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Conference on 'Malnutrition matters'
Symposium 1: Living with coeliac disease

Are we diagnosing too many people with coeliac disease?

Imran Aziz* and David S. Sanders

Department of Gastroenterology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

This review will try to address the question of whether we are diagnosing too many people with coeliac disease. The key reasons for diagnosing coeliac disease may be that it is a common condition affecting up to 1% of the adult population. Delays in diagnosis are common. The average time delay reported by Coeliac UK (National Medical Patient Charity), for patients with symptoms prior to the diagnosis being made is 13 years. For every adult case detected, it is estimated that there are eight cases not detected. Patients with coeliac disease have an associated morbidity and mortality. In addition, quality of life studies suggest that the majority of patients benefit from a gluten-free diet (GFD). Furthermore, the GFD reduces or alleviates the risk of the associated complications. All of these facts could even be used to support the argument for screening! However, conversely the tests for coeliac disease are not 100% sensitive and specific. In addition, we do not know whether patients with milder symptoms will derive less benefit from treatment and are at less risk of complications. Furthermore, evidence presented in this review suggests that actual outcomes for screening studies in an adult population have revealed poor uptake and subsequently difficulties with adherence. What little published data that are available also infers that individuals recognised through screening programmes could have been detected if carefully questioned for symptoms. There is evidence to suggest that diagnosing celiac disease is cost-effective and that the diagnostic costs are offset by reduced medical expenditures, reduced hospital and general practice attendances, but this view depends on the population prevalence of coeliac disease. We believe on the basis of the evidence presented in this review that we are not diagnosing too many adults with coeliac disease. However, the authors consider case-finding with a low threshold for serological testing to be the optimal approach. If you look for coeliac disease you will find it.

Coeliac disease: Coeliac testing: Coeliac serology: Screening: Case finding

Historically, coeliac disease was felt to be a rare condition diagnosed in children presenting with typical gastrointestinal symptoms of malabsorption. However, our understanding of coeliac disease has rapidly evolved over the decades to a point where we now recognise that the condition more commonly present in adults and that patients' can present with a wide variety of symptoms. There is now a debate of whether too many adults are being diagnosed and this review will discuss the implications of diagnosing coeliac disease and whether adopting a low threshold for case-finding is of benefit.

What is the prevalence of coeliac disease?

The prevalence of adult coeliac disease in Europe is approximately 1%[1]. As such it certainly meets one of the screening criteria of being a common disease. There has been an increase in recognition of coeliac disease, which is attributed to several factors; novel serological assays, advances in endoscopy allowing ease of duodenal biopsy, the realisation that patients often do not have gastrointestinal symptoms and a possible real increase in the prevalence of coeliac disease over time[2,3]. Despite these

Abbreviations: EMA, endomysial antibody; GFD, gluten-free diet; HR, hazard ratio; tTG, tissue transglutaminase.

***Corresponding author:** Dr Imran Aziz, fax +44 114 2712692, email imran.aziz@sth.nhs.uk

Table 1. Sensitivity and specificity of coeliac serologies

Test	Sensitivity range (%)	Specificity range (%)
IgA EMA	68–100	89–100
IgA tTG	38–100	25–100
IgA DGP	79–98	80–95
POCT	80–98	91–100

DGP, deamidated gliadin peptides; EMA, endomysial antibody; POCT, point of care testing; tTG, tissue transglutaminase.

improvements for every adult patient currently diagnosed, it is estimated that there are eight cases undetected[4]. Furthermore, adult presentations are now much more frequent than paediatric (9:1 Coeliac UK National Patient Charity, membership data 2005). At face value, these factors could all be used to support the view that we are not diagnosing enough individuals with coeliac disease; however, the issue is more complex and requires further discussion.

How do we make the diagnosis of coeliac disease?

