Best Practice & Research Clinical Gastroenterology 29 (2015) 493–501

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

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The prevention of coeliac disease

M.Luisa Mearin, MD, PhD, Associate Professor of Paeditrics, Paediatric Gastroenterologist *

Dept. of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands

Keywords:
Coeliac disease
Prevention
Early nutrition
Breast feeding
Screening

A B S T R A C T

Primary prevention of coeliac disease is currently not possible. Previously, a 'window of opportunity' was suggested for primary prevention, by introducing gluten between four and six months of age. However, results from recent prospective studies establish that the timing of gluten introduction and the duration or maintenance of breastfeeding do not influence the development of the disease. Secondary prevention is possible through early diagnosis and treatment. Since coeliac disease is severely underdiagnosed, the only way to achieve large-scale secondary prevention is by mass screening. Prospective studies indicate that important health problems, such as reduced foetal growth and birth weight, delayed growth in height and weight in children, and reduced bone mineral density in both children and adults can be prevented by mass screening. Adherence to a strict gluten-free diet may be considered as tertiary prevention.

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Coeliac disease (CD) is a common but frequently unrecognized disease, partially because of its variable clinical presentation and symptoms that range from malabsorption with chronic diarrhoea, poor growth in children, abdominal distension and weight loss, to nonspecific signs and symptoms like fatigue, osteoporosis or iron deficiency anaemia [1]. Extra-intestinal symptoms such as arthritis or neurologic manifestations are also frequent [2,3]. In addition, CD may be asymptomatic as in the case of 43% of the children identified by family screening [4]. For every child diagnosed with CD there are

* Dept. of Paediatrics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 5262824, +31 71 5262806; fax: +31 71 5248198.
E-mail address: M.L.Mearin_Manrique@lumc.nl.

http://dx.doi.org/10.1016/j.bpg.2015.04.003
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seven who have unrecognised, and therefore, untreated disease [5–7]. Screening studies have shown that CD has a frequency of 1%–3% among Europeans, corresponding to about five million people in the European Community. These studies further suggest that CD is the most common food intolerance in Europe and the USA [3,5,6,8,9]. CD increases the overall mortality risk [10], reduces the quality of life [11] and yields extensive negative economic consequences [12]. According to an estimate by the Dutch Celiac Disease Society (www.glutenvrij.nl) the necessary gluten-free diet results in an added cost of €1200–1300 per patient a year, corresponding to €6.0–6.6 billion in financial burden to Europe if all five million cases of CD were considered (www.CDEUSA.com). The patient's health status improves with a gluten-free diet, but primary prevention would even be more beneficial [13]. For these reasons, CD may be considered a public health problem [3,14]. Prevention is defined as any activity that reduces the burden of mortality or morbidity from disease, taking place at the primary, secondary or tertiary level [15]. Primary prevention avoids the development of a disease. Secondary prevention is aimed at early disease detection, thereby increasing opportunities for interventions to halt disease progression and the emergence of symptoms. Tertiary prevention focuses on reducing the negative impact of an already existing disease by restoring function and reducing disease-related complications.

Primary prevention

Primary prevention in CD implies that gluten tolerance is acquired, since CD patients do not develop it or lose it later on in life [16]. This hypo-responsiveness to dietary protein antigens in the intestine is a phenomenon termed 'oral tolerance' [17]. Animal experimental models have suggested possibilities for induction of gluten tolerance: intravenous or intranasal administration of multiple doses of gliadin to mice allowed down-regulation of the specific immune response [18]. Breastfeeding protected young inbred AVN strain rats from CD-like lesions [19]. Currently, however, primary prevention of CD is not possible. Previous retrospective studies suggested a 'window of opportunity' for primary prevention by introducing gluten between four and six months of age [20,21] during which breast feeding provided a protective effect [22]. Based on these results, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends that gluten should not be introduced before 17 weeks of age and not later than at 26 weeks, preferably concurrent with the period of breastfeeding [23].

Breastfeeding is an environmental factor that has been associated with the induction of oral tolerance [24]. Many studies have evaluated the role of breastfeeding and the risk of developing CD. A systemic review and meta-analysis which included all the studies published on this topic between 1966 and 2004 found that breast fed children had a 52% risk reduction of being affected by CD compared to those who were not breast fed during the time of gluten introduction [pooled OR 0.48; 95% CI: 0.40–0.59] [22]. Some studies on this topic reported CD prevention [22,25–27] while others did not [28,29]. A systematic review published by the PreventCD group (www.preventcd.com) showed that the principal difficulties in interpreting and comparing studies investigating the effect of early nutrition in the development of CD arise from the inability to randomise and blind such studies, their retrospective nature and its associated parental recall bias [30]. The best method to investigate the effect of environmental factors in the development of CD, nutritional or otherwise, is to perform prospective, randomised, placebo-controlled interventions among young children with long-term follow up. However, results from the recent prospective studies PreventCD, CELIPREV, MoBa, Generation R and TEDDY, establish that the timing of gluten introduction and the duration or maintenance of breast-feeding do not influence the development of CD [4,29,31–33].

