Screening for coeliac disease in the general population and in high-risk groups

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Abbreviations: CD, Coeliac disease; GFD, Gluten-free diet; NPV, Negative predictive value; PPV, Positive predictive value; QALY, Quality-adjusted life year.

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ABSTRACT

Background: Coeliac disease (CD) occurs in approximately 1% of the Western population. It is a lifelong disorder associated with impaired life quality and an excess risk of comorbidity and death.

Objectives: To review the literature on screening in CD in relation to the current WHO criteria for mass screening.

Methods: We performed a PubMed search to identify papers on screening indexed in PubMed with a publication date 1900 until 1st of June 2014. When an abstract was deemed relevant, the corresponding paper was read in detail.

Results: CD fulfils several WHO criteria for mass screening (high prevalence, available treatment, difficult clinical detection), but it has not yet been established that treatment of asymptomatic CD reduces the excess risk of severe complications, leads to higher life quality or is cost-effective.

Conclusion: Current evidence is not sufficient to support mass screening for CD, but active case-finding may be appropriate, recognizing that most patients with CD will still be missed by this strategy. Although proof of benefit is still lacking, screening may be appropriate in high-risk groups.

Keywords: coeliac, Gluten-free diet, support

Introduction

Coeliac disease (CD) occurs in about 1% of the Western population.[1, 2] A recent multinational study in Europe found big differences in CD prevalence with the lowest prevalence (0.3%) in Germany and the highest in Finland (2.4%) despite using common criteria for CD diagnosis.[3]

The prevalence of CD seems to be increasing.[4-7] A true increase in prevalence is probably one explanation, but other factors may also have contributed. Increased awareness of the complications of CD (including the mortality excess[8]), in combination with the advent of serological tests with high sensitivity and specificity[9-12] mean that active case finding in CD has increased dramatically in the last decades. Among groups where screening is now becoming more and more common are first-degree relatives, and patients with type 1 diabetes[13, 14].

The main objective of this paper was to review the literature on screening for CD, in relation to the established criteria for mass screening established by the World Health Organization (WHO).

Methods

This project was part of a wider effort, initiated by the British Society of Gastroenterology (BSG) and the Oslo group,[15] to establish recommendations for the care of coeliac patients. JFL and DSS coordinated that overall effort. As part of a major review on clinical management of CD [14], we briefly described the role of screening for CD. In the current paper we expand that discussion, and look at the background of screening, and the pros and cons for CD screening, including the impact that such detection of CD will have on dietary adherence, outcome and quality of life.

The working group for the present paper was made up by of seven authors from six different countries (Britain: n=2; and one author each from Sweden, Finland, Italy, Argentina and the US). Four authors (JFL, TC, KK and JAM) carried out the literature searches, the data collection and took the main responsibility for the writing of the paper. JB, FZ and DS provided important feedback, and contributed to crucial revising of the paper. All authors stand behind the paper. JFL wrote the first draft.

The recommendations of this paper were based on a systematic literature review in PubMed for the time period 1900 until June 1, 2014 (search criteria have been listed in the appendix). Initially we carried out seven PubMed searches (Appendix) but given the large number of hits for three of these, we limited our literature review to the remaining four terms combined with British and American spelling of coeliac disease (search terms: “definition”, “cultural”, “diagnostic delay”, and “undiagnosed and (complication or comorbidity)”). The parts of this paper dealing with CD prevalence, treatment (gluten-free diet, GFD) and serological sensitivity/specificity were based on personal knowledge of the authors. Finally, CD screening in general was discussed within the author group.

Results

WHO stipulates a number of criteria that need to be met to support mass screening (Table 1). While it is evident that CD readily meets many of these criteria, others have not yet been met. For example CD is more prevalent than some disorders for which there is already mass screening (e.g. phenylketonuria, PKU), but it is unclear whether early detection of CD has a positive societal impact. In contrast, detecting a child with PKU will allow prevention of devastating consequences for the development and life quality of that child.

Prevalence of CD

I) That the disease is common and well defined. In much of the western world, CD affects about 1% of the population, but the prevalence varies between countries (e.g. 0.3% in Germany,[3] 0.7% in Italy,[3] 0.7-0.8% in the US,[16, 17] and 1.8% in Sweden[2]). There are reports of even higher prevalence in certain calendar- and age-specific population-strata in Sweden[18].

The proportion of individuals with CD who have received a physician-assigned diagnosis of CD also varies (e.g. 25% in Finland and 6% in Italy)[3] probably reflecting the general awareness of CD in each country. The ratio between diagnosed and undiagnosed CD has implications for screening since with a large proportion of undiagnosed CD, the arguments for screening become stronger. Despite slightly varying prevalences of CD, it is one of the most common lifelong diseases in any Western country (especially in children). While prevalences of CD may be lower in some non-Western countries[19, 20] there are also reports of extremely high prevalences in others[21]. We conclude that this WHO condition is fulfilled.

