UK National Screening Committee

Screening for Coeliac Disease in Adults

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

Summary

There is insufficient new evidence to support the establishment of a screening programme for coeliac disease in adults in England.

1 Introduction

Coeliac disease

A review undertaken by Dr David Sanders on behalf of the UK National Screening Committee (NSC) in 2008 determined that screening for coeliac disease in adults should not be supported by the NSC due to; the lack of clear understanding of the natural history of individuals with coeliac disease, a lack of evidence on early recognition being beneficial, financial limitations that had not been considered in the cost-effective models, the lack of evidence that patients detected by screening would adhere to a gluten free diet and the lack of literature showing the acceptability of the test to histologically confirm the diagnosis of coeliac disease.[1]

This review will build upon the previous review in a selective criteria review format, focussing on the criteria identified as unmet or only partially met in the previous 2008 review. These included natural history, prevalence, diagnosis, treatment, and services. Using these criteria a literature search up to March 2013 on coeliac disease since the last review of literature in 2008 was undertaken, and combined with the previous review to assess the key, highlighted areas against the UKNSC criteria.[2] 329 additional papers in English were retrieved. 24 were considered relevant. Several more papers were accessed through cross referencing and reference searching. No major UK trials have been undertaken during the period considered.

The aim of the review is to advise the UK NSC NSC on whether the literature published since 2008 warrants a larger, more detailed review to take place and whether the current policy recommendation should be retained.

2 The Condition

2.1 The condition should be an important health problem

2 2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Coeliac disease, also known as gluten sensitive enteropathy, is defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley or rye) in genetically susceptible individuals. According to the 2008 review[1] coeliac disease used to be considered an uncommon gastrointestinal condition[3,4] with an estimated incidence in the United Kingdom (UK)

in 1950 of one in 8000.[5] Clinicians recognised infant or childhood presentations with overt symptoms of malabsorption (or failure to thrive).

More recently there has been a shift in understanding about the disease and studies from Northern Ireland, Nottingham and Sheffield in the 1990s and early 2000s assessed the prevalence of coeliac disease as 1% in the adult population.[6-8] Cohort studies of healthy volunteers in Europe and the USA described the prevalence as 0.5-1%.[9,10] A European multinational study found differences between 0.6% in Germany to 2.4% in Finland. The same criteria for diagnosis were used.[11] The prevalence also appears to be rising although this may be due to better diagnosis in high risk groups, better testing and greater awareness of the disease as well as a true rise.[12-15] NICE guidance published in 2009; Recognition and Assessing Coeliac Disease concluded that; "In national studies in the UK, the prevalence of coeliac disease ranges between 0.8% and 1.9%.[16] This is broadly similar to other international studies. Among first-degree relatives of people with coeliac disease, the majority of studies report a prevalence of coeliac disease between 4.5% and 12%. There is limited evidence that the prevalence of coeliac disease is twice as high in females as in males."

Adult presentations are now more frequent than paediatric (9:1 Coeliac UK National Patient Charity – membership data 2005) with the commonest age for presentation being during the 5th decade.[17,18] Patients with adult coeliac disease rarely present with malabsorption but usually describe non-specific or subtle gastrointestinal symptoms (for example, non-specific abdominal pain, irritable bowel type symptoms or even upper gastrointestinal symptoms). A substantial proportion of patients present with extra-intestinal manifestations. The 2008 review also described the "coeliac iceberg" of people with potential, latent and atypical coeliac disease for whom the natural history and role of treatment is not at all clear.[1]

Publications in 2012[19-21] outline three types of gluten related disorders. Coeliac disease which is an auto immune disease, one of allergic origin and the third which is immune mediated. This has resulted in a large increase in the adoption of gluten free diets.

Reactive coeliac disease is defined as; diagnosed auto-immune coeliac disease with persistent or recurrent malabsorption and atrophy of the bowel villi despite 6 to 12 months of a strict gluten free diet. The true prevalence is unknown but it is rare. It is treated with steroids and immunosuppressive drugs. It is associated with complications and mortality.[22]

