COELIAC DISEASE The debate on coeliac disease screening-are we there yet?

ARTICLE *in* NATURE REVIEWS GASTROENTEROLOGY &#38 HEPATOLOGY · JULY 2014

Impact Factor: 12.61 · DOI: 10.1038/nrgastro.2014.119 · Source: PubMed

2 AUTHORS, INCLUDING:

Alessio Fasano
Massachusetts General Hospital
399 PUBLICATIONS **12,630** CITATIONS

SEE PROFILE

COELIAC DISEASE

The debate on coeliac disease screening—are we there yet?

Carlo Catassi and Alessio Fasano

The majority of patients with coeliac disease are undiagnosed, leading to debate about the utility of screening. The heterogeneous clinical presentation, which includes asymptomatic forms, can partially explain the difficulties faced when identifying coeliac disease. Now, Kurppa and colleagues add another element to the debate by strengthening the arguments for general screening.

Catassi, C. & Fasano, A. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 8 July 2014; doi:10.1038/nrgastro.2014.119

The long-standing debate on the pros and cons of serological screening for coeliac disease will be fuelled further by a recent study by Kurppa and colleagues.[1] The researchers screened 3,031 at-risk family members of patients with coeliac disease, which identified 148 people who had asymptomatic coeliac disease (positive for endomysial antibodies). Of these patients, 40 were eligible to participate in the next stage of the study and were randomly assigned to either continue a regular, gluten-containing diet (controls) or to start treatment with a gluten-free diet (GFD); at 1 year, the control patients were offered a GFD and were evaluated again after another year. After the first 1-year follow-up, patients on the GFD, as expected, showed an improvement in intestinal morphometry values and reduced serum levels of antibodies associated with coeliac disease compared with untreated patients. Furthermore, the GFD group also had reduced gastrointestinal symptoms and anxiety as well as an improved perception of their own health (on the basis of the visual analogue scale). Only social function scores improved more in the group on the gluten-containing diet compared with those on the GFD. Most of the parameters described above improved when patients in the group on the gluten-containing diet were later switched to the GFD. Kurppa and co-workers concluded that apparently asymptomatic patients with coeliac disease benefit from serological screening and subsequent GFD, and that their results support active screening of people who are at risk of coeliac disease.[1]

This Finnish study provides a missing piece in the coeliac disease puzzle. Although the connection between coeliac disease and gluten was established almost 65 years ago, this study is the first randomized, controlled trial to provide evidence that treatment with a GFD is associated with a multidimensional improvement in the histological, serological and clinical features of coeliac disease. Despite some limitations of the trial, particularly the small sample size and the lack of blindness upon the intervention, this study carries a strong message. That is, so-called 'silent' cases of coeliac disease (a considerable proportion of patients detected by serological screening) are often patients who are accustomed to living with a bad health status, which can be improved by treatment with a GFD. This finding removes one of the major conceptual obstacles to serological screening for coeliac disease, both in at-risk groups (for example, people with a family history of coeliac disease) and the general population—the ethical argument of 'no return on investment' for apparently healthy patients with coeliac disease. The long-term benefits of treating patients with coeliac disease detected after screening, however, remain unclear. The benefits are particularly unclear with regard to the prevention of complications (such as the risk of lymphoma-related mortality) and the general quality of life, which can be negatively affected in treated adult women in the long term (the effect was not seen in men).[2]

In addition to the data from Kurppa and colleagues, a more favourable attitude toward mass screening for coeliac disease is now being found for many other reasons. Firstly, the case-finding process (looking for the disease in at-risk groups only) is cheap and ethically sound, but has proven to be a poorly effective strategy for detecting undiagnosed coeliac disease in the wider population. For example, the proportion of clinically detected coeliac disease remains <30% in countries with high disease awareness, such as Norway,[3] and might be critically low in developing countries. In India, only a few thousand cases of coeliac disease have been detected out of the estimated 5–10 million affected individuals.[4] Secondly, the increased prevalence of gluten-related disorders (not only coeliac disease but also noncoeliac gluten sensitivity)[5] is contributing to the breakdown of barriers against the GFD, with the consequence that gluten-free food is more easily available at lower prices than previously. The public attitude toward the GFD is also favourably changing over time.

> "...their results support active screening of people who are at risk of coeliac disease"

Interestingly, a Swedish survey of patients with screening-detected coeliac disease and their families that was published in 2011 showed that the most common opinion among both affected adolescents and their parents was that future mass screening for coeliac disease should be "a right for everyone" and should be offered as early as possible.[6] At what age should a general screening program for coeliac disease be performed? New data on the natural history of gluten sensitization sheds light on this previously unanswered question. In a cohort of newborn babies from families at risk of coeliac disease who were prospectively followed from birth, it was found that the majority of participants who developed coeliac disease had evidence of autoimmunity within the first 5 years of life.[7] Although gluten sensitization might occasionally take place at any age,[8] these results suggest that an efficient screening

programme for coeliac disease might be carried out by testing school-age children (for example, at the age of 6 years). One country has introduced mass screening for coeliac disease during childhood. Since 1993, the San Marino Republic (32,538 inhabitants) has performed general coeliac disease screening in children when they enter primary school (age 6 years), at low cost and with a positive response from the population.[9] The screening program led to increased disease awareness among doctors and to the general education of people about coeliac disease. The program also resulted in people volunteering for screening; non-symptomatic relatives of affected children were often investigated and diagnosed with coeliac disease.[9]