There is currently an ongoing debate on how to define CD. Our research group recently published a paper on definitions of CD where CD was defined as "a chronic small intestinal immune-mediated

enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals".[15] The related non-coeliac gluten sentivitity[15, 22, 23] was defined as "one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded".[15] The definition of CD has important implications for CD screening since most research on complications and life-quality so far has been performed in individuals with biopsy-verified CD, and data cannot automatically be extrapolated to non-coeliac gluten sensitivity. The risk of complications may also vary with underlying histopathology in CD[24].

Serology – Sensitivity and specificity

II) That screening tests are simple, safe and accurate. The WHO stipulates that for mass screening to be an option, screening tests with high sensitivity, specificity,[25] positive predictive value (PPV) and negative predictive value (NPV) must be available. For any of the available tests a most important aspect is that the testing should be carried out when the patient is on a gluten-containing diet. It is therefore of crucial importance that the patient remains on a normal diet throughout the investigation for CD, and our discussion assumes this will be so.

So-called antigliadin antibodies used in the 1980s and 1990s have low PPV even in high-risk groups; and have therefore largely been replaced by the more specific endomysium (EMA) and tissue transglutaminase antibodies (TTG). The introduction of endomysium antibodies was initially promising since their sensitivity and specificity seem to be at least 90-95%, but over time issues regarding interobserver reliance/interpretability, and cost, have limited its use as the first-line-screening tool for CD. Though TTG antibodies can also be elevated in non-CD diseases, such as liver disease,[26] gastrointestinal infections[27] and certain heart diseases[28, 29], TTG like EMA offers

high sensitivity and specificity[30]. One further test has recently gained some popularity. This is for deamidated gliadin peptide antibodies (DGP). One meta-analysis however found that TTG performs better than DGP.[31]

TTG therefore is often used for screening of high-risk groups, but has also been used in large-scale screening projects of the general population including that of a multi-national European study encompassing more than 29,000 individuals.[3] In the European multi-centre study, 75% (n=292/391) of individuals with positive TTG were positive for EMA but only 2.6% of those with borderline TTG values (n=10/384).[3] In the 147 individuals with both positive EMA and positive/borderline TTG, 100 had an enteropathy typical of CD, equalling 68%.[3] When Hopper *et al* screened a population of 2000 individuals undergoing endoscopy (for various indications) the PPV for CD (as defined by villous atrophy) in TTG+ individuals was 28-29%,[32] but with a much higher figure reported in a general population study by Katz *et al*[33] as well as by Sugai *et al* [34]. Even a PPV of around 30% compares favourably with the PPV of e.g. guaiac faecal occult blood (FOB) testing for colorectal cancer (a test which has already been accepted for screening in a number of countries). As in the case of FOB screening however confirmatory testing is recommended (in the case of CD in adults, through small intestinal biopsy[14]).

One further aspect to consider in the use of TTG is that when determining TTG (TG2 antibodies) by ELISA, it is important to bear in mind that the performance of the commercial ELISA TTG assays may vary depending on the quality of the TTG antigen [35]. The method of extraction, the purity of TTG and the production and processing of recombinant antigen may all have an effect on test results[35-37]. Furthermore, as TTG can exist in two divergent conformations (open extended or closed) dependent on the activity of the enzyme,[38] this also influences the performance of the assay, the open TTG being the superior antigen[39]. For the above-mentioned reasons the different commercial TTG-ELISA tests can yield differing numbers of false-negative or false-positive results.

Sequential strategies may also be used to increase the positive predictive value[2, 40].

When screening may be insufficient

Under certain circumstances, a negative screening test cannot rule out CD. This will occur when the pre-test probability of CD is elevated. For instance, individuals with severe gastrointestinal symptoms, especially those with a family history of CD, should undergo small intestinal biopsy even in the absence of elevated antibodies[41]. Similar arguments apply to children with growth failure and individuals with severe gastrointestinal symptoms and at the same time another autoimmune disease such as type 1 diabetes, thyroid disease or Addison's disease. Although, IgG-based serology tests have developed in recent years, a combination of IgA deficiency and gastrointestinal symptoms may also constitute an indication for biopsy. One way to effectively exclude CD in IgA deficient individuals is to perform an HLA-test first thereby ruling out CD in those negative for DQ2 or DQ8. Differential diagnoses such as common variable immunodeficiency (CVID) or and severe giardia should also be considered.

Screening is culturally acceptable

A third WHO criterion is that a screening test should be culturally acceptable. There are areas in the world,[42] where blood testing may not be culturally but in the majority of countries (including those where earlier research has shown a high prevalence of CD), blood testing is culturally accepted.