Histological demonstration of small bowel villous atrophy remains the gold standard method for making a diagnosis of coeliac disease. However, there are a number of serological tests that have been reported to be accurate in identifying patients who should then be referred for a duodenal biopsy. Endomysial antibody (EMA) testing was introduced in the 1980s[5]. It is highly accurate with sensitivity and a specificity of 95% or more in patients with overt villous atrophy[6–10]. However, it is subjective, labour intensive and the substrates (monkey oesophagus and umbilicus) are limited[11]. In 1997, tissue transglutaminase (tTG) was identified as the antigen recognized by the EMA. Tests for detecting antibodies to this were devised using human recombinant or guinea pig tTG[12]. The advantage of these assays is that they are generally cheaper than EMA and more reliable[7,13]. One weakness of the tTG test is that the accuracy of the assay varies between manufacturers[14]. The best assays have a higher sensitivity than EMA and a comparable specificity, both about 98%[13–18]. The cohort studies that comprise the majority of the evidence for the performance of each test are of high quality, but too heterogenous to provide pooled data[7]. Instead ranges for sensitivity and specificity are given (see Table 1)[9,13–17,19–31].

Although EMA and tTG appear to be sensitive and specific, these observations are based on carefully selected high coeliac disease prevalence populations. In lower population prevalence (for example 1%) the positive predictive value of the test falls. In a low population prevalence as seen in screening, the specificity of the test has to be near perfect for the positive predictive value to remain above 90%[13].

Our group performed serological testing and concurrent duodenal biopsies on 2000 consecutive adults attending for gastroscopy[32]. We identified seventy-seven new cases of coeliac disease (seven were antibody negative). In this referral population, tTG had sensitivity and specificity of 91%, a negative predictive value of 99% but a positive predictive value of just 28%. EMA had a positive predictive value of 71% and a negative predictive value of 99%. This study highlights the poorer performance of the tests in this heterogenous group which, perhaps, more accurately reflects typical clinical practice.

The sensitivity of the serological tests also falls when histological grades less than Marsh grade 3 (villous atrophy on duodenal biopsy) are considered. In these circumstances, the sensitivity falls well below 90%[16,33,34]. This is a clinical problem that is difficult to evaluate as most studies have excluded patients without villous atrophy[11]. Nevertheless, although imperfect these tests are substantially better than the majority of serological tests used in clinical practice. However, the diagnosis must be verified by the presence of villous atrophy on a duodenal biopsy.

What are the complications of coeliac disease?

One reason to support the view that we are diagnosing too many cases of coeliac disease is that the complications of the disease are not significant enough to warrant early detection. This issue warrants further discussion. Coeliac disease is associated with complications such as infertility, reduced bone mineral density, increased risk of autoimmune disease and malignancy. However, complications may not affect those with clinical and subclinical diseases equally. Tursi *et al.* studied 549 patients with coeliac disease; 251 (45·7%) with classical symptoms, 262 (47·7%) subclinical and thirty-six (6·6%) silent disease. Of the eighteen who developed complications (seven malignant and eleven non malignant) fourteen had classical symptoms (5·6% of classical group) and four had subclinical disease (1·5% of subclinical). No one with silent disease developed complications[35]. Ludvigsson compared risk of mortality in people with coeliac disease, duodenal inflammation and positive serology with normal biopsies, i.e. latent coeliac disease. Overall hazard ratio (HR) for death in coeliac disease was 1·39, in inflammation was 1·72 and in latent disease was 1·35[36]. This would suggest that the risks of undetected coeliac disease are small. This is supported by two further European studies of screen-detected coeliac disease, which found no overall increase in mortality in seropositive individuals[37,38]. Conversely, two further studies found an increased mortality in patients with undiagnosed coeliac disease[39,40].

Undiagnosed coeliac disease may even have protective effects in populations in which overweight has become the norm. One population-based study found no increase in cancer or all-cause mortality in adults over 50 years of age with undiagnosed coeliac disease, but there was a trend towards lower BMI, glucose intolerance, serum cholesterol and arthritis. With the exception of reduced bone mineral density, older adults with undiagnosed coeliac disease had limited comorbidity and no excess mortality compared with controls[41].

Infertility

Untreated coeliac disease in women is associated with infertility, increased miscarriage rates and low birth

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weight[42]. While unfavourable outcome is well documented in those with classical coeliac disease, it is less clear whether those with clinically silent coeliac disease face the same risks. In one large study, 1149 babies born to mothers with known coeliac disease were compared with 929 babies born to women diagnosed with coeliac disease after the birth. Undiagnosed maternal coeliac disease was a risk factor for unfavourable birth outcomes such as intrauterine growth retardation (OR 1·62), low birth weight (OR 2·13), very low birth rate (OR 2·45), preterm birth (OR 1·71) and caesarean section (OR 1·82). Coeliac disease diagnosed before pregnancy was not associated with these adverse fetal outcomes [43]. Others have found that unfavourable outcome in pregnancy is not associated with undiagnosed coeliac disease[44].