The natural history of coeliac disease remains unclear. Mortality is increased but the extent is still contested. In a study published in 2009 in individuals who are diagnosed with coeliac disease there was an increased hazard ratio for risk of death compared to the general population; coeliac disease of 1.39; (95% confidence interval [CI], 1.33-1.45; median follow-up, 8.8 years), those with inflammation 1.72 (95% CI, 1.64-1.79; median follow-up, 7.2 years), and those with latent disease an HR 1.35 (95% CI, 1.14-1.58; median follow-up, 6.7 years). The absolute mortality rate was 10.4 (95% CI, 10.0-10.8) per 1000 person-years in coeliac disease, 25.9 (95% CI, 25.0-26.8) in inflammation, and 6.7 (95% CI, 5.7-7.6) in latent coeliac disease. Excess mortality was 2.9 per 1000 person-years in coeliac disease, 10.8 in inflammation, and 1.7 in latent coeliac disease. This risk increase was also seen in children. Excluding the first year of follow-up, HRs decreased somewhat.[23]

It is still considered that many cases of coeliac escape diagnosis and are exposed to the risk of long-term complications such as infertility and lymphoma but that these complications are less frequent than previously reported.[21] A study of 6,987 Finnish adults drawn in 1978-80 stated that the prognosis of unrecognised coeliac disease was good with regards to overall mortality and did not support screening to detect asymptomatic coeliac disease.[24] Rubio-Tapia have the longest follow up study of 45 years and they suggest that there is a 4 fold increase in risk in death of undiagnosed coeliac disease. However, this study was in young males, had wide confidence intervals (95% CI 2-7.5) and the number of cases, 15 was very low.[14] Even where there is an excess risk of death in undiagnosed cases, which would be the cases that could benefit from screening, comparison to the risk in diagnosed cases suggests that the benefit of screening would be questionable.

There is evidence that undiagnosed maternal coeliac disease has a negative effect on intrauterine growth and birth weight, and is associated with increased preterm birth and caesarean section rates. Evidence suggests an association between undiagnosed coeliac disease and an increased risk of fractures. Undiagnosed coeliac disease is associated with an increased risk of non-Hodgkin's and Hodgkin's lymphoma and small bowel cancer, but overall rates are low."[25]

Conclusion

Coeliac disease is a relatively common disease in the adult population in the UK. The full natural history and clinical course of undiagnosed (the cases that would be identified by screening) and thus untreated populations are poorly understood.

2.3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

To date there are no interventions for the primary prevention of coeliac disease. However, a study led by Alessio Fasano at the University of Maryland,looking at the impact of delaying the introduction of gluten into the diet of babies who are at risk of coeliac disease and identifying if this will protect them, in part at least, from developing the syndrome, is due to report in 2017.[26]

3 The Test

3.1. There should be a simple, safe, precise and validated screening test.

3.2. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

3.3. The test should be acceptable to the population

NICE guidance for recognition and assessment of coeliac disease advises that serological testing for IgA tissue transglutaminase (tTGA) is the first-choice test. Although this was for diagnosis of patients with clinical symptoms or who are considered to be at high risk for the disease, this is the best review of testing for coeliac disease available.[25] They concluded that IgA tTGA and IgA EMA serological tests show high levels of sensitivity and specificity in the diagnostic process for coeliac disease and that combination testing with IgA tTGA and IgA EMA did not appear to substantially improve accuracy in the diagnostic process. These were studies looking at people

with suspected coeliac disease and likely to be of limited usefulness in the screening context. Newer tests for deamidated gliadin were considered to have potential but required further evaluation as did point-of-care tests and self tests.

A Spanish study published in 2009 tested 1868 healthy people via an occupational health department for tTGA and EmA. If the blood test was positive: duodenal biopsy, DQ2/DQ8 genotyping, clinical feature recording, blood tests, and densitometry were performed. Since over 98% of individuals had tTGA less than 2 U/mL, this value was established as the cut-off limit of normality. Above 2 U/ml was considered a positive test if confirmed twice in the same sample. Twenty-six of the 1868 individuals (1.39%) had positive markers for coeliac disease (18 males, eight females, mean age 37.7 ± 11.0 years). Of the 26 patients with positive markers, seven were positive for both EmA and tTGA, one was positive only for EmA, and the remaining 18 were positive only for tTGA. The sensitivity of EmA for gluten sensitive enteropathy (GSE) diagnosis was 46.6%, whereas the sensitivity of tTGA was 93.3% ($P = 0.04$). The sensitivity ratio demonstrated a two-fold sensitivity for tTGA compared with EmA to diagnose the whole spectrum of Gluten Sensitive disease.[27] This confirms the NICE guidance that tTGA is the serological test of choice.