PreventCD (Prevent Coeliac Disease) is an international, prospective, randomised, placebo-controlled interventions study among 994 infants with the HLA-DQ2 and/or –DQ8 alleles and a first degree family member with CD [4]. From 2007 to 2010, infants were randomised to a double-blind dietary intervention with either 100 mg of gluten daily or a placebo. The intervention took place when the children were between four and six months of age. The children were screened regularly for CD. Breastfeeding for at least six months was encouraged. Gluten intake was quantified and the breast feeding analysed. The results showed that the development of childhood CD is not

related to the time of gluten introduction, presence or duration of breastfeeding, gestational age, birth weight, the first degree family relative with CD (mother, father or sibling) or to rotavirus vaccination. On the contrary, female gender and HLA make-up are significantly related to the development of CD.

The Italian Baby study on weaning and CD CELIPREV is a prospective, multicentre, intervention trial in a cohort of 707 children with a familial risk for CD, followed from birth and randomised to gluten introduction at age 6 or 12 months of age [31]. The results showed that neither delayed gluten introduction nor breastfeeding modified CD risk, although gluten introduction at the later time point was associated with a delayed disease onset. A high-risk HLA genotype was an important disease predictor.

The Norwegian Mother and Child Cohort Study (MoBa) is a prospective population-based pregnancy cohort study, conducted by the Norwegian Institute of Public Health. Participants were recruited from all over Norway from 1999 to 2008, 38.7% of invited women gave informed consent to participate. CD was identified in 107.000 children through questionnaires and linkage to the Norwegian Patient Register [29]. The authors found that delayed gluten introduction (i.e. >6 months old) and breastfeeding (>12 months old) were associated with a modest increase in the clinical diagnosis of CD. They also established that gluten introduction under continued breastfeeding was not protective.

The results of the Generation R project, a population-based prospective cohort study from foetal life until young adulthood in Rotterdam, the Netherlands, show that the risk for CD autoimmunity is not affected by gluten introduction beyond six months of age or by breastfeeding during the first six months of life [32].

The Environmental Determinants of Diabetes in the Young (TEDDY) is a multinational study that follows children at high genetic risk for type 1 diabetes, wherein development of CD is a secondary outcome. TEDDY studies 6403 children with a genetic predisposition for CD (HLA DQ2 or DQ8) [33]. Gluten introduction prior to 17 weeks or later than 26 weeks of life was not associated with an increased risk for CD when adjusted for country, HLA type, gender, and family history of CD.

The development of gluten peptides or a T-cell vaccination would enable specific interference with T-cell function in CD and potentially be a primary preventive measure for CD. Accordingly, the development of the Nexvax2 vaccine as immunotherapy to induce gluten tolerance has commenced and is in phase 1 clinical trials (ImmusanT, Cambridge, MA).

Secondary prevention

Early diagnosis and treatment of CD represents secondary prevention. There are two different approaches to achieve this: case-finding and mass screening. Active case-finding refers to liberal diagnostic testing of patients with CD-associated symptoms and/or conditions. Non controlled trials have shown that this approach can increase the incidence of CD [34–36]. However, controlled prospective studies have shown that the majority of screening-detected CD cases have no associated symptoms or conditions. Consequently, secondary prevention may only be achieved on large scale by mass screening in the general population [4,31,37]. CD screening can be done by measuring the CD specific serum antibodies against tissue transglutaminase type 2 (TG2A), anti-endomysium (EMA) or deaminated gliadin peptides (DGPA) [3,38]. CD screening among high risk groups i.e. first-degree relatives of CD patients, those with immune-mediated conditions such as type 1 diabetes mellitus, autoimmune thyroid disease, or patients with selective IgA deficiency, and patients with Down, Turner and Williams syndrome, is advised by evidence-based guidelines [3,39,40]. In general, first-degree family members of CD patients have an increased risk for CD ranging from 2 to 20%, depending on the gender and HLA-haplotype [4,41,42]. Recent prospective studies in these children have shown that the disease can be detected at a very early age, and that about 50% of them already have CD by age three years [4,31]. Moreover, girls with familial risk for CD have a higher risk of developing the disease, and by three years old their incidence of CD is 7.2% compared to 3.4% in boys [4]. Homozygous HLA-DQ2 children develop early CD more frequently than heterozygous ones: 14.9% versus 3.9% respectively, followed by HLA-DQ8 positive children 0.9% ($p < 0.001$). In addition, by the

Table 1
Principles of Wilson and Jungner for mass screening applied to coeliac disease and to the changes in knowledge in the last ten years.

