Proposal for assessing coeliac disease against UKNSC screening criteria
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What is the prevalence of coeliac disease in the adult population?

Coeliac disease or gluten sensitive enteropathy is defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley or rye) in genetically susceptible individuals. Coeliac disease has historically been considered as an uncommon gastrointestinal condition[1,2]. The estimated incidence in the United Kingdom (UK) in 1950 was one in 8000 [3]. In addition, most clinicians expected to recognise infant or childhood presentations with overt symptoms of malabsorption (or failure to thrive). However, there has been a paradigm shift in our conceptual understanding of coeliac disease. Recent studies in the UK (Northern Ireland, Nottingham and Sheffield) assessing the prevalence of coeliac disease in the general population have consistently reported that coeliac disease affects approximately 1% of all adults.[4-6] Similar findings have been described by epidemiological studies screening cohorts of healthy volunteers in other European countries and the USA (0.5-1%).[7,8] Adult presentations are now more frequent than paediatric (9:1 Coeliac UK National Patient Charity – membership data 2005). The commonest age for presentation is during the 5th decade [9,10]. Patients with adult coeliac disease rarely present with symptoms suggestive of malabsorption, far more commonly they describe non-specific or subtle gastrointestinal symptoms (for example, non-specific abdominal pain, irritable bowel type symptoms or even upper gastrointestinal symptoms). Any gastrointestinal presentation of coeliac disease is now broadly described as the typical (classical) form. However, a substantial proportion of patients have no gastrointestinal symptoms but alternatively present with extra-intestinal manifestations (Table 1).

Table 1: Symptoms in patients presenting with coeliac disease

Associated gastrointestinal presenting symptoms
Abdominal Pain
Diarrhoea
Steatorrhoea
Bloating
Non-specific gastrointestinal
Associated non- gastrointestinal symptoms
Weight loss
Fatigue or 'tired all the time' (TATT)
Arthralgia, arthritis and myalgia
Skin rash (dermatitis herpetiformis) and aphthous ulcers
Depression
Neuro-psychiatric symptoms

In addition, there are also a number of associated conditions (Table 2) which may/should prompt the clinician into investigating patients for coeliac disease.

Table 2: The prevalence of coeliac disease in associated conditions (ranges are based on prevalence studies which have primarily been performed in secondary care).

Associated conditions	**Prevalence of coeliac disease**
First-degree relatives	4-22.5%[7,11-13]
Dermatitis herpetiformis	69-89.5%[14,15]
Iron deficiency anaemia	2.7-5.7%[16-19]
Vitamin B_{12} and folate deficiency	
Irritable bowel	0-11.4[20]
Type 1 diabetic patients	2-8%[21-24]
Thyroid disease	2-6% [25,26]
Infertility	4.1-8%[27-29]
Osteopenia/Osteoporosis	1-7%[30,31]
Ataxia of unknown cause	1.9-16.7%[32]
Down's syndrome	4-17% [33-36]
Abnormal liver function	9-9.3%[37,38]
Addison's disease	1.2-12.5%[39,40]
Alopecia areata	1-2%[41,42]

Is the natural history of the disease understood and is there therefore a latent period in which the disease could be found?

In order to understand whether there is a latent period for individuals with undetected coeliac disease first we must understand the modern definitions of coeliac disease. Patients with adult coeliac disease have been considered typically to complain of gastrointestinal symptoms suggestive of malabsorption. This manner of presentation is now described as mentioned earlier is the classical (typical) form.[43,44] We now recognise that patients do not always have gastrointestinal symptoms (silent or atypical form) but may present insidiously, for example with the symptoms and associated conditions delineated in Tables 1 & 2.

