Coeliac disease

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Introduction: Coeliac disease is a common but often under diagnosed condition with important complications. It is due to immune-mediated gluten intolerance and may present in a number of ways. It has become more frequently diagnosed due to the recognition of the atypical presentations. In recent years, more sensitive and specific serological markers have been developed but the gold standard of diagnosis remains duodenal biopsy. Compliance with a strict, lifelong gluten-free diet is the cornerstone of management, improving symptoms and reducing complications of the disease.

Sources of data: For this review, we focused on papers published on coeliac disease in recent years. Particular emphasis was given to clinical papers examining new methods for the diagnosis of coeliac disease or newer therapies for managing complications. The main source was PubMed and the major gastroenterology journals.

Areas of agreement: Coeliac disease is more common than once thought with a prevalence of around 1%. Diagnosis should always be confirmed with a duodenal biopsy. Management of coeliac disease with a gluten-free diet remains the cornerstone of treatment.

Areas of controversy: Some complications of coeliac disease, especially neurological, are not widely accepted despite growing support from the literature. Management of enteropathy-associated lymphoma has been difficult, and the optimal therapy is not known.

Growing points: Current understanding is such that coeliac disease is the most widely understood autoimmune condition. 'Atypical' presentations are becoming the most common presenting features of coeliac disease.

Areas timely for developing research: Alternatives to the gluten-free diet are about to go into clinical studies. Similarly, better serological screening tests may obviate the need for duodenal biopsy.

This review will try to summarize the current understanding of coeliac disease with regard to diagnosis, management, complications and future perspectives.

Keywords: coeliac disease/associations/complications

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Introduction

Coeliac disease is defined as a state of heightened immunological responsiveness to ingested gluten in genetically susceptible individuals.[1] Historically, it has been considered as an uncommon condition but recent studies have shown that coeliac disease affects around 1% of society.[2–5] Despite such a high prevalence, the average delay in diagnosis is reported to be 13 years (Coeliac UK). The estimated ratio of diagnosed to undiagnosed individuals is 1:8.[6] There may be many reasons why coeliac disease remains unidentified in the majority, and this review will attempt to examine this important issue as well as providing an overview of current diagnosis and management.

Why does coeliac disease appear to be more common?

Historically, coeliac disease was felt to be uncommon with a population prevalence of around 1:8000 and patients would present with obvious gastrointestinal symptoms such as steatorrhoea, diarrhoea, weight loss and anaemia.[7] The reason for an increased number of cases detected maybe due to improvements in serological markers and increased clinical suspicion. However, a recent Finnish report has observed an increasing prevalence in coeliac disease over a 20-year period. This novel suggestion requires further confirmation.[8]

Several autoantibodies have been used to initially identify coeliac disease. Historically, both anti-reticulin antibodies and the anti-gliadin antibodies (AGA) were found to be of limited value (with low sensitivity and specificity). Gliadins, in particular, were reported to have a high false-positive rate in patients with other causes of mucosal damage in the gastrointestinal tract.[1] Many centres have now stopped using AGA but there may still be value in patients with immunoglobulin A deficiency (if using IgG AGA) or for neurological manifestations of coeliac disease.[9] However, recent reports of deamidated AGA have suggested a much improved accuracy.[10]

Endomysial antibodies (EMA) and anti-tissue transglutaminase antibodies (tTG) have been found to be superior to AGA and when used in combination have sensitivity and specificity greater than 95% (Table 1 shows detection characteristics for AGA, EMA and tTG).[1,11]

Recognition of the coeliac iceberg has also contributed to increased detection of cases of coeliac disease (Fig. 1).[12] This concept demonstrates the clinical variability of coeliac disease and helps to understand its systemic nature. The highest stratum of the iceberg (above the waterline) describes patients with typical symptoms that are gastrointestinal. These patients are usually healthcare seeking and present to gastrointestinal

Table 1 Operating characteristics of serological markers to detect the coeliac disease in adults.

Serological test	Sensitivity (%)	Specificity (%)	Positive predictive value	Negative predictive value
IgG AGA	57–78	71–87	0.2–0.9	0.4–0.9
IgA AGA	55–100	71–100	0.3–1.0	0.7–1.0
IgA EMA	86–100	98–100	0.98–1.0	0.8–0.95
IgA tTG	77–100	91–100	>0.9	>0.95
IgA tTG and EMA	98–100	98–100	>0.9	>0.95

IgG, immunoglobulin G; IgA, immunoglobulin A; AGA, anti-gliadin antibodies; EMA, endomysial antibodies; tTG, tissue transglutaminase.