In Figure 1, we propose an updated strategy of population screening for coeliac disease. As HLA-DQ2 and/or HLA-DQ8 genotypes are a necessary component of the development of coeliac disease, determination of HLA genotype is recommended as the first-level test, in order to exclude a considerable proportion of the population (~60–70%)[10] from further testing. These days, HLA determination can be performed at birth with a single drop of whole blood dried on filter paper. Currently available methods enable a cheap yes/no determination, without any further characterization of single HLA genes in negative cases. In Western countries, the expected prevalence of coeliac disease in HLA-positive children is 2.5–4.5%,[10] that is, in the same range seen in at-risk groups (such as patients with type 1 diabetes) that are usually screened for coeliac disease. In these selected cases, serological screening with the IgA class anti-transglutaminase antibody could be performed at school entry or before in clinically suspected cases. Further serological testing might be required later in life, particularly in symptomatic patients and/or at-risk groups.

We are aware that several arguments against coeliac disease screening still exist, particularly economic considerations. Nevertheless, in our view it is time to reconsider a more active policy of serological coeliac disease testing, for example, performing the anti-transglutaminase antibody determination at least once in children undergoing blood testing for any reason. After all, as the sinking of the *Titanic* dramatically showed, it is the submerged part of the iceberg that might cause major disasters.

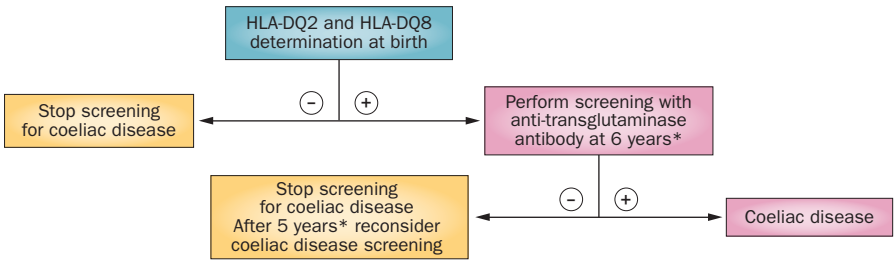

Figure 1 | A proposal for an updated screening algorithm for coeliac disease in the general population. *Repetition of serological screening might be anticipated in patients with symptoms of suspected coeliac disease.

*Department of Pediatrics, Università Politecnica delle Marche, via F. Corridoni 11, 60123 Ancona, Italy (**C.C.**). Division of Pediatric Gastroenterology and Nutrition and Center for Celiac Research, Massachusetts General Hospital for Children, and Celiac Program, Harvard Medical School, 175 Cambridge Street CPZS-574, Boston, MA 02114, USA (**A.F.**). Correspondence to: C.C.*
catassi@tin.it

Competing interests
C.C. is a consultant for Dr Schaer and Menarini Diagnostics. A.F. is a co-founder and stock holder in Alba Therapeutics.

1. Kurppa, K. *et al.* Benefits of a gluten-free diet for asymptomatic patients with serologic markers of celiac disease. *Gastroenterology* http://dx.doi.org/10.1053/j.gastro.2014.05.003.
2. Hallert, C. *et al.* Living with coeliac disease: controlled study of the burden of illness. *Scand. J. Gastroenterol.* **37**, 39–42 (2002).
3. Størdal, K., Bakken, I. J., Surén, P. & Stene, L. C. Epidemiology of coeliac disease and co-morbidity in Norwegian children. *J. Pediatr. Gastroenterol. Nutr.* **57**, 467–471 (2013).
4. Makharia, G. K. *et al.* Issues associated with the emergence of coeliac disease in the Asia–Pacific region: a working party report of the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology. *J. Gastroenterol. Hepatol.* **29**, 666–677 (2014).
5. Sapone, A. *et al.* Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med.* **10**, 13 (2012).
6. Rosén, A. *et al.* Mass screening for celiac disease from the perspective of newly diagnosed adolescents and their parents: a mixed-method study. *BMC Public Health* **11**, 822 (2011).
7. Lionetti, E. *et al.* Prevalence and natural history of potential celiac disease in at-family-risk infants prospectively investigated from birth. *J. Pediatr.* **161**, 908–914 (2012).
8. Catassi, C. *et al.* Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. *Ann. Med.* **42**, 530–538 (2010).
9. Alessandrini, S., Giacomoni, E. & Muccioli, F. Mass population screening for celiac disease in children: the experience in Republic of San Marino from 1993 to 2009. *Ital. J. Pediatr.* **39**, 67 (2013).
10. Megiorni, F. *et al.* HLA-DQ and risk gradient for celiac disease. *Hum. Immunol.* **70**, 55–59 (2009).