Osteoporosis

Coeliac disease is known to cause metabolic bone disease with 32–80% of adult coeliac patients having bone mineral density measurements more than one standard deviation below the population mean[45]. Corazza *et al*. demonstrated that those with silent or subclinical disease do not have loss of bone mineral density or metabolic bone derangement to the extent of those with classical disease[46]. Other small studies support this finding[47].

The importance of reduced bone mineral density lies is in its translation to fracture risk. In a large population-based cohort study comprising 4732 subjects with coeliac disease, West *et al*. found a very modest overall increased risk of fracture (HR 1·3)[48]. The risk of osteoporosis and associated fracture risk seen in coeliac disease could be considered as so low as to be insufficient in itself as a justification for mass screening.

Malignancy

Historical estimates for the risk of cancer in coeliac disease are based on hospital series of patients with severe symptomatic disease, often with cancer at the time of diagnosis. More contemporary population studies with less selection bias suggest far lower relative risks.

Card *et al.* in a prospective population-based cohort study of 865 patients with coeliac disease found no increase in the risk of incident malignancy (standardised incidence ratio 1·02)[49]. The risk of non-Hodgkin's lymphoma was also lower than previously reported. Likewise, West *et al*. report a large population-based cohort study that found only modest increases in overall risk for malignancy (HR 1·10) and mortality (HR 1·17), giving absolute excess rates of six and seventeen per 10 000 person years, respectively. Notably, there was reduced risk of breast cancer (HR 0·35) and lung cancer (HR 0·34)[50].

As with other complications of coeliac disease, it is not known whether malignancy affects those with silent disease to the same extent as those with symptomatic disease.

Two European case–control studies found a threefold increase in risk for non-Hodgkin's lymphoma in those with coeliac disease but only in those with detected disease[51].

Lohi *et al*. report a population-based study in which stored sera were tested for coeliac antibodies and this was cross referenced with the National Cancer Register. Coeliac autoantibody positivity did not increase the overall risk of malignancy. Unrecognised autoantibody positivity was associated with increased risk of lymphoproliferative disease and carcinoma of the oesophagus but overall numbers were small[52].

Thus, it could be suggested that most of the complications are not as significant as previously reported. Nevertheless given the current evidence base we would still have to consider that these complications may occur in patients who are undiagnosed and that the recognition of coeliac disease in the main may result in avoidance or reversal of many of the complications we have discussed.

How do patients fare on a gluten-free diet?

A gluten-free diet (GFD) is an effective, non-toxic treatment for coeliac disease, but there are drawbacks, and the benefits in asymptomatic disease are much less clear. In symptomatic disease, a GFD improves symptoms, reduces malignant complications and mortality[53]. The disadvantages, which include expense and possible weight gain, contribute to the burden of illness and a decreased quality of life. This is reflected in low adherence rates of 36–96% for adults[54]. Those with atypical or silent coeliac disease may have a higher quality of life at baseline than those with symptomatic disease and therefore not derive the same benefits[55]. A recent systematic review could not demonstrate a difference in adherence rates between symptom- and screen-detected individuals. This perhaps suggests that both groups derive some benefit[56].

Cost effectiveness

Perhaps the strongest argument for considering diagnosing coeliac disease or even supporting a mass screening programme for adult coeliac disease is potential cost savings to any health system as a whole. In the adult population, screening may be cost effective if there is a relatively high prevalence of coeliac disease or when the standardised mortality ratio for untreated coeliac disease is >1·5. Below this level there is a loss of cost effectiveness[57]. A good example of this is the serological testing for coeliac disease in patients with symptoms of irritable bowel syndrome[58]. However, this would be considered as testing a high risk group and thus not screening.

Dorn and co-workers modelled the costs of five diagnostic strategies using combinations of serology and endoscopy[59]. As the pre-test probability of coeliac disease increases, a greater number of individuals will have positive serology and therefore proceed to endoscopy. The greater number of gastroscopies required substantially increases the cost of avoiding a false-positive result. Dorn also noted that the additional testing for IgA deficiency was expensive. Nevertheless other research groups have suggested that screening may be cost-effective[60]. Costs around the time of diagnosis may be increased but overtime this can be offset by reduced medical expenditures, reduced hospital and general practice attendances[61,62].