The GFD

IV. That a treatment is available. This condition is clearly fulfilled in CD. GFD is an effective treatment for CD, and in symptomatic patients the benefits of the dietary treatment are well established, as it has been shown to decrease clinical symptoms as well as reduce the excess risk of complications. [43-45]

Nevertheless, the advantages of dietary treatment in screen-detected apparently asymptomatic individuals remain doubtful, and it is by no means settled that GFD results in similar health gains.[46-50 51] However, it is important to note that many screen-detected CD patients are not truly asymptomatic at diagnosis, and may once on a GFD recognize that they had suffered from CD-related symptoms before the diagnosis. It is suggested that many undiagnosed coeliac patients accept a state of chronic vague ill health as a normal condition, but recognize this only after they have been placed on a GFD[47, 52, 53 54]. A recent randomized study also showed that apparently asymptomatic EMA positive subjects seem to benefit from their serological screening and subsequent GFD [55], thereby supporting earlier evidence from Dickey *et al* [56]. Some authors have however suggested that EMA positivity in individuals with normal mucosa constitute a separate entity (potential CD), different from CD[57].

A strict GFD sets major limitations on daily life, it is expensive and difficult to maintain[58, 59]. Furthermore, removal of gluten from baked products makes them less palatable than comparable products in the normal diet. Due to these unpleasant aspects, the adherence with the GFD often remains inadequate[60]. Individuals found through screening programs to have CD may feel themselves healthy and they do not expect to gain health on treatment similar to those detected due to symptoms. Consequently, screen-detected subjects may be even less willing to adhere to a strict GFD.[53, 61 62] The possible non-adherence to GFD is an essential issue when weighing the harms and benefits of CD screening, as a low rate of adherence would abolish any advantages of screening. It is important in this regard to recognise that good dietary adherence can be achieved in screen-detected CD patients (adherence rates of 85% in symptom-detected CD patients and 79-91% in screen-detected ones),[53, 63] even after long-term treatment[52, 64]. However, there is evidence to suggest that dietary lapses could be more common in the initially asymptomatic screen-detected patients than in the symptomatic ones[53]. Furthermore, patients suffering from type 1 diabetes mellitus and found to have CD by risk-group screening, may evince lower dietary adherence rates than reported in screening studies in general (40-63%)[65-67].

When prescribing GFD to healthy screen-detected patient, one should remember that GFD is not nutritionally optimal and may have adverse consequences. GFD may potentially expose individuals to high sugar and low fibre and mineral intake[68, 69], which again might cause different long-term negative health consequences such as constipation[70]. In addition, there is concern that patients might gain undesirable weight while on a GFD[71, 72]. Altogether, it would thus be essential to evaluate the consequences of GFD treatment before any screening programs for the disease are instituted.

Diagnostic delay

V. That clinical detection is difficult. Typically CD is characterized by diarrhoea, malabsorption and failure to thrive in childhood although during the last two decades the age of diagnosis has shifted upward and many patients have only minor symptoms.[73-75] Due to the inconsistency of the symptoms, a substantial proportion of coeliac patients have a previous diagnosis of irritable bowel syndrome[76 77]. Unfortunately these symptoms do not predict CD in general population studies [2, 33, 78, 79]. Furthermore, increasing numbers of CD patients are diagnosed because of extraintestinal symptoms or by screening of at-risk groups[73, 74]. Probably due to the vague nature of presenting symptoms, the delay from first symptoms to CD diagnosis has been reported to be unacceptably long, at between 5 and 10 years, for many persons[73, 80-85], and the need for earlier diagnosis, even by mass screening has been advocated.

Untreated disease leads to complications

VI. That if undiagnosed and untreated the disease will lead to severe complications. The WHO stipulates that prevention of complications shall follow upon disease detection if mass screening is implemented. This statement is conditional on two facts:

a) That undiagnosed disease confers complications; and b) that these complications can be prevented by the "treatment", in this case the GFD. Given the importance of genetic factors in the aetiology of CD, it may be assumed that comorbidity linked to underlying shared risk factors cannot be modified by diagnosing CD and introducing a GFD.

It seems clear that the majority of gastrointestinal symptoms in CD are alleviated after the introduction of a GFD, but the evidence is less clear whether most complication are influenced by GFD. Weaknesses of previous research in this area include lack of strict evaluation of GFD, low study power, short follow-up, and a difficulty in disentangling the effects of age at diagnosis, and duration of gluten exposure, which will both be linked to early diagnosis.

It should be noted that duration of disease is not equal to diagnostic delay. In the recent Proconsul study, complications in CD were associated with a short diagnostic delay[86], but it cannot be ruled out that earlier celiac diagnosis was prompted by symptoms and signs from the celiac complication.