Of the 26 patients with positive markers 21 underwent an intestinal biopsy, which disclosed the following histological findings: 6 Marsh 3, 9 Marsh I and 6 Marsh 0. Marsh pathological categorisation goes from Marsh 0 no pathology to Marsh 4 the worst level of histological disease. Thus, 0.80% of subjects initially tested had a biopsy proven lesion of the gluten sensitive spectrum (1:125) and 0.32% had villous atrophy (1:312) but all had low Marsh scores and thus limited disease histologically. All Marsh 3 patients were positive for both EmA and tTGA All Marsh I, 2 and 3 patients had tTGA values higher than 2 U/mL but lower than the cut-off recommended by the manufacturer of 8 U/mL. This suggests that tTGA does relate to the level of intestinal damage and a sharp fall off of sensitivity in milder forms of the disorder. Thus the researchers suggested a normal cut off point of 2 U/mL rather than that advised by the manufacturer of 8 U/mL.[27] There was no follow-up of any missed cases. The study does not indicate if any of the people screened were on a gluten free diet. It is possible that some people self diagnose gluten allergy and take up a gluten free diet by choice. The blood test would be negative and cases could be missed. Requiring those screened to be on a gluten diet for at least six weeks prior to the test may reduce the acceptability of the test. There is limited evidence on this.

Lewis et al in 2010 published the results of a meta-analysis of deamidated gliadin peptide antibody and tissue transglutaminase antibody as screening tests for coeliac disease. They concluded that IgA-tTG should be used where the probability of coeliac disease is low. This would be the case in a screening context.[28]

Conclusion

The present screening test of choice is the serological test tTGA. There is evidence that it is sufficiently sensitive for screening purposes but this requires further investigation in the screening context. This was also the conclusion of Sanders.[1] The cut off point for screening is not agreed.

3.5. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

The NICE guidance for the diagnosis of patients with clinical symptoms includes an algorithm which is relevant to the screening context. The guidance states that after a positive blood test for coeliac disease those identified should be referred to an intestinal specialist for intestinal biopsy. This is an invasive procedure which may not be acceptable to non symptomatic people and may reduce the acceptability of the screening test.

NICE identifies a number of areas for further research including: Whether a repeat serological test might be performed before biopsy, and if so how often, how reliable serological tests are compared to intestinal biopsy, how many people with coeliac disease are misdiagnosed and what the implications are of misdiagnosis.[29]

Lewis et al suggested that "future research may also include a diagnostic randomized trial comparing the costs of different diagnostic strategies and their effects on treatment decisions and subsequent patient outcomes, including symptoms and signs, quality of life, and the consequences of false-negative and false-positive test results."[28]

NICE guidance for diagnosis of clinically suspected cases of coeliac disease is presently being reviewed.[30]

Conclusion

There is an agreed policy of diagnosis of patients presenting with clinical symptoms which would be relevant, but might need additional steps to reduce invasive interventions and avoid non compliance from people identified as positive when screened but who are asymptomatic.

4. The Treatment

4.1. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

4.2. There should be agreed evidence- based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

NICE advice (last updated May 2010) on the treatment of coeliac disease is for a gluten free diet that is healthy and nutritious.[29] Pure uncontaminated oats can be included when the gluten free diet has been well established as some people may be additionally sensitive to oats. The guidance does not include evidence on new or experimental treatments (such as enzyme therapy, wheat that has been genetically engineered to be free of the peptide sequences that cause coeliac disease, selective inhibition in the small intestine of tissue transglutaminase and correction of intestinal barrier defects).[31,32]

An Australian review of the evidence on treatment in 2008 states that; a gluten-free diet is an effective treatment for coeliac disease but the goals of long-term management of patients are poorly defined.[33]

A major concern is the ability of patients to keep to a gluten free diet. This may be due to issues such as; the cost of obtaining gluten free products, difficulty in identifying if food is gluten free, dislike of gluten free foods or unwillingness to accept the hassle of managing one's diet. A case control postal survey of 573 people, of whom 225 were confirmed coeliac disease patients and 348 age and sex matched controls, found 65 percent full adherence to a full gluten free diet with 31 percent partial adherence and 4 percent non-adherence. The survey was administered from Leeds University. However, 80 percent of those on a gluten free diet reported difficulty adhering to it. There were negligible differences in quality of life scores when comparing full versus partial/non gluten free patients (P=>0.05). There was a stepwise reduction in quality of life and increasing likelihood of anxiety/depression associated with increasing degrees of difficulty adhering to the diet(P=<0.0001). Demographic assessment suggested that an affluent background and a university education promotes greater gluten free diet adherence.[34]