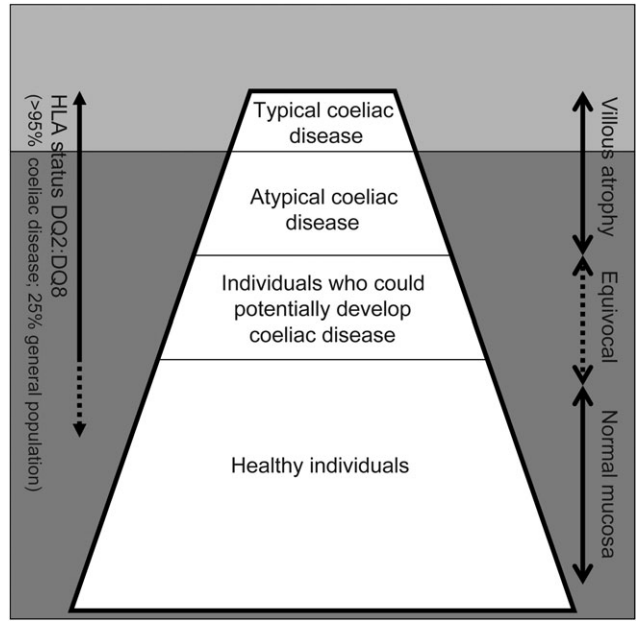

Fig. 1 The 'coeliac iceberg'
HLA, human leukocyte antigen. Reproduced with permission (*BMJ*).

services where the diagnosis may be made. The subsequent stratum (just under the water) contains those patients considered to have atypical presentations of coeliac disease (no gastrointestinal symptoms). This includes isolated iron deficiency anaemia, osteoporosis and persistently abnormal liver function tests (particularly the transaminases).[13–16] Other atypical presentations include those with ataxia and/or peripheral neuropathy,[9,17] those found via family screening and those in high-risk groups undergoing screening, e.g. paediatric type 1 diabetes mellitus.[18]

There are further levels to this iceberg. Latent coeliac disease describes two groups of patients. Those who have at some stage had a normal duodenal biopsy while on a regular diet and subsequently

develop villous atrophy (with histological changes) later in life. Or the converse of this clinical situation also exists—patients who have histological features of villous atrophy but continue on a gluten containing diet and at re-biopsy 2 years later, now have normal duodenal mucosa. The phenomenon of latent coeliac disease is rare and has only been described in case reports. In clinical terms, it is accepted that patients with coeliac disease will continue to have histological evidence of small bowel damage unless gluten is withdrawn from their diet.

The fourth stratum of the iceberg describes individuals with positive serological testing but normal histology on duodenal biopsy. This circumstance may be found in first-degree relatives of patients with coeliac disease,[5] as well as those with autoimmune diseases such as hypothyroidism,[19,20] type 1 diabetes[21,22] and Addison's disease.[23] These conditions have been found to share similar polymorphisms in the class II major histocompatibility complex on chromosome 6, notably in the DR3 and DR4 loci.[24]

A recent report of children with type 1 diabetes (who were screened for coeliac disease) was intriguing. This study demonstrated that over a period of 3 years almost 50% of the children with a positive antibody normalized their serological levels spontaneously. This may suggest that some form of immune tolerance occurs.[25]

A further contributing factor in the rising number of cases of coeliac disease is the wider use of duodenal biopsy. The gold standard for diagnosis of coeliac disease is villous atrophy on duodenal histology. With improvements in endoscopic technology, multiple samples can be taken from the upper gastrointestinal tract with minimal risk. Recent studies from our unit and others have shown that more cases of coeliac disease will be identified when routine duodenal biopsies are taken.[26] Furthermore, targeting duodenal biopsies to those patients in higher risk groups may be more cost effective.[27]

What constitutes a diagnosis of coeliac disease?

