Celiac Disease Prevention

M. Luisa Mearin

The incidence and prevalence of celiac disease (CD) have risen over time, the clinical presentation has changed dramatically in the last decades and the disease remains frequently unrecognized or undiagnosed [1, 2]. There are good biomarkers for CD and evidence based guidelines for its diagnosis [3, 4], but patients often report a delay in diagnosis that may last for years [5, 6]. In addition, CD remains frequently unrecognized and, therefore, untreated. Untreated disease is associated with long-term complications, such as chronic anaemia, delayed puberty, neuropsychiatric disturbances, infertility, small-for-date-births, osteoporosis, and, rarely, malignancy and it can reduce the quality of life [7–9]. Treatment with a gluten-free diet (GFD) reduces the burden of morbidity and mortality associated with untreated CD. Thus, prevention would be beneficial [10].

Prevention is defined as any activity that reduces the burden of mortality or morbidity from disease, taking place at the primary (avoiding disease development), secondary (early detection and treatment) or tertiary level (avoiding complications by improved treatment) [11].

The purpose of this chapter is to review the knowledge on the primary prevention of CD.

A summary of the effectivity of some primary preventive strategies is presented in Table 1.

M. L. Mearin (✉)
Department of Pediatrics, Leiden University Medical Center, Willem Alexander Children's Hospital, Leiden, Netherlands
e-mail: l.mearin@iumc.ni

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Table 1 Summary of effectivity of some primary preventive strategies for celiac disease

Strategy	Effectiveness
Breastfeeding	No
Breastfeeding at gluten introduction into the diet	No
Age at gluten introduction into the diet	No
Quantity of gluten intake early in life	Probably
Type of diet early in life	Perhaps
(Intestinal) infections	Probably
Type of delivery	No
Antibiotics	No
Microbiota	Unknown

1 Early Feeding

Data from prospective studies of large cohorts such as PREVENTCD, CELIPREV [12, 13], Generation Rotterdam [14], the Norwegian Mother and Child Cohort Study (MoBa) [15] and the Environmental Determinants of Diabetes in the Young (TEDDY) have shown that *breastfeeding and/or gluten introduction during the period of breast feeding*, do not protect against the development of CD [16].

Two randomized trials on the *age at gluten introduction into the diet of young children* did not show a relationship between early (4 months of age) or late (6 or 12 months of age) age at gluten introduction and CD development at 5 years of age [12, 13]. Interest in the quantity of gluten consumed by young children as a possible preventive risk for CD development has been present since the results of a retrospective observational study in Sweden indicated that large amounts of gluten (>16 g/day) at the time of first introduction increased the risk of CD [17]. The same group of investigators found a lower risk of CD in a big population of children born in 1997, who ingested till the age of 2 years significantly less gluten-containing cereal (24 g/day), compared to another matched population born in 1993 with a higher gluten intake (38 g/day) [18]. Also, the results from the observational TEDDY cohort, in which gluten intake was assessed by dietary questionnaires, found that high intake (>5.0 g/day) of gluten during the first 2 years of life was associated with an increased risk of CD [19]. They also found that the risk for CD increased for every 1-g/d increase in gluten consumption (HR, 1.50 [95% CI, 1.35–1.66] with an absolute risk by age of 3 years if the reference amount of gluten was consumed of 20.7% and of 27.9% if gluten intake was 1-g/d higher than the reference amount [20]. Analysis of the data from the PREVENTCD cohort showed that the amount of gluten consumed at 11–36 months of age did not influence the risk for CD development [20, 21], but further analyses of the data in this cohort are ongoing.

Recently, a secondary analysis of the Enquiring About Tolerance (EAT) trial suggested that high gluten intake from age 4 months reduced later CD development

[22]. However, the small sample size and methodological limitations of the study do not permit drawing conclusions on advisable gluten intake in infancy to prevent CD [23].