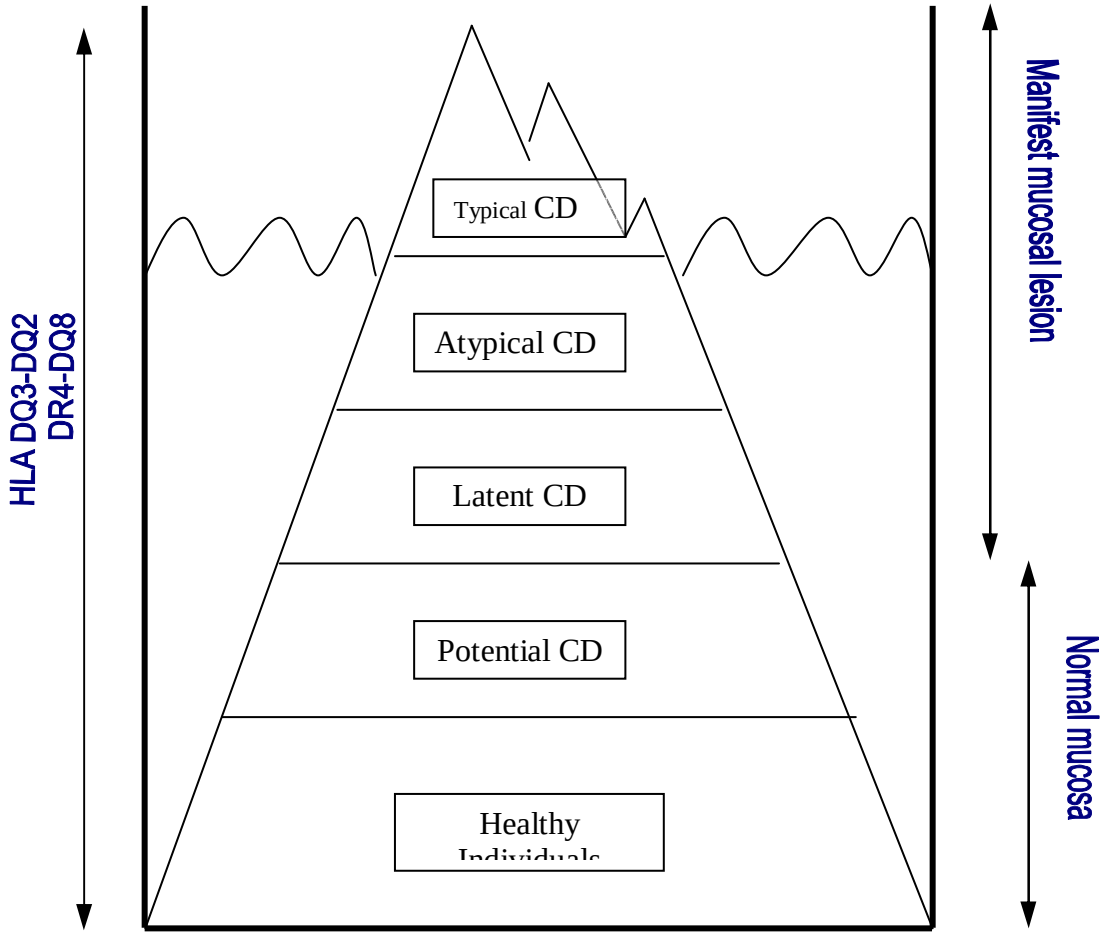

Figure 1: The Coeliac Iceberg

Critically (when considering the issue of screening) there are further levels to this iceberg. Latent coeliac disease describes 2 groups of patients. Those who have at some stage had a normal duodenal biopsy whilst on a regular diet and subsequently develop coeliac disease (with histological changes) later in life. The converse of this clinical situation also exists, patients who have histological features of coeliac disease but continue on a gluten containing diet and at re-biopsy 2 years later, now have normal duodenal mucosa. This phenomenon has only been reported in case reports and we still consider that in clinical terms patients with coeliac disease will continue to have evidence of histological changes unless gluten is withdrawn from their diet.[44,45]

Further down the iceberg are patients with potential coeliac disease.[44,45] These are individuals who do not have the histological changes consistent with coeliac disease but have features that suggest that they could potentially develop coeliac disease.

1. A positive antibody titre, in particular endomysial antibody - but normal duodenal mucosa.
2. Increased intraepithelial lymphocytes on biopsy.
3. Increased density of intraepithelial lymphocytes expressing gamma/delta T cell receptors.
4. HLA pattern consistent with coeliac disease (HLA –DQ2).
5. A positive rectal gluten challenge.

Any screening policy which is implemented may inadvertently recognise individuals with latent or potential coeliac disease – this area is still predominantly a research interest in gastroenterology with unknown clinical implications.