Principles	2005	2015(Ref.)
1. The condition should be an important health problem.	Yes: Frequent, high morbidity in clinical cases	Yes, and important complications in undetected cases, improvement of health in cases detected by mass screening [50,54]
2. There should be an accepted treatment for the disease.	Yes: GFD	Yes: GFD. Novel or adjunctive treatments being explored [67]
3. Facilities for diagnosis and treatment should be available.	Yes: detection of specific CD antibodies, small bowel biopsies, GFD	Yes, and better, easier and cheaper diagnostic methods. Non-invasive diagnosis possible in a group of children [3,9]
4. There should be a recognizable latent or early symptomatic stage.	Yes: Detection of specific CD antibodies	Yes: Detection of specific CD antibodies. Increased pathology in undetected CD [52–54]
5. There should be a suitable test for disease detection.	Yes: Detection of specific CD antibodies	Yes, and also as point of caret (rapid) tests [56,57]
6. The test should be acceptable for the population.	Unknown	Yes: information from prospective studies [4,48,49]
7. The natural history of the condition, including development from latent to declared disease, should be understood.	Unknown	Yes: information from prospective studies [52–54]
8. There should be an agreed-on policy of whom to treat as patient.	Clinically diagnosed	Increasing evidence of health improvement by early treatment in asymptomatic cases [50,54]
9. The costs of case finding should be economically balanced in relation to possible expenditure on medical care as a whole.	Few cost-effectiveness studies so far	Increasing evidence on cost-effectivity [12,55]
10. Case finding should be a continuous process.	Yes: New cases continue to appear	Yes, and implementation of mass screening in a European country [47]

GFD = gluten-free diet; CD = coeliac disease; specific CD antibodies against tissue transglutaminase type 2 (TG2A), anti-endomysium (EMA) or deaminated gliadin peptides (DGPA).

age of three years homozygous HLA-DQ2 girls are much more frequently affected than boys (20.7% versus 9.5%) ($p < 0.001$) [4].

However, mass screening for CD has been a controversial subject for years. This is especially related to: 1) Compliance to the ten principles for early disease detection elaborated by Wilson and Jungner [43] (Table 1); and 2) The scarcity of information on the effect of diagnosis and treatment in patients identified by mass screening with absent or subtle symptoms [44]. On the other hand, results from prospective studies have recently provided additional information on these aspects. One of these studies is the cross-sectional CD screening project ETICS-PreventCD [45], carried out in the general population before and after the Swedish CD epidemic [9]. A two-phase screening study was performed wherein 13,279 children from two Swedish birth cohorts were included: those born during (1993) and after the epidemic (1997). The results of the cohort born during the CD epidemic reported the highest prevalence of CD in Europe: 3% at 12 years of age [46]. Two additional points in the ETICS-PreventCD study were established. First, that 12 year old children born after the epidemic still have the highest frequency of CD in Europe (2%). Second, that mass screening in children is possible [9]. It is interesting to note that mass screening for CD has already be well accepted and implemented in the European republic of San Marino [47]. Likewise, there was a general acceptance to mass screening in both 12 year old Swedish children and American adults in a preventative healthcare setting [48,49]. One of the traditional arguments against mass screening is the assumption that minimally or asymptomatic patients would not adhere to a gluten-free diet treatment. However,

long-term follow-up in young Dutch children and the results of the 12 years old Swedish children show a high gluten-free diet adherence in adolescents whose disease was detected by screening [50,51].

Recent results from the Generation R project showed that undiagnosed CD in women is associated with reduced foetal growth and birth weight [52], and in children with reduced bone mineral density and delayed growth by age six years [53]. In addition, prospective studies show that treatment with gluten-free diet among CD patients detected by mass screening results in health improvement, in both children as in adults [50,54].

According to the few health economic evaluations based on cost per life-years saved, mass CD screening may be conducted over a wide age range, if there is a relatively high CD population prevalence, and assuming a standardised mortality ratio of 1.5 or higher for untreated cases [55]. In addition, an incremental cost-efficiency ratio of 48,960 USD per quality-adjusted life-year (QALY) for CD screening versus non screening in young adults, was demonstrated [12]. However, with the recent improvement in diagnostic testing for CD, especially with the introduction of the rapid point of care tests (POC) to determine CD specific antibodies [56,57], the costs of mass screening will decrease as its effectiveness increases. All these results support active screening for CD. The discussion on mass screening for CD may be reopened in the future. For this purpose, the development and analysis of health economic evaluations of mass CD screenings at different ages, utilizing different strategies, will be necessary. In addition, the willingness to pay for mass CD screening should also be studied. Swedish parents were willing to pay for school-based CD screening of their children, but only a minority of them were amenable to paying for the whole costs of the screening for their child [58].