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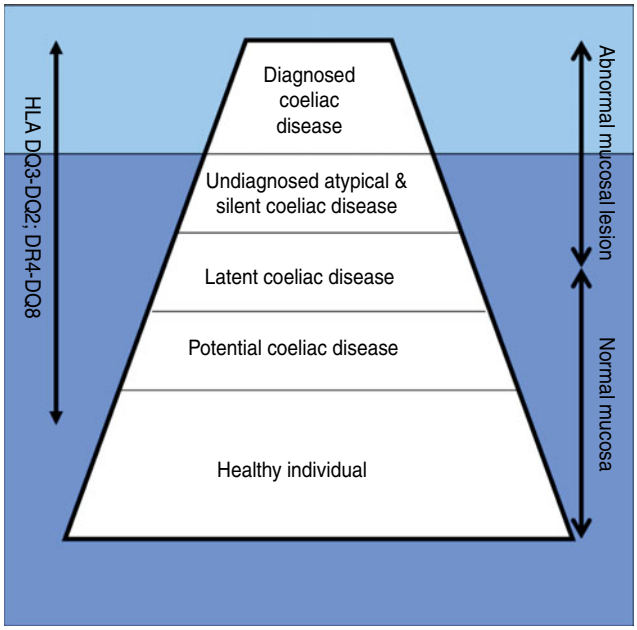

Fig. 1. (colour online) The iceberg model showing the hidden forms of coeliac disease that lie below the waterline (HLA, human leucocyte antigen).[63,64]

Could we hypothesise that screening would be a legitimate approach for detecting coeliac disease?

Population screening could be considered as the most extreme approach to increasing detection of undiagnosed patients with coeliac disease. Mass screening aims to detect disease early before symptoms are manifest. In order to determine whether coeliac disease may have such a latency period, we must first be clear on the definition of coeliac disease. The complex clinical spectrum of coeliac disease is often represented as an iceberg (Fig. 1)[63,64]. Patients above the waterline present with typical gastrointestinal symptoms such as diarrhoea. The next 'layer' comprises patients with non-gastrointestinal manifestations such as fatigue, osteoporosis or ataxia; this can be termed atypical disease. Below this are patients with latent coeliac disease. These are patients who have had a normal small bowel biopsy but subsequently develop biopsy-positive coeliac disease (villous atrophy) or the reverse, a patient with biopsy-positive coeliac disease who continues on a normal diet and is later shown to have normal small bowel biopsies. A recent study provided further insight into this controversial problem. A group of children (*n* 1320) with type 1 diabetes underwent repeated coeliac serological testing. Forty-nine of the 1320 children were tTG positive (3·7%). More than 40% of those who were initially seropositive converted back to antibody negative status without the initiation of a GFD[65]. A small proportion of these tTG positive children underwent gastroscopy and duodenal biopsy. Villous atrophy was present in twenty out of twenty-six that were biopsied. In those children, a GFD was instituted. Although the investigators have commented on fluctuating antibody levels it could be suggested that if no GFD intervention had occurred then a repeat biopsy at a later stage may have shown normal mucosa. This could also be called latent coeliac disease in a paediatric population. These observations have only been described in a paediatric type 1 diabetes cohort and these results cannot clarify the position for children who do not have co-existing type 1 diabetes, nor is there a comparable large study in adults.

Several studies in adults have identified individuals who were initially serologically negative but later developed a positive antibody with villous atrophy on duodenal biopsy[2,39]. This suggests that the concept of latent coeliac disease is more than just an isolated occurrence and poses significant challenges to any screening programme.

The next layer in the epidemiological iceberg comprises those patients with potential coeliac disease. These individuals have normal (or near normal) small bowel biopsies but some features which suggest that they could possibly develop coeliac disease in the future such as positive coeliac serology, or a compatible human leucocyte antigen type.