Morbidity and mortality in undiagnosed CD

Mortality

A number of studies have examined mortality in undiagnosed CD[6, 51, 87-90]. Two of these have shown excess mortality[6, 90]. Of particular interest is the study by Rubio-Tapia, which is the only study with extensive follow-up duration[6]. That study found an almost 4-fold increased risk of death

in young men with positive CD serology, but confidence intervals were wide (95%CI=2.0-7.5), the number of participants with CD low (n=14) and the population studied was restricted (military recruits) so results may not be generalizable. It is also not clear, how many of these individuals would have been diagnosed applying modern aggressive case-finding for CD[91] as many individuals diagnosed in screening studies have a history of CD-associated symptoms.[47] Other larger-scale studies have shown no increased risk of death in undiagnosed CD (numbers of screened adults: 16,847;[89] 7,527;[87] and 6,987[88]).

Autoimmunity

Studies on undiagnosed CD and autoimmune disease are difficult to carry out since patients with autoimmune disease are often screened for CD, and because the onset of autoimmune disease is often gradual (in contrast to mortality, but also to some extent to malignancy). As far as we know, none of the studies looking at undiagnosed CD and mortality have looked at development of autoimmune disease.[6, 51, 87-90]

Cosnes *et al* investigated 924 patients with CD. While they concluded that the GFD had a protective effect against autoimmunity, this effect was weak since it did not remain statistically significant when the authors adjusted for other co-variates in their multivariate analyses (p=0.07).[92] The Cosnes *et al* study also found that a *late* diagnosis of CD decreased the risk of autoimmune disease.[92] Finally, two Italian studies have suggested that GFD may decrease the prevalence of thyroid autoantibodies[93, 94], but whether it protects against hypo- or hyperthyroidism is still unclear.

We may however want to consider the effect of a GFD not only upon the cumulative incidence of autoimmune disease in those with CD but also upon the control of disease in individuals who already have an autoimmune disease (other than CD). Diagnostic delay of CD is common in type 1 diabetes[95] and the longterm consequences of this are unknown. Recent Swedish data however indicate that long term CD is associated with excess morbidity in type 1 diabetes[96-98]. Hansen *et al* screened children with type 1 diabetes, but did not see an improvement of HbA1C in diabetes patients who were detected with CD and then recommended a GFD.[99] A British study of adults with type 1 diabetes however found that patients with undiagnosed CD had worse HbA1C (8.2) than controls (7.5)(p=0.05) at baseline, but when after 1 year the authors compared HbA1C values, there was no difference between those adhering to a GFD and those with poor adherence.[100]

Malignancy

A recent meta-analysis even suggested that the overall malignancy risk in diagnosed CD was not elevated compared to that of general population-based controls,[101] but individual cancers, such as lymphoproliferative cancer and gastrointestinal cancers,[102, 103] may still be positively associated with CD. One reason for a seemingly neutral association between diagnosed CD and risk of overall cancer (or a very limited risk increase) is that high relative risks for less common cancers (lymphomas) may be compensated for by lower relative risks for common cancers such as breast cancer.[104, 105]

We know of three studies so far exploring cancer risk in undiagnosed CD, none of which found any increase in overall cancer but study power was limited.[89, 106, 107] In addition to these there are at least another two case control studies specifically of lymphoma, which have shown an excess risk in CD. Catassi *et al*[108] found a 3.1-fold excess of Non Hodgkin Lymphoma among Italian individuals with undiagnosed CD and 16.9 for gut lymphoma. The latter of these figures closely mirrors the odds

ratio of 15.7 for the occurrence of gut lymphoma in undetected CD from Johnston and Watson in Northern Ireland[109]. As with mortality however one must consider the risk in those with diagnosed disease. Since the risk of NHL remains greater in diagnosed disease at about 4 to 6 fold[24, 103, 110] (and that of small bowel lymphoma (SBL) may be even higher in this group[111]) , again a substantial societal benefit in the reduction of cancer occurrence or death from mass screening for celiac disease seems unlikely.

Considering that the overall risk of malignancy in CD does not seem to be increased more than marginally,[101] most interest with regards to the potentially protective effect of GFD focuses on lymphoproliferative malignancy. That earlier research on undiagnosed CD has failed to show an association with malignancy, including lymphoproliferative malignancy argues against GFD playing a major role. At the same time, it should be noted that most earlier studies have been underpowered to examine the relationship between GFD and lymphoproliferative malignancy (number of CD patients with lymphoma or non-Hodgkin lymphoma: 9,[112] 9,[44] and 9[103]). In an effort to examine the role of GFD, Olén *et al* reviewed patient charts (the researchers were blinded to CD status) of 59 patients with both CD and lymphoma, as well as 137 CD patients *without* lymphoma. This nested case-control study was still underpowered to confirm a suspected relationship between poor dietary compliance and future lymphoma (OR=1.83; 95%CI=0.78-4.31).[113]

Current data implies that there is a protective effect of GFD against lymphoma, although that has not yet been comprehensively proven.