A new field of interest is the type of overall diet of young children after the weaning period and its relationship with CD development. In the prospective study of dietary patterns of young children in the Generation R project in the Netherlands, it was found that a diet characterized by high consumption of vegetables and grains and low consumption of refined cereals and sweet beverages, was associated with lower odds of CD autoimmunity [24].

Thus, *modulating the diet early on life* represents a possible preventive strategy for CD development and prospective, randomized trials, especially using different quantities of gluten in well characterized cohorts are mandatory.

2 Infections

(Intestinal) infections might change gut permeability and lead to the passage of immunogenic gluten peptides through the epithelial barrier, activating an autoimmune reaction against gluten peptides in genetic predisposed children. In such a case, prevention of infections may offer opportunities for primary prevention of CD.

Data from the PREVENTCD cohort showed no correlation between the risk for CD development and the parental-reported gastrointestinal infections in the first 18 months of life [12]. However, the TEDDY study found that parental-reported early gastrointestinal infections increased the risk of CD autoimmunity within the following 3 months (HR 1.33; 95% CI 1.11–1.59). This effect was observed particularly in those children with non-HLA-DQ2 genotypes who had been breastfed for <4 months, as well as in children born in winter and introduced to gluten before the age of 6 months [25].

Viral infections, especially Reovirus and Enterovirus have been reported as a trigger for CD development [26, 27]. In vitro, Reovirus infection induced a disruption of intestinal immune homeostasis and initiated loss of oral tolerance and T-helper inflammatory immunity to dietary antigens. In CD patients anti-Reovirus antibodies were significantly overrepresented in comparison to health controls [26]. Recently, metagenomics of the faecal virome of the TEDDY cohort showed that there is an interaction between cumulative enteroviral exposures between 1 and 2 years of age with cumulative gluten intake by 2 years of age in relation to the risk of CD and that the effect of Enteroviruses on the risk for CD autoimmunity is higher when greater amounts of gluten are consumed [28].

Seroreactivity to microbial antigens has been found in patients with freshly diagnosed CD, indicating that microbial infection might have a role in the early development of the disease [29]. Recently, crystal structures of T cell receptors in

complex with HLA-DQ2 bound to bacterial peptides, demonstrate that molecular mimicry underpins cross-reactivity towards the gliadin epitopes suggesting microbial exposure as a potential environmental factor in CD [30].

3 Type of Delivery

It has been hypothesized that the mode of delivery (vaginal or caesarean section) may influence the risk for CD development, since infants born vaginally and during emergency caesarean section are colonized by faecal and vaginal bacteria of the mother, have a more diversified microbiota and this might influence the development of the mucosal immune system [31]. However, prospective studies have found no association between the type of delivery and the risk of developing CD [32–34].

4 Antibiotics

Analysis of prospective cohorts have shown that there is no evidence between the exposure to antibiotics during pregnancy or during the first years of life and CD development [35].

5 Microbiota

CD development has been linked to the composition of the gut microbiome involved in the development of early oral tolerance [36]. An association between the HLA-DQ genotype associated to CD (HLA-DQ2 and/or DQ8) and the intestinal microbiota composition has been reported in a prospective cohort of high-risk children [37]. A sub analysis of 10 CD cases and 10 matched controls, suggested altered early proportions of *Firmicutes* and members of the *Actinobacteria* phylum (*B. Longum*) in children who later progressed to CD [38]. Also, analysis of the breastmilk of the mothers of children in the PREVENTCD cohort that later developed CD showed more abundance of certain microbial species that the milk samples from mothers whose children remained healthy [39]. A recent Scottish study found a distinct microbiota profile in children with CD representing a specific biomarker of active CD [40]. However, at this moment, it is not clear whether the microbes identified in CD contribute to the pathogenesis of the disease or are the result of it. Results of prospective studies such as the Celiac Disease Genomic, Environmental, Microbiome, and Metabolomic (CDGEMM) will possibly provide answers to these open questions [41].

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