As demonstrated by the coeliac iceberg, the presence of relevant symptoms is not essential for a diagnosis of coeliac disease. In addition, positive serological testing alone is not sufficient to confirm the diagnosis as there are a number of pitfalls to this assumption. First, falsely positive gliadin antibodies occur in a variety of other conditions such as inflammatory bowel disease.[28] Similarly, EMA is a qualitative test dependent upon the degree of immunoflourescence seen and positivity has been correlated with the degree of villous atrophy. Individuals with lesser degrees of atrophy may be EMA negative.[29] tTG has been found to be falsely positive in other autoimmune disease. For these reasons, the diagnosis of coeliac disease cannot purely be based upon serological results. An additional

consideration is antibody negative disease. Coeliac disease is associated with immunoglobulin A deficiency (IgA)[30] which may render both EMA and tTG negative as these antibodies are IgA-based. IgG-based tests are available but are still under investigation. Antibody negative coeliac disease can occur in individuals with a normal serum IgA level and may account for up to 9% of all cases of coeliac disease.[31] These individuals are often older and have more severe symptoms suggesting a diminished immunological response and therefore negative serology.[31,32]

One of the commonest reasons for diagnostic uncertainty is that the individual has already commenced a gluten-free diet prior to the biopsy with subsequent histological improvement. It is essential that all individuals under the investigation for coeliac disease remain on a gluten *containing* diet until a duodenal biopsy is performed.

Furthermore, the number of biopsies taken is important as there appears to be histologically variable grades of villous atrophy within the same individual.[33] Current advice is that four or five biopsies should be taken from the second part of the duodenum (or more distally). In our recent work, the duodenal bulb frequently revealed villous atrophy (when placed in a separate specimen container and marked for the attention of the gastrointestinal pathologist). There has been interest in adjuvant techniques for improving diagnostic yield such as the use of dye spraying with magnification endoscopy[34] or confocal laser endomicroscopy,[35] however these techniques require further training and as yet have not obviated the need for biopsy. When diagnostic uncertainty exists one strategy is to repeat biopsies following a period of gluten challenge (at least four slices of bread per day for 4–6 weeks) or consider jejunal biopsies via enteroscopy.[36]

Taking this into account, all diagnoses need duodenal biopsy confirmation. In those individuals with negative serology, other causes of villous atrophy need to be considered and often a second biopsy required to exclude processing anomalies (for example, tangential sectioning of a duodenal biopsy sample). A further helpful test is HLA haplotyping. Around 95% of patients with coeliac disease carry the HLA–DQ2 allele with the rest usually being HLA–DQ8 positive.[1,24] Despite 15–20% of Caucasians carrying the HLA–DQ2 haplotype, the absence of these haplotypes virtually excludes coeliac disease.

What are the implications of a diagnosis of coeliac disease?

Anaemia

Although some patients with coeliac disease may present with ron-deficiency anaemia, the non-specific symptom of 'tiredness all the

time' is very common,[3,15] this is attributed to the presence of a low ferritin, folate or vitamin B_{12}. These nutritional deficiencies may occur in up to 50% of coeliac patients at the time of presentation. Generally, these deficiencies correct on a gluten-free diet but patients may benefit symptomatically from replacement while this becomes established.

Malignancy

Untreated coeliac disease is associated with a number of complications. The best recognized is malignancy. The overall relative risk of all types of malignancy in coeliac has probably been historically overestimated. The relative risk is likely to be less than 2-fold when compared with the general population. Although small intestinal lymphoma may have a 50-fold increased relative risk (compared with the general population), this is still a rare condition. Thus, the overall number of cases and absolute risk remains low. Improvements in small intestinal imaging modalities such as wireless capsule endoscopy may help to target high-risk individuals such as those with refractory symptoms or ulcerative jejunitis.

Other associated malignancies include oesophageal (proximal and distal), small intestinal adenocarcinoma and colonic cancer.[37,38] Intriguingly, patients with coeliac disease may have lower rates of breast and lung cancer.[37] Risk of cancer appears to reduce over time, particularly in patients who adhere strictly to the gluten-free diet. Prior studies demonstrated increased cancer incidence at all sites and found correlation with the lack of adherence to the gluten-free diet.[39] A confounding factor may be age at diagnosis of coeliac disease with older patients appearing to have a higher risk of neoplasia.[40]

Bone mineral density

Coeliac disease is known to be associated with reduced bone mineral density (both osteopaenia and osteoporosis). The prevalence of abnormal bone mineral density is reported to be around 40% and leads to an increased fracture risk.[41] This increased relative risk is small overall as bone mineral density usually improves (or remains stable) once gluten has been excluded from the diet. Additionally, the excess fracture risk is small overall even when considering elderly patients where the risk is highest and has been calculated to be two to three additional hip fractures per 10 years of follow-up.[42] Potential protective factors include a lower rate of smoking and a higher rate of hormone replacement therapy use in coeliac patients.[43]

Table 2 Prevalence of coeliac disease in associated autoimmune conditions and other groups where case-finding should be considered.