In the 2009 Spanish study almost 70% of subjects with positive serology adhered to the follow-up program, which included a gluten free diet. The authors acknowledged that adherence has been reported by different studies and ranged from less than 10% (4) to 90%. They suggested that adherence is highly dependent on the patient-doctor relationship and confidence. They also comment that; "adherence in this and other studies of coeliac disease detected by screening is similar to or better than that reported for other diseases, such as hypercholesterolemia or coronary heart disease, in which specific diets or changes in lifestyle are required to prevent life-threatening complications."[27]

In the same study 18 of the 26 positive cases accepted follow-up. This is a 69.2% adherence to the mass-screening program, with a mean follow-up of 28 months (range, 20 to 33). Overall, nine of 10 patients (90%) (5 Marsh 3 and four Marsh I) had a complete histological and/or serological response to a gluten free diet. A dramatic clinical improvement was observed in both Marsh I and Marsh 3 patients; response was complete for two of the 10 patients (one Marsh 3 and one Marsh I) and partial for five (three Marsh 3 and two Marsh I). The main reason for Marsh I patients' adherence to the diet was the presence of osteopenia (thinning of the bones) (four of five Marsh I patients) which is caused by malabsorption and is a symptom of coeliac disease. In contrast, osteopenia was only diagnosed in one Marsh I patient of the four who did not follow a gluten free diet. No differences were found for either the number or the severity of symptoms between patients who followed a gluten free diet and those who did not. At the end of follow-up, those patients who followed treatment showed an improvement in the mean value for all symptoms. This was statistically significant for distension (P = 0.014), flatulence (P = 0.028) and abdominal pain (P = 0.007).[27]

The case for a dietary treatment of screen detected and thus mainly asymptomatic people is less clear and there is no clear evidence of health gain.[35,36] Adherence to diet by screen detected people was reported to be between 79 and 91 percent compared to 85 percent in symptom detected people.[35,37]

Conclusion

A gluten free diet is the treatment of choice. It is adhered to best by patients with clinical symptoms that respond to the diet. Adherence is related to education and affluence. The health gain for treating people identified by screening with a histological diagnosis but with no clinical symptoms remains unclear.

4.3. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme

Sanders identified that within the NHS there is a lack of appropriate dietetic services for coeliac disease patients.[1] There is no new evidence on this issue.

5. The Screening Programme

5.1. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high- quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened

5.2. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

The 2008 UK NSC review of the case for screening for coeliac disease concluded that coeliac disease "did in many ways fulfil the World Health Organisation criteria for screening but the real/actual benefit of population screening remains questionable." This was because of; a lack of knowledge of the natural history of undetected cases of coeliac disease, financial limitations due to the lack of support services for patients after the diagnosis and the lack of evidence on whether patients detected through screening programmes would adhere to a gluten-free diet. The alternative approach of active case-finding was considered to be a way of increasing information on which the case for screening could be decided.[1]

The Spanish team[27] suggest that their study showed that all the cases with abnormal histological findings also had clinical features related to the disease. Thus, they consider that a screening programme would not identify people with coeliac disease without symptoms. They felt that their study did not provide evidence about the adherence to a gluten free diet of people identified without symptoms. They considered that the study provided a strong argument for case finding of symptomatic patients as a viable alternative to screening. They also concluded that; "coeliac disease in the general population is frequent and is clinically relevant, irrespective of the severity of the histological lesion. Mass screening programs are useful for identifying

these patients in order to initiate either a gluten free diet or close follow-up monitoring."[27] The study was of a population who were all of working age and were followed up by the Catalan Coeliac Society. These conditions may not be applicable to a less well defined UK population being followed up in an NHS gastroenterology services.