Any mass screening programme will inevitably recognise individuals with the borderline position of latent or potential coeliac disease. This was highlighted by a recent study that identified twenty-six out of 1868 adults with positive coeliac serology[66]. Six of the twenty-six had villous atrophy on biopsy and were diagnosed with coeliac disease. Of the remaining twenty, five refused biopsy and the rest had lesser degrees of enteropathy or normal small bowel. They are now in the unenviable position of having a 'not quite' diagnosis. Should they have repeat biopsy? When should they be retested? Are they at risk of complications and should they follow a GFD? Do those without overt symptoms follow a more indolent course? At present we do not have the answers to these questions.

The implication for screening is that it may affect the age at which we test people. Do we identify those early in life who have a genetic predisposition to coeliac disease and offer regular follow up? Or should we attempt to avoid those with potential rather than established coeliac disease by screening in adulthood, allowing sufficient time for the development of coeliac disease?

In certain populations, the prevalence of coeliac disease is higher than in the general population and many of these groups are already subject to a targeted screening approach.

Is case-finding a pragmatic approach?

Although the investigational process for population screening and case-finding maybe the same, there is an important ethical difference between them. If a patient seeks medical help then the physician is attempting to diagnose the underlying condition; for example, patients with coeliac disease who present with symptoms of irritable bowel syndrome. This would be classified as case-finding and clearly it is the patient who has initiated the consultation and in some sense is consenting for investigation. Conversely, individuals found to have coeliac disease through screening programmes, may have considered themselves as 'well' and it is the physician or healthcare system that is identifying them as potentially ill. There

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Table 2. Offer serological testing to children and adults with any of the following signs, symptoms and conditions[8]

Signs and symptoms	Conditions
• Chronic or intermittent diarrhoea • Failure to thrive or faltering growth (in children) • Persistent or unexplained gastrointestinal symptoms including nausea and vomiting • Prolonged fatigue ('tired all the time') • Recurrent abdominal pain, cramping or distention • Sudden or unexpected weight loss • Unexplained iron deficiency anaemia, or other unspecified anaemia	• Autoimmune thyroid disease • Dermatitis herpetiformis • Irritable bowel syndrome • Type 1 diabetes • First-degree relatives (parents, siblings or children) with coeliac disease

Table 3. Consider offering serological testing to children and adults with any of the following[8]

- Addison's disease
- Amenorrhoea
- Aphthous stomatitis (mouth ulcers)
- Autoimmune liver conditions
- Autoimmune myocarditis
- Chronic thrombocytopenia purpura
- Dental enamel defects
- Depression or bipolar disorder
- Down's syndrome
- Epilepsy
- Low-trauma fracture
- Lymphoma
- Metabolic bone disease (such as rickets or osteomalacia)
- Microscopic colitis
- Persistent or unexplained constipation
- Persistently raised liver enzymes with unknown cause
- Polyneuropathy
- Recurrent miscarriage
- Reduced bone mineral density
- Sarcoidosis
- Sjogren's syndrome
- Turner syndrome
- Unexplained alopecia
- Unexplained subfertility

may be negative ramifications for insurance, other family members and quality of life. A high index of suspicion should enable the astute physician to diagnose coeliac disease.

The best example of case-finding in clinical practice is a study by Hin and his general practitioner colleagues in Oxfordshire[67]. Hin recognised that there was a mismatch between the suggested prevalence of coeliac disease and the number of cases that were being recognised in primary care. Hin created a short-list of symptoms including anaemia, irritable bowel syndrome type symptoms, family history of coeliac disease, other autoimmune diseases and tired all the time. The investigators serologically tested 1000 patients and detected thirty new cases of coeliac disease. This work has since been validated by a second group of UK researchers[68].

To further improve our detection rates a wide variety of presentations and associations is described in the recent National Institute for Health and Clinical Excellence guidelines drawn up to improve recognition and diagnosis of coeliac disease (Tables 2 and 3)[8]. Presentation without gastrointestinal symptoms (atypical) is frequent and these patients may initially be overlooked.

Conclusion

In conclusion, adult coeliac disease is common with a large number of undetected cases still present in the community. We and others have demonstrated a delay in the diagnosis for patients with coeliac disease; perhaps the important change in our clinical practice (both in primary and secondary care) is to have a low threshold for case-finding and serological testing. We do not believe we are diagnosing too many cases of coeliac disease; in fact we would suggest that if you look for coeliac disease you will find it.

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