Although adult screening studies have reported a population prevalence of 1% for coeliac disease, there has also been a serological study in UK children. [46] Children aged 7.5 years participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population based birth cohort study established in 1990 were recruited. 5470 children were tested, using EMA and 54 tested positive for IgA-EMA (1.0%; 95% confidence interval 0.8 to 1.4). However, none of these individuals were gastroscoped or biopsied, thus it is not clear whether these children have villous atrophy in the presence of a positive EMA (ie coeliac disease) or if they only have a positive EMA in isolation (ie potential coeliac disease Figure 1) and will develop coeliac disease over the course of their lives. Even if these children do have villous atrophy we still have to speculate on why the vast majority of cases are currently presenting in middle age? It maybe that this is a problem in recognition or detection – alternatively there may be another 'missing co-factor' required before individuals manifest overt symptoms, villous atrophy or extensive enough villous atrophy (along the length of their small bowel) to develop overt symptoms (a form of small bowel 'decompensation'). Further evidence to support this view may come from our understanding of coeliac disease from a genetic perspective. Coeliac disease is strongly linked with HLA-class II alleles (DQ2 or DQ8 in excess of 90% of all cases), however HLA-linked genes only account for 40% of the familial risk, hence other non-HLA linked genes or non-genetic factors (for example, environmental factors or bacteria) must also play a role in the development of coeliac disease.[47,48]

Although this data suggests there may be a latent period – we still have no clear understanding of what the natural history of individuals with coeliac disease would be/is and if early recognition would be beneficial.

Is there a good test whose sensitivity, specificity and positive predictive value for the general population is known? (and is this test likely to be acceptable?)

Patients with coeliac disease may initially be recognised by using non-invasive serological tests. Historically, IgG and IgA gliadin antibodies were the serological markers first used but the performance of these tests was variable and they were not particularly sensitive or specific. However, in 1984 EMA was described. The detection of this IgA class antibody by direct immunofluorescence to antigens present in monkey oesophagus and thereafter human umbilicus resulted in a far greater specificity than the gliadins. There were limitations to the use of EMA – 1) the use of rhesus monkey oesophagus (an endangered species), 2) it is a qualitative test which involves subjective interpretation of the immunofluorescence staining, 3) EMA negativity in patients with lesser degrees of villous atrophy.

The more recent development of Tissue Transglutaminase antibody (TTG) has provided the clinician with an alternative to EMA. Current reports validating TTG in clinical practice give a sensitivity of 91-95% [49-52] and a negative predictive value of near 100% [53]. False positive TTG results may occur in chronic liver disease, myeloma, monoclonal gamopathy, and type 1 diabetes [54,55]. TTG has a similar sensitivity and specificity to EMA but TTG is a quantitative test (enzyme linked immunoabsorbent assay) which is quicker/easier to perform and cheaper.[56] The positive predictive value of both EMA and TTG is in excess of 90%.[1,2] Many centres now use TTG as the first line test and then perform EMA in patients who are TTG positive. This approach is pragmatic and cost-effective but has not been adopted universally. Some centres (including our own) still perform EMA and TTG as a paired serological test in order to not miss EMA negative cases. Both EMA and TTG may be negative in the presence of IgA deficiency (as they are both IgA based tests). Coeliac disease is reported to be

more common in individuals who are IgA deficient. For this reason the IgA immunoglobulin level should also be requested when investigating a patient for coeliac disease. If IgA deficiency is detected the immunology laboratory may then independently perform an IgG TTG level.

Based on the currently available data it would appear that EMA, TTG or a combination could ensure an excellent sensitivity, specificity and positive predictive value when investigating individuals for coeliac disease. However, we cannot comment with certainty on how valid this strategy would be for population screening. Previous population screening studies have used these serological markers initially and then biopsied individuals who have a positive antibody result. Thus antibody negative coeliac disease (a well recognised condition that may affect 6.4% to 9.1% of all cases) would not be diagnosed. [49,51]

Although an initial serological test is likely to be acceptable to the general population thereafter there is likely to be a ***drop out rate*** as some individuals may be unwilling to undergo a gastroscopy and duodenal biopsy (which is necessary to histologically confirm the diagnosis).

Do those who have been found to have coeliac disease either by screening or incidentally have as good an outcome as those found by virtue of clinical suspicion or case finding?

There is a paucity of literature in this area. There are initial reports that reduced bone mineral density (a complication that may affect up to 50% of patients with newly diagnosed adult coeliac disease) is similarly prevalent in individuals who have been detected via a screening programme. In addition, instituting a gluten-free diet may improve or at least protect screened individuals with coeliac disease from further reductions in bone mineral density. However, these observations are based on sample sizes of less than 20.[61]

Another observation pertains to the likelihood of malignancy or death. Historically both mortality and the risk of malignancy (in particular gastrointestinal malignancy) associated with coeliac disease were reported to be significantly higher than that of the general population.[62] However, recent population-based studies have described only a modestly increased risk and importantly this risk appears to fall as time from diagnosis increases (in those patients that are compliant on a gluten-free diet) [63-70]. The reduction in mortality and malignancy in contemporary studies may suggest that historically only the most severe cases were being diagnosed.