Pregnancy and fertility

Adverse pregnancy outcome in maternal *undiagnosed* CD has now been confirmed by a number of studies, [114-116] including two recent papers that both found increased risk estimates for preterm birth in undiagnosed CD (Sweden: 1.71[117]; Denmark: 1.33[116]), but not in diagnosed CD. This association strongly argues that a CD diagnosis and a GFD introduced before pregnancy influence the pregnancy outcome. As both studies were of clinically diagnosed cases, they do not however clearly demonstrate a benefit to screening for asymptomatic ones.

That undiagnosed CD has a negative effect on birth outcome cannot automatically be translated into an effect on fertility. The largest screening study for CD in subfertile/infertile couples so far found no association with CD[118], and the two largest cohort studies to this date[119, 120] have found that overall fertility in CD is similar to the of general population controls, even though the Swedish study found a fertility decrease in the last two years before diagnosis followed by catch up fecundity after diagnosis[119]. It cannot be ruled out that the decrease in fertility just before diagnosis seen in that paper is due to undiagnosed CD,[119] but it might also be due to other comorbidity which lead to testing for CD, or that women postpone pregnancy when they undergo extensive medical investigations.

Advantages of undiagnosed CD?

Although we do not argue that patients with symptomatic CD should remain undiagnosed, several papers suggest that the prevalence of hypertension,[121] hypercholesterolemia[121, 122] and obesity[123] is lower in undiagnosed CD than in the general population,[121] potentially protecting against cardiovascular disease. In fact, some authors have argued that screen-detected children without

symptoms should not always be treated with GFD.[52] The largest study on diagnosed CD and cardiovascular disease however found a small but statistically significant increased relative risk for both incident ischemic heart disease and death from ischemic heart disease.[124] Such a risk increase does however translate in a substantial absolute risk considering that cardiovascular disease is common (in celiac individuals aged 60+ years, the excess risk was 20 myocardial infarctions per 1000 person-years[124]).

Life quality aspects of screening of CD

In symptomatic CD the GFD results in rapid recovery from symptoms paralleled with improvement in quality of life[53 125 46, 126, 127] (Table 2). However, screen-detected CD patients may have considered themselves healthy before the diagnosis, and now the stigma of a chronic disorder[128] and need of major dietary restrictions may potentially even increase their self-perceived burden of illness and impair their quality of life[129-131].

Prospective studies on quality of life in CD patients detected by screening of at-risk groups or in populations in general are limited (Table 2). According to these studies quality of life in screen-detected coeliac patients at or before diagnosis, especially in those who are asymptomatic, is often similar to,[46, 53, 126 50, 125] or lower [47, 52, 53] than that found in control populations. In screen-detected patients, GFD treatment does not necessarily result in improvement of life-quality[46, 53, 126] but some studies imply that the diet may have a positive impact in health and well-being in these patients also [47, 52, 53 125]. Still, data suggest that screen-detected patients without symptoms may experience the diagnosis of CD more negatively than patients having symptoms[48, 53]. This would suggest that early detection of CD by mass screening in a healthy adult population would not unequivocally result in self-perceived health gain. Furthermore, data on long-term treatment in screen-detected patients is

scarce[52, 64]. These issues call for comprehensive studies before implementation of large-scale CD screening programs.

Cost-benefit of screening

VII. That testing and treatment is cost-effective. As has been outlined above the likely benefit or even the potential harm to undetected coeliac patients from screen detection is as yet poorly defined. In addition symptomatic undiagnosed CD and diagnosed CD are both likely to confer increased costs to the individual patient and to society, but these costs are shared differently in different countries. Determining whether screening and detection of asymptomatic CD will lead to health gains at an acceptable cost or even to economic benefits is therefore extremely difficult. A number of studies have however been conducted in this area. Some of these consider only the costs of detecting a new case by varying screening strategies, or apply only to specific high risk groups, and there are very few which have attempted to model both costs and health benefits to determine the cost of gaining a quality adjusted life year (QALY), and only three of these refer to general population screening. In a UK context perhaps the most influential of these papers to date has been the HTA (Health Technology Assessment) sponsored study by Dretzke *et al*[132] (the only such study considered in the development of the current UK national guidelines, and one specifically looking at newly diagnosed type I diabetic children). This study found that serological testing followed by confirmatory biopsy and treatment with GFD provided additional QALYs at an incremental cost of between £12,250 and £20,160 when performed in children with newly diagnosed type 1 diabetes. To derive these estimates the authors assumed among other things that untreated asymptomatic CD would cause the loss of 4 years of life, and reduce quality of life from 88% of optimal (the assumed baseline for treated disease) to 82% of optimal. Another prominent analysis by Hershcovici *et al* has examined the cost effectiveness of mass screening. This paper found that the cost for each QALY gained through mass CD screening is about 49,000 USDs (Table 3).[133] However, it is

