of IGA-tTG-2 may alert a clinician to individuals who are more likely to show mild enteropathy on duodenal biopsies. In such patients, the importance of establishing gluten intake around the time of OGD is paramount in providing an appropriate diagnosis; in 'true' PCD, the individual will be adequately exposed to gluten and should not be mistaken for those who have partially healed their atrophic enteropathy by reduction of dietary gluten.

This study has provided follow-up data on the largest cohort of PCD patients to date. For most patients (70.7%), adoption of a GFD was associated with clinical improvement. A randomised clinical study of 23 patients conducted over one year reported that 100% of those who eliminated dietary gluten showed clinical improvement [16]. A more extensive prospective study similarly corroborated such trends [10]. Despite this, the present research has further highlighted a proportion of individuals who did not gain complete symptomatic improvement from a GFD. Interestingly, additional investigation of these individuals revealed that 50% had a non-CD cause of their symptoms, including IBD, lymphocytic colitis and IBS. The clinical use of this finding is clear: if the GFD doesn't work, consider an alternate underlying diagnosis.

Elli et al. demonstrate that some individuals with CD can withstand occasional gluten ingestion without subsequent symptoms or mucosal damage [23]. This implies that gluten ingestion in CD may not be a binary decision and the future of treatment may be a personalised diet. This study was the first to analyse the outcomes associated with PCD patients who reported reducing but not eliminating gluten. It has broadly demonstrated that self-reported reduction is not adequate for controlling PCD's clinical manifestations. However, this conclusion is limited by the inability to retrospectively quantify the exact amount of gluten and the sample size of six patients.

Like those who remained partially exposed to gluten, the majority of patients (88.2%) who maintained their normal diet after diagnosis continued to experience clinical features of CD. A randomised clinical study corroborated this trend, reporting that symptoms were largely unaltered in those who remained exposed to gluten one-year post-diagnosis [16]. The patients in the present study who continued to experience clinical features of CD can be described using a rule of thirds; one-third opted to go gluten-free, one-third progressed to show VA, and one-third chose to remain exposed to gluten despite ongoing issues. A similar proportional trend was noted by Biagi et al. in 2013 [12]. This said, a small amount of evidence within the literature suggests a minority of PCD patients may improve clinically despite ongoing gluten exposure. Kondala et al. reported spontaneous improvement in 3/24 PCD patients who continued to consume a GCD [24]. The present research has added to this small body of evidence by describing three individuals who rectified their haematinic deficiency on supplementation alone despite continued exposure to gluten. However, 100% of patients who progressed during the study consumed gluten prior to endoscopy. Put simply, everyone who progressed to VA continued to consume gluten, but not everyone who continued to consume gluten progressed to VA. This raises an interesting debate about the need for a GFD in PCD; while there is clear use for the GFD in symptomatic PCD, in situations where a patient has minimal or a lack of symptoms, is the adoption of an onerous GFD

necessary with regular follow-up? Volta et al. took this position, suggesting that asymptomatic PCD patients need not adopt a GFD [10]. Conversely, others have opposed this view suggesting all patients with PCD should adopt a GFD [13,16]. Given the findings of this research, it seems most appropriate to explain uncertainty to patients with asymptomatic PCD and support those who choose to remain exposed to gluten with regular follow-up.

The observational element of this research has an obvious disadvantage; its inability to attribute causation to findings. Furthermore, GFD adherence was assessed using patient self-report. While this was in discussion with a coeliac-specialist gastroenterologist, it is vulnerable to bias. We should also acknowledge that a diagnosis of PCD was given in the absence of an HLA-DQ genotype for a minority of patients. This study design permitted ethical investigation and follow-up of the largest cohort of PCD patients to date. Furthermore, it allowed for greater proximity to real-life, increasing external validity. This said, its retrospectivity means the follow-up period was not constant between patients. A mixed design with retrospective selection followed by prospective follow-up may be superior in future.

5. Conclusion

Though it may be tempting to conclude that PCD is CD's lesser counterpart, this study provides evidence which demonstrates that, in many ways, PCD is not significantly different to CD. Mild enteropathy does not necessarily equate to mild symptoms, and although extraintestinal manifestations may be more common when VA is present, every individual on the CD spectrum should be investigated for all manifestations of the disease. Post-diagnosis with PCD, adoption of a GFD appears to result in clinical improvement, while continued exposure is associated with ongoing clinical features of CD and increased risk of progression to VA. However, time to progression is unpredictable and the adoption of a GFD may be challenging. Therefore, asymptomatic PCD patients may choose to continue a GCD. In such patients, regular follow-up is paramount.

Conflict of interest

David S Sanders receives an educational grant from Schaer (a gluten-free food manufacturer). The other authors disclose no conflicts of interest.

Contributors

MN, WJH, AR, SAR and DSS developed the study. MN and WJH identified the participants and collected the data. MN and EAG analysed the data and wrote the manuscript. All authors reviewed and approved the final manuscript.

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