The issue of whether to screen or not for coeliac disease is one that gastroenterological experts debate periodically. In 2009 Alessio Fasano, Director for the University of Maryland Centre of research for Coeliac disease made the case for screening. Fasano considered screening to be a good public policy because: the disease is prevalent, early clinical detection is difficult because the disease manifests itself at different ages and with a wide range of symptoms, tests are highly sensitive and specific, screening is cost effective, there is an effective treatment and untreated disease can lead to complications.[38]

In 2012 the specialist team in Sheffield suggested in a review that; coeliac disease is common and that for every one patient diagnosed eight are not and that treatment enhances quality of life and reduces complications but that; the test is not 100% sensitive and specific, there is no evidence that patients with milder disease benefit from treatment and screening take up would be low and diet adherence poor.[39]

They considered that screening would diagnose too many people and make any cost effectiveness arguments for screening invalid. However, they did support case finding in primary care with a low threshold for serological testing as the sensitivity and specificity of diagnostic testing is higher in at risk populations. They proposed a large, European, prospective, multicentre study to assess the benefits of mass screening longitudinally to clarify an optimum screening strategy.[39]

As screening would primarily be focussed on detecting non-symptomatic people and as the disorder can start at any point in life there is no clear age when screening should occur, nor how often it should be undertaken.

Conclusion

There is insufficient new evidence on the natural history, the positive benefits of screening and an appropriate testing strategy to change the conclusions of the 2008 review recommending against a UK screening programme for coeliac disease in adults.

5.6. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

A 2010 cost effectiveness study of mass screening, using data from primary care in the US but undertaken in Israel, examined the cost-effectiveness of mass screening for coeliac disease in young adults compared to no screening.[40] The analysis was based on a state-transition Markov

model, with a lifetime horizon. The authors stated that the perspective of the third-party payer was adopted. A systematic review of the literature was undertaken using MEDLINE database to identify the relevant data. The projected costs were $24.94 with no screening and $158.64 with screening. The corresponding QALYs were 26.9031 and 26.90579. The incremental cost per QALY gained with screening over no screening was $48,960 (£32,961 at 09/07/13 exchange rates). The most influential inputs were the time from onset of symptoms to diagnosis of coeliac disease, the utility of treated coeliac disease, and the prevalence of coeliac disease. At a threshold of $50,000 per QALY screening was not considered cost-effective with a time to diagnosis of less than 5.9 years (6 years in the base case), or with a utility for treated coeliac disease of less than 0.978 (0.98 in the base case). The acceptability curve showed that the probability of screening being cost-effective was 60%. The authors concluded that mass screening was cost-effective, but shortening the time from symptoms appearing to diagnosis by increasing the awareness of medics and instituting active case finding, could reduce the value of screening. This paper also assumed that the standardised mortality ratio was 1.6 for patients with symptoms but undiagnosed and 1.01 for patients on a gluten free diet. However, most studies state a relative risk of mortality of 1.3 to 1.4 making the case for screening less cost effective.

The Centre for Reviews and dissemination at York University reviewed the study and considered that the study had been undertaken along conventional guidelines but that there was little detail of the studies used to derive the data and that the studies had been carried out in several countries. They considered the analysis consistent with the perspective of the third-party payer.[41]

A study published in 2006, also from Israel using US data, suggested that mass screening was only cost effective in populations with a “relatively high prevalence” and if the standard mortality of those not treated was higher than 1.5. They do not say what a relatively higher prevalence would be nor provide the evidence that there is a raised mortality for non-treated coeliac disease patients.[42] Sanders suggests that the most contemporary study in the UK (2004) gave a hazard ratio of 1.3 for patients with coeliac disease which may be even lower for less active cases of the disease.[1] This remains the only UK based such study.

5.7. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost- effective intervention could be introduced or current interventions increased within the resources available.

Case-finding in general practice and relevant medical specialities is potentially a more cost-effective option. There have been no RCTs comparing the two models.

5.8. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

This would be developed as a screening programme was established.

5.9. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

Sanders identified that within the NHS there is a lack of appropriate dietetic services for coeliac disease patients.[1] There is no new evidence on this issue.

5. 10. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

This would be developed if a screening programme was established.

6. Conclusions

There is insufficient new evidence to warrant changing the current policy not to recommend or to warrant undertaking a larger, more detailed review on coeliac disease at this time.

6.1. Implications for policy

Coeliac disease is a common disorder with considerable implications for quality of life. Enhanced training of general practitioners and physicians and a lower threshold for serological testing for coeliac disease could shorten the time between the development of clinical symptoms and treatment. Active case finding is potentially a more cost effective alternative to screening.

6.2. Implications for research

Consideration should be given to undertake an RCT into the outcomes of screening for coeliac disease.

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