Associated conditions	Prevalence of coeliac disease (%)
Dermatitis herpetiformis	~70
Type 1 diabetic patients	2–8
Thyroid disease	2–6
Addison's disease	1–12
Alopecia areata	1–2
Primary biliary cirrhosis	2–7
Autoimmune hepatitis	3–5
Idiopathic ataxia	1–7
Subfertility	4–8
Downs' syndrome	4–17
Iron-deficiency anaemia	3–7
Irritable bowel symptomatology	0–11
Peripheral neuropathy	Up to 23

Autoimmunity

Coeliac disease is associated with a number of other conditions some of which are autoimmune in origin as shown in Table 2. In most cases, coeliac disease is identified subsequent to the original diagnosis often because symptoms may be misconstrued as due to the original diagnosis. A good example of this is persistent tiredness in patients with thyroid disease. The effect of concurrent coeliac disease on other autoimmune diseases has not been well studied as can be seen by the paucity of outcome data in patients with both coeliac disease and type 1 diabetes.[44]

There have been some studies suggesting that patients who are not compliant with the gluten-free diet are more likely to develop other autoimmune conditions. This may be related to the finding that patients with coeliac disease have a high prevalence of other organ-specific autoantibodies.[45] Additionally, following a gluten-free diet, the level of these antibodies has been found to fall.[46] However, this is a controversial perspective with other studies suggesting that the development of further autoimmune conditions is independent of gluten exposure and may be related to specific HLA haplotypes.[47]

Reproductive problems

Infertility, reduced fertility and an increased risk of an adverse outcome during pregnancy (miscarriage, low birth weight and intrauterine growth retardation) have all been attributed to undiagnosed coeliac disease. However, these risks may be less than historically described.[48,49]

Sepsis

Functional hyposplenism may occur in up to 30% of patients with coeliac disease—for this reason, vaccination with pneumovax and haemophilus influenza type b vaccines are advised. A recent population database study has described a hazards ratio of 2.6 for sepsis and 3.9 for pneumococcal sepsis.[50]

Neurological manifestations

An unusual but more frequently recognized presentation of coeliac disease is with neurological symptoms. Studies in this area have historically described ataxia and peripheral neuropathy as presenting features for atypical coeliac disease[51–53]

However, more recently two groups have also demonstrated subclinical neuropathy being present in patients who were diagnosed with coeliac disease (and did not present with neurological symptoms).[17]

Work done in Sheffield has also described the phenomenon of neurological gluten sensitivity—these patients may have positive serology but either minimal or no changes on duodenal biopsy.[51] Treatment with a gluten-free diet can arrest or improve neurological symptoms.[52]

The underlying pathophysiology is not fully determined but changes in the humoral response have been described.[52] In addition, excess tissue transglutaminase type 2 deposits have been found in duodenal samples in such patients (even when structurally normal at conventional histology).[9] tTG is ubiquitous and therefore tTG antibodies may themselves be pathogenic in some patients.[54]

Management and follow-up

Coeliac disease is treated by lifelong adherence to a gluten-free diet. In the vast majority, this leads to resolution of symptoms and a reduction in long-term risks of the complications noted in the previous section. A gluten-free diet, however, is no light undertaking, and national guidelines recommend the involvement of a dietitian to provide education about the gluten-free diet and prevent dietary imbalance.[36] Further help can be obtained from Coeliac UK, particularly the local patient groups who can provide support and information about gluten-free living. Advice about local stores and restaurants with decent gluten-free menus can also be obtained from such groups. This is of importance as eating out has been shown to be difficult for patients with coeliac disease and contributes to social isolation.[55]

Patients with coeliac disease should also be followed up on an annual basis to allow assessment of compliance with the diet, manage complications and detect any micronutrient deficiencies.[36] A single study has suggested that compliance may be improved by follow-up in a specialist clinic.[56] There has been recent interest in dietitian-led follow-up, particularly with the increase in number of cases detected. However, dietitian-led clinics should have support from local gastrointestinal physicians if further investigations or interventions are required.[57]

Management of metabolic bone disease, either osteopaenia or osteoporosis, is also of importance in coeliac disease. In our unit, patients are assessed for risk at diagnosis and referred to the local metabolic bone clinic for DEXA scanning. Often, calcium and vitamin D supplementation along with the gluten-free diet is all that is required; however, some patients will be found to have significant osteoporosis and may require other therapies such as bisphosphonates.