important to note that this cost, and the conclusion that mass screening in young adults is cost-effective is again based on a number of assumptions. The authors of the Hershcovici *et al* paper assumed that the standardized mortality ratio was 1.6 in patients with symptoms ("undiagnosed"), and 1.1 in patients on a GFD ("diagnosed").[133] However, most studies on mortality in diagnosed CD have found relative risks of deaths of around 1.3-1.4 [8, 104] (and in a Swedish study,[8] it was estimated that 83% of patients adhered to the diet). Hence, with a smaller gap between the mortality risk estimates between diagnosed and undiagnosed coeliac patients, mass screening may not be cost-effective. This is well illustrated by the study by Shamir *et al* (Table 3)[134], which though finding on an assumption of an SMR of 1.6 for undetected disease, screening to be cost effective, showed in a sensitivity analysis that if the SMR fell to 1.3 then the cost per QALY rose to over $100,000. Cost-effectiveness analyses are also dependent on degree of adherence to a GFD, and where Hershcovici *et al* assumed a dietary adherence of 80% in patients with symptomatic CD, [133] others have found the lowest dietary adherence in screen detected asymptomatic patients .[49] Finally, cost-effectiveness is dependent on duration of symptoms before diagnosis. Hershcovici *et al* reported that mass screening would be effective if diagnostic delay was 6 years of more. With increased awareness of CD, diagnostic delay is likely to decrease. At present, some studies suggest that the delay is ≥6 years[80, 85] but others that it is less (4.9 years[135]). Finally Park *et al*[136] recently compared two different strategies to prevent bone loss and fractures in patients with undiagnosed or subclinical CD. Their study found that symptomatic at-risk screening was more cost-effective than universal serological screening. Though again the assumptions of their base model can be challenged, they found that screening of symptomatic and high risk subjects was a dominant strategy when compared to universal screening producing greater QOL gains at lower cost. Furthermore this strategy remained the more cost effective option when testing the sensitivity of the model to variation in their assumptions.

We conclude that more data on the cost-effectiveness of mass screening for CD in the general population is needed.

When and how often should we screen?

It should be clear to all that for so common a disease as CD, and with so successful a therapy as GFD, any patient with symptoms that might be due to CD should be tested. In this paper however we are primarily concerned with the asymptomatic. For them as should be clear from the forgoing we cannot point to definite benefit from the detection of CD (either in the reduction of symptoms – since they have by definition none, or an increase in the quality or the quantity of life). Furthermore, unlike in congenital diseases such as congenital hypothyroidism where screening once is enough to rule out disease, CD can start at any age, and having a negative CD serology test does not rule out future CD.

With regard to the second of these issues, there is at least one CD screening method with an exceptionally high negative predictive value: HLA-screening. Patients with a negative HLA will not develop CD and one strategy to avoid repeated CD screening is to first perform an HLA test. One drawback of HLA screening is its extremely low positive predictive value (PPV)(1 in 25 DQ2-DQ8 individuals will develop CD, i.e. the PPV is around 4%), while giving the patient and his/her physician the impression that the patient is "positive for CD".

No simple work around exists however for the lack of clear evidence of the benefit of screen detection. It is not unreasonable to assume however that there is a marginal benefit of such detection (as has been assumed in the cost efficacy studies of screening previously discussed), and any such benefit is likely to be greatest in high-risk groups where the PPV of a positive screening test will be greatest. On this basis therefore it is generally assumed that the screening of high-risk groups is reasonable, but direct evidence for this is lacking at present in almost all cases.

Special circumstances – High risk groups

First-degree relatives

The prevalence of CD in first-degree relatives is around 10%,[16, 137, 138] with significantly higher prevalence figures in monozygotic twins, families with multiple affected or siblings who share the HLA susceptibility alleles.[139]

Type 1 diabetes

Up to one in three DQ2+ individuals with type 1 diabetes expresses TTG.[140] Type 1 diabetes is also one of the most common autoimmune diseases in patients with CD, [92] and the relative risk for future type 1 diabetes in patients with CD has been estimated at 2.4.[141] Of note, that relative risk is almost identical to the future risk of type 1 diabetes in whites who are DQ2,[142] suggesting that the increased risk of type 1 diabetes may not be affected by dietary adherence.