Although small bowel lymphoma may be 50 times more common in an individual with coeliac disease this relative risk does not take into account the low annual incidence of 0.5-1 per million. Thus the absolute risk for patients with coeliac disease is comparatively modest. This data could be used to support screening as it can be inferred that early detection and commencing a gluten-free diet will ensure a reduction in both mortality and malignancy. It must be stressed that these observations are based on case-finding cohorts and that there are no studies currently

reporting the screening and long-term follow-up of individuals found to have previously undetected coeliac disease. It is possible that the cases of coeliac disease that are currently undetected may have a different ***natural history*** to those individuals who are currently presenting with clinical symptoms or through active case-finding by clinicians. This currently undetected group may have a more indolent form of coeliac disease and thus may be less likely to develop significant complications.

Intriguingly individuals with coeliac disease may have a reduction in the risk of breast cancer and also have been noted to have a reduction in the prevalence of both hypertension and hypercholesterolemia.[62,68,69,70,71]

Controversially it could be suggested that undetected coeliac disease may provide a benefit to an individual in a Western society with the progressive epidemic of obesity. This suggestion still requires to be substantially validated.

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 to controls, this is still an improvement from their undiagnosed state. This benefit is particular noticeable in patients who have presented with typical symptoms. [72-76] Despite some evidence showing that overall quality of life is improved in screen detected patients this benefit appears to be short lived with subsequent poor compliance to a gluten free diet[75,77-79]

Thus it is not entirely clear whether individuals with undetected coeliac disease will benefit from a screening programme.

Do we have the resources to do the tests and treatments?

The antibody profiles are cheap (in the UK this may be as little as £15). Thereafter the cost of gastroscopy and biopsy would have to be considered in patients who are antibody positive. A recent cost-effectiveness study using the American Medicare costing system and a Markov model was able to demonstrate that screening would be a cost effective approach (if using an EMA initial strategy alone).[80] The base-case analysis suggested that the cost was US$ 44,941 per year of life saved (This is based on using an incremental cost-effectiveness ratio (ICER) of EMA strategy versus no screening). This figure falls within the range of the £20,000 for Quality-adjusted life years (QALY's) sometimes used within the UK healthcare system. A major limitation of this study is based on setting the Standardised Mortality Ratio at 1.5. The authors describe that if the SMR for coeliac disease is less than 1.5 then there is a sharp rise in the ICER rendering mass screening ineffective.[80] This is an important point as the most contemporary UK study of this nature suggested that the hazard ratio for mortality was 1.3 in patients with coeliac disease.[71] The authors described that the hazards ratio in the first year was 2.1 and that this dropped to 1.1 within 12 months of the diagnosis. This data could suggest that the SMR is lower than 1.5. In addition, there may be a lower SMR for ***indolent*** undetected cases (who as mentioned earlier may have a different natural history).[71]

A further financial limitation may be the absence of the appropriate support after the diagnosis has been made. Currently within the UK the provision of dietetic services is inadequate to cope with existing referral patterns.[81] Patients with coeliac disease have indicated that they perceive the optimal care/support package to be a dietetic coeliac clinic but with gastroenterological consultant support.[82] This is currently only the case in a few UK centres.

An alternative model could be that of active case-finding. One example of this is the Oxford general practice study.[83] Hin and colleagues undertook a policy of investigating patients for coeliac disease who fulfilled predefined criteria based on symptoms and disease associations (which can be seen in Tables 1 and 2). By taking this approach these investigators diagnosed 30 previously undetected adult cases of coeliac disease from 1000 patients that they tested in primary care. Further evidence for a cost-effective approach comes form the model used to asses the relationship between irritable bowel syndrome and coeliac disease.[20,84]

Reviewer's conclusions

Although coeliac disease does in many ways fulfil the World Health Organisation criteria for screening - the real/actual benefit of population screening remains questionable. There are significant limitations due to our lack of knowledge in terms of the natural history of undetected cases of coeliac disease. In addition, there are financial limitations which have not been considered in cost effectiveness models - such as the current absence of an adequate provision of support services for patients after the diagnosis.

Finally, it is very unclear whether patients detected through screening programmes would adhere to a gluten-free diet. The ethical issues of converting a 'healthy individual' into a patient may result in poor uptake of such a programme. An alternative approach such as active case-finding may yield useful information that will help to inform this debate further. In addition, the possibility that the Quality and Outcomes Framework (QOF) recommended by the Department of Health may incorporate coeliac disease into its strategy will further support the likelihood of a successful case-finding approach.

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