In general, when considering quality of life, the initial improvement on a gluten-free diet (after 1 year) may not be sustained at the same level in the long term. Although patients with coeliac disease may have a reduced quality of life compared with controls, this is still an improvement from their undiagnosed state. This benefit is particularly noticeable in patients who have presented with typical symptoms.[58,59]

Oats

The issue of adding oats to the gluten-free diet has been controversial in the past but recent studies have found it to be safe.[60] Theoretically, patients with coeliac disease should tolerate oats; however, care is required as oats have traditionally been contaminated with wheat flour during the milling process.[36] Additionally, there is evidence that some patients with coeliac disease are sensitive to oats leading to recurrent symptoms.[61] In our practice, we reintroduce oats once patient's symptoms have resolved and their antibodies have become negative. Therefore, if symptoms recur, the most likely cause is intolerance of oats.

Recurrent symptoms

Some patients will not improve on the gluten-free diet or will relapse. The most common reason for recurrent symptoms is continued gluten exposure and may be from what appear to be trivial sources. Referral back to the dietitians in this circumstance is helpful in identifying the source of gluten exposure. Other causes for recurrent symptoms

include development of associated gastrointestinal conditions such as exocrine pancreatic insufficiency, ulcerative jejunitis/ileitis, lymphoma and refractory coeliac disease.

The association between coeliac disease and irritable bowel syndrome has been debated but coeliac disease can present with functional symptoms.[13] Patients with coeliac disease may also experience symptoms consistent with irritable bowel syndrome while taking a gluten-free diet.

Exocrine pancreatic insufficiency has been shown to be associated with coeliac disease. A recent study showed that up to a third of patients with recurrent symptoms may have reduced exocrine pancreatic function and that enzyme supplementation was beneficial in the majority.[62]

Colonic inflammation has been described in coeliac disease and is well recognized to cause recurrent or continued symptoms in those on a gluten-free diet. Microscopic colitis (divided into lymphocytic colitis and collagenous colitis) has been reported to be 10 times more common in patients with coeliac disease than the general population.[28] Patients do not always present with bloody diarrhoea and may have diarrhoea alone. Colonoscopy and a full series of biopsies are required to confirm the diagnosis as these conditions can be patchy in nature.

In our unit, patients with recurrent symptoms have repeat antibodies checked to assess compliance and if positive are referred back to the dietitian. Antibody negative patients undergo repeat gastroscopy with duodenal biopsy, colonoscopy with colonic biopsies and assessment of pancreatic function using faecal elastase-1. If negative and symptoms persist then further investigations such as glucose hydrogen breath testing or small intestinal wireless capsule endoscopy may be performed.

Future developments

Recent research has focused on better detection of coeliac disease using near patient testing kits similar to capillary glucose devices. These kits require a small amount of blood following a finger prick and assess for tTG positivity. One concern about such kits being widely available is that individuals may have a false-positive result and impose a gluten-free diet upon themselves without histological verification, involvement of a dietitian or assessment of bone mineral density.[63]

Most complications of coeliac disease are improved by strict adherence to the gluten-free diet. Enteropathy-associated T-cell lymphoma, however, once established has a uniformly poor outcome. Steroids, azathioprine and other chemotherapeutic agents have had

disappointing results. A recent case series using cladribine (a purine analogue) has shown potential benefit, however, randomized trials are required.[64]

Despite improvements in the quality of gluten-free foods, some patients still find elements of the diet difficult. There has therefore been interest in dietary supplements (peptidases) that digest gluten in the food prior to entry into the small intestine, however, clinical trials in this area are awaited.

Conclusion

Coeliac disease is a common condition affecting around 1% of society. The presentations are protean and patients are increasingly diagnosed later in life. Having a high index of suspicion and an aggressive case-finding strategy appear to have the most cost-effective detection rates. Complications of coeliac disease are generally ameliorated by adherence to the gluten-free diet. More work in this area is required to determine whether non-diet-based therapies are safe and effective in coeliac disease.

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