Between 2% and 12% of all type 1 diabetes patients have CD.[16, 99, 143, 144]

Down syndrome and Turner syndrome

Although, most studies so far have been small, the prevalence of CD seems to be increased in both Down syndrome[148-150] and Turner syndrome[151, 152]. The only direct analysis of screening cost effectiveness in either of these conditions of which we are aware is the one by Swigonski *et al*.[153] This study though it focuses on the prevention of lymphoma, does also address the total number of QALYs resulting from a screening strategy in this group. It is notable in suggesting that screening

causes a reduction in QUALYs, and though this is based on the assumption that having to eat a GFD represents a 1% reduction in QOL, that assumption is perhaps no more unreasonable than any of those considered in the analyses of general population screening above.

Iron-deficiency anaemia

CD may cause iron-deficiency anaemia through malabsorption, but also through an ongoing inflammation and potentially also through occult bleeding[145 146]. CD is also more common in patients with iron-deficiency anaemia and gastrointestinal symptoms including IBS[147], and we suggest that both these risk groups undergo testing.

Bone mineralization disorders / Osteoporosis and osteomalacia

CD is associated with an increased risk of fractures,[154-156] with relative risks of around 2 for fractures after CD diagnosis. An earlier study found a similar relationship (Odds ratio around 2) for fractures prior to diagnosis in patients with CD.[156]

Discussion and Recommendations

There is an ethical difference between aggressive case-finding among the symptomatic, and screening for disease in the general population where a diagnosis of CD in asymptomatic individuals may not confer clear benefits. Decisions on screening therefore should be carefully considered. In this paper we have tried to review the pros and cons of mass screening for CD against the established WHO criteria for mass screening, and a summary of key-points in relation to screening is given in Table 4. Though CD meets many of these criteria, the outcome of undetected asymptomatic disease, the effect upon the life expectancy and quality of life with GFD in these patients and therefore the cost efficacy of screening remains unclear. Screen-detected CD will have economic implications, leading to both higher and lower costs, for different actors, and whether mass-screening is economically sound is dependent on a number of assumptions. Though studies to date assuming that GFD improves quantity and quality of life in the asymptomatic, and is itself cost free, suggest that screening may be cost effective, to achieve certainty we need more data to reduce the number of such assumptions which must be made.

Neither the current NICE guidelines[157] on recognition and assessment of CD, nor the corresponding British Society of Gastroenterology (BSG) guidelines[14] recommend mass screening for CD in the UK. Both guidelines do however recommend that serological testing for CD should be conducted in a wide range of clinical situations ranging from, the presence of potential symptoms of the disease (diarrhoea, failure to thrive (in children), gastrointestinal symptoms, prolonged fatigue, sudden or unexpected weight loss and anaemia), through the presence of associated conditions (autoimmune thyroid disease, dermatitis herpetiformis, irritable bowel syndrome or type 1 diabetes) to the presence of CD in a first degree relative.

Based on our literature review we suggest that screening of high risk groups may well be cost effective even if the benefit gained is small, however proof of such benefit is still lacking. We recommend that future research should provide data on the outcomes of undiagnosed and of treated asymptomatic CD.

In conclusion, we cannot recommend mass screening at the present stage. Though current diagnostic recommendations will only lead to the discovery of a minority of patients with CD, it is not yet clear that the detection of more would be of benefit to those detected.

Conflict of Interest

TC: Grant support: Coeliac UK: Crohn's and Colitis UK: Spouse is an employee of AstraZeneca.

DSS: has received an educational grant from Dr Schär (a gluten free food manufacturer) to undertake an investigator led research study on gluten sensitivity. Also has received an educational grant from both Biocard and Simtomax to undertake an investigator led research study on point of care tests

JAM: Consultant for Alvine inc, Bayer, Flamentera, ActiogeniX, Shire, grant support from Alba Therapeutics, Biocard.

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953 **Table 1. Summary of WHO criteria**

WHO Criteria	Valid in Coeliac disease	Comment
That the disease is common and well defined	++	There is an agreement that the disease occurs in about 1% or more of the Western population. Disease criteria have however been debated.
Screening tests are simple, safe and accurate	++	Screening tests with tissue transglutaminase have high sensitivity and specificity but the positive predictive value is well below 100%. However when combined with sequential endomysial antibody testing the positive predictive value increases.
The screening test should be culturally acceptable	+++	Only very rarely is screening not culturally accepted
Treatment is available	+++	A GFD is beneficial for both symptoms and mucosal injury, but may not protect against many future complications of CD
Clinical detection is difficult	+++	Symptoms and signs vary. Some individuals with CD are asymptomatic. Most people with CD remain undetected.
If undiagnosed and untreated the disease will lead to severe complications	+	Symptomatic patients will most often be relieved of symptoms. It is less clear if asymptomatic patients will benefit from clinical diagnosis and treatment with a GFD. It is not known if asymptomatic individuals are at risk of severe complications.
Testing and treatment is cost-effective	+	There is little research in this field, and existing research has often been based on the assumption that CD goes undiagnosed for many years. With increasing awareness of CD, diagnostic delay is likely to have decreased in recent years.