Tertiary prevention

Adherence to a gluten-free diet might reduce the long-term complications of CD, like chronic anaemia, infertility, autoimmune disorders, malignancy and osteoporosis [59], and it should be considered as a tertiary preventive measure. Adhering to a gluten-free diet may seem simple but the abundance of gluten-containing food in the daily diet may be challenging and such treatment may considerably affect the patient's quality of life [11,60,61]. In addition, the gluten-free diet may have negative nutritional consequences. For example, it has been reported that 72% of Italian CD adolescents were overweight and consumed an unbalanced diet rich in fat and protein, poor in carbohydrate, and deficient in calcium, iron and fibre [62]. Gluten-containing cereals such as wheat, barley, and rye are important sources of dietary iron, fibre, calcium, folate and vitamin B12, thus the treatment with a gluten-free diet can lead to micronutrient deficiencies [63,64]. Naturally gluten-free (pseudo) grains such as buckwheat or quinoa are rich in group B vitamins [65], but commercially available gluten-free products do not frequently contain the same amount of micronutrients as the often enriched wheat flour products that they aim to replace [66]. The preceding reasons emphasise the need to develop adjunct therapies to the gluten-free diet to increase treatment adherence and reduce gluten exposure [67]. These novel adjuvant therapies should be tested in well-designed clinical trials, in both adults and children, before they can be safely used in practice. The results of on-going and future studies on the use of enzymes that enhance gluten degradation (Alvine Pharmaceuticals, San Carlos, CA, USA), epithelial tight junction regulators that reduce permeability for gluten peptides (Lazarotide, Alba Therapeutics, Baltimore, MD, USA) or polymers that bind ingested gluten (BioLineRx, Jerusalem, Israel) will be important to assess their contribution to the tertiary prevention of CD.

Another problem for tertiary prevention is the absence of sensitive and non invasive biomarkers to monitor compliance to the gluten-free diet. Presently, the gold standard for this purpose is consultation with an expert dietician, but this may prove to be time-consuming for patients, and local expertise may be unavailable [68]. Determination of serum TG2A or DPGA is usually used during the follow-up of the patients as these markers improve with gluten elimination [69]. However, mucosal damage may still persist without TG2A or DPGA and thus, antibody testing may be negative in patients with partial adherence to the gluten-free diet [70,71]. The validation of the novel method recently described to

measure gluten immunogenic peptides in stools may represent a step forward in the assessment of dietary adherence [72].

Practice points

- At present, primary prevention of CD is not possible.
- Results from recent prospective studies establish that the timing of gluten introduction and the duration or maintenance of breast-feeding do not influence the development of CD.
- In order to reduce the mortality and morbidity due to CD, the (paediatric) gastroenterologist can act at the secondary and tertiary levels of prevention.
- The current available diagnostic procedures have to be adequately used for case-finding and the avoidance of underdiagnoses.
- Since CD is severely underdiagnosed, the only way to achieve large-scale secondary prevention is by mass screening.
- Screening for CD should be performed in first degree family members of CD patients and in other high risk groups such as patients with Down, Turner and Williams syndrome.
- About 50% of the children with a first degree relative with CD develop the disease at the age of three years.
- Adherence to the gluten-free diet should be encouraged for CD patients.

Research agenda

- Future prospective studies on the primary prevention of CD should investigate the effect of different intervention strategies including nutrition, immunomodulation and the role of the microbiome. Large, multicentre studies with long-term follow-up in different countries and continents are needed.
- The best method to investigate the effect of environmental factors in the development and/or prevention of CD is to perform prospective, randomised, placebo-controlled interventions in young children with long-term follow up.
- The development of gluten peptides or a T-cell vaccination would be a potential primary preventive measure for CD.
- The discussion on mass screening for CD may be reopened in the future. For this purpose, health economic evaluations of CD mass screenings at different ages, utilizing different strategies will be necessary.
- Studies on the implementation of mass screening of CD in different countries should be carried out.
- The development of novel or adjunct therapies to the gluten-free diet will improve tertiary prevention in CD. These therapies should be tested in well-designed clinical trials, in both adults and children.
- The development of sensitive and non-invasive biomarkers to monitor the adherence to a gluten-free diet will improve tertiary prevention in CD.

Conflicts of interest

None.

Acknowledgements

The author thanks Dr. D.C. Amado for editing the manuscript.

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