954 *CD, coeliac disease. GFD, Gluten-free diet*

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959 **Table 2. Quality of life (QoL) studies in screen-detected coeliac patients**

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Reference	***Country***	***Study design***	***No of screen-detected patients (asymptomatic)***	***QoL instrument***	***Main finding***
Mustalahti 2002 [125]	Finland	Prospective	19 (14)	PGWB	At diagnosis QoL similar to that in controls; QoL improved significantly after 1-year's GFD
Johnston 2004 [46]	UK	Prospective *	14 (ND)	SF-36	At diagnosis QoL similar to that in controls; no change after 1-year's GFD
Viljamaa 2005 [64]	Finland	Cross-sectional	53 (32)	PGWB, SF-36	After long-term GFD, QoL was comparable to controls
Korponay-Szabo 2007 [47] §	Hungary	Prospective *	32 (5)	Generic child health questionnaire	Global general health, bodily pain, general health perceptions, parental emotional impact lower than in controls; QoL improved after 1-year's GFD
Whitaker 2009 [48]	UK	Cross-sectional	51 (19)	Self-made questionnaire	A quarter of the asymptomatic screen-detected patients regretted being diagnosed
Van Koppen 2009 [52] §	Netherlands	Prospective *	32 (20)	TNO-AZL# DUX 25#, CDDUX#	Social functioning, problem behavior, anxiety, positive mood, liveliness affected in cases vs. control population. Improvement on GFD

Nachman 2009 [126]	Argentina	Prospective	(8)	SF-36	At diagnosis QoL similar to that in controls; no change after 3 month's GFD
Ukkola 2011 [53]	Finland	Prospective	146 (23)	PGWB	In all group, at diagnosis QoL was lower than that in controls; QoL improved after 1-year's GFD. In asymptomatic group QoL similar to that in controls at diagnosis; no change after 1-year's GFD
Nordyke 2011 [50] §	Sweden	Cross-sectional*	148	EQ-5D	Before diagnosis QoL in screen-detected CD similar to controls
Nordyke 2013 [158] §	Sweden	Prospective	103	EQ-5D	Screen-detected cases with unrecognized CD experienced similar QoL at diagnosis. On diet boys reported less pain
Myleus 2014 [159] §	Sweden	Cross-sectional	238	Kidscreen	Comparable HRQoL as their peers
Kurppa 2014 [55]	Finland	Randomized , prospective	40	PGWB SF36, VAS	Anxiety alleviated and perception of health improved in favor of GFD, but social functioning reduced in favour of gluten consumption

961 PGWB=Psychological General Well Being , GFD=Gluten free diet, SF-36=Short For-36. ND=No
962 data.

963 # Quality of life scales. For an explanation, see the original paper by Van Koppen [52]

964 *Detected by mass-screening; other studies include patients detected by risk-group screening

965 § Study based on children and/or adolescents. All other studies were based on adults.

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Table 3. Cost effectiveness of mass screening for coeliac disease.

	Shamir et al [134]	Hershcovici et al [133]
Utility of life with untreated asymptomatic CD	100%	Irritable bowel syndrome 76% Iron deficiency anemia 73% All other presentation 100%
Utility of life on GFD	100%	98%
SMR for untreated asymptomatic CD	1.6	All assumed symptomatic. With SMR 1.6
SMR in GFD	1.1	1.1
Sensitivity of screening	85%	IgA TTG 95% IgG TTG 98.7%
Prevalence of CD	0.5%	0.9%
Specificity of screening	90% TTG 95% EMA	IgA TTG 98% IgG TTG 98.6%
Costs of screening from	2004 Medicare fees	2004 Medicare fees
Cost of GFD	Not considered	Not considered

EMA, Endomysial antibodies

GFD, Gluten free diet

SMR, Standardized Mortality Ratio

TTG, Tissue transglutaminase antibodies

Table 4. Key-points: Screening for CD

Coeliac disease occurs in about 1-2% of the Western population
The varied presentation makes the disease difficult to diagnose, and there are screening tools available
There are still few data on complications from undiagnosed CD
We recommend active case-finding, but not mass screening

Appendix

PubMed search Jan 1, 1900 until June 1, 2014. Number of hits searching for "(Coeliac or coeliac)" and the below terms.

Additional term	***Hits***
+ Prevalence*	3612
+ Definition	101
+Cultural	353
+Treatment *or* gluten*	141912
+Sensitivity and specificity*	1376
+Diagnostic delay	157
+undiagnosed and (complications or comorbidity)#	123

E.g. PubMed search:

** Abstracts and/or titles not examined in detail.*

Example of search strategy: ((coeliac or coeliac) and undiagnosed and (complications or comorbidity)) AND ("1900/01/01"[Date - Entrez] : "2014/06/01"[Date - Entrez])