Gluten Introduction and the Risk of Coeliac Disease: A Position Paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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ABSTRACT

Background: The European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommended in 2008, based on observational data, to avoid both early (<4 months) and late (≥7 months) introduction of gluten and to introduce gluten while the infant is still being breast-fed. New evidence prompted ESPGHAN to revise these recommendations.

Objective: To provide updated recommendations regarding gluten introduction in infants and the risk of developing coeliac disease (CD) during childhood.

Summary: The risk of inducing CD through a gluten-containing diet exclusively applies to persons carrying at least one of the CD risk alleles. Because genetic risk alleles are generally not known in an infant at the time of solid food introduction, the following recommendations apply to all infants, although they are derived from studying families with first-degree relatives with CD. Although breast-feeding should be promoted for its other well-established health benefits, neither any breast-feeding nor breast-feeding during gluten introduction has been shown to reduce the risk of CD. Gluten may be introduced into the infant's diet anytime between 4 and 12 completed months of age. In children at high risk for CD, earlier introduction of gluten (4 vs 6 months or 6 vs 12 months) is associated with earlier development of CD autoimmunity (defined as positive serology) and CD, but the cumulative incidence of each in later childhood is similar. Based on observational data pointing to the association between the amount of gluten intake and risk of CD, consumption of large quantities of gluten should be avoided during the first weeks after gluten introduction and during infancy. The optimal amounts of gluten to be introduced at weaning, however, have not been established.

Key Words: children, coeliac disease, gluten, infant feeding, nutrition, recommendations

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BACKGROUND

Coeliac disease (CD) represents a unique disorder in which consumption of a food ingredient, namely gluten, in conjunction with genetic susceptibility, is essential for the development of an insidiously evolving autoimmune reaction affecting the gut and other organs (1). CD is a permanent condition that affects approximately 1% to 3% of the general population in most parts of the world, except for populations in which the HLA risk alleles (HLA-DQ2 and/or DQ8) are rare such as in South East Asia (2–4). Identifying preventive strategies that would reduce the prevalence of CD has been a major target of research in recent years (5,6). Investigated preventive strategies relate to early infant feeding practices, namely to the possible protective effect of breast-feeding

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(BF), the introduction of gluten while the infant is still being breast-fed, and the age when gluten is introduced into the infant's diet.

In 2008, based on the available evidence obtained exclusively from observational studies, the Committee on Nutrition of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) concluded that it is prudent to avoid both early (<4 months of age) and late (≥7 months of age) gluten introduction and to introduce gluten while the infant is still being breast-fed, because this may reduce not only the risk of CD but also type 1 diabetes mellitus and wheat allergy (7). In 2012, the American Academy of Pediatrics, also based on the findings from observational studies, stated in its position paper that BF has a protective effect on the occurrence of CD (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.4–0.89) (8). This, alongside the American Academy of Pediatrics recommendation that complementary foods should be preferentially introduced while the infant is being breast-fed, between 4 and 6 months of age, without mentioning gluten specifically (9), reinforced the emphasis on the importance of BF, as well as the age of gluten introduction, in the prevention of CD. These recommendations were based on observational studies. Two, recent, randomised controlled trials (RCTs) examined the effect of the age of gluten introduction on the risk of developing coeliac disease autoimmunity (CDA) (defined as positive serology) or CD during childhood in children at genetic risk for CD. Evidence from these RCTs showed that the age of gluten introduction into the infant's diet, whether early or late, influences the incidence of each during the first 2 years, but not the cumulative incidence and prevalence of CD during childhood, and, thus, indicated that primary prevention of CD through nutritional interventions is not possible at the present time (5,6). A systematic review that evaluated evidence from prospective observational studies published up until February 2015 also showed that BF, any or at the time of gluten introduction, had no preventive effect on the development of CDA or CD during childhood (10).

AIM

The aim of this document was to develop recommendations regarding gluten introduction in infants and the risk of developing CDA or CD during childhood based on the present knowledge.

METHODS

This document was developed in accordance with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group procedure (11).

COMPOSITION OF THE GROUP

The recommendation development group was convened to support the development of this document. This group included experts in the fields of paediatrics and paediatric gastroenterology and nutrition as well as experts in systematic review and GRADE methodology.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

All members of the group disclosed any potential conflicts of interest (see Table S1, *http://links.lww.com/MPG/A604*). Experts with a potential conflict of interest abstained from making decisions about specific questions/recommendations being addressed. Similarly, declarations of a potential conflict of interest were obtained from external peer reviewers. No funding for the development of these guidelines was received except for partial coverage of travel expenses provided by ESPGHAN.

DEFINING THE CLINICAL QUESTIONS

The first stage of the development of these recommendations involved specifying the clinical questions. A systematic review (10) was specifically performed by the PreventCD Study Group to assist with the development of this document. Five specific questions from this systematic review taken into consideration in the present document are as follows:

(1) **BF and CD**. *Does any BF compared with no BF reduce the risk of developing CD?*
(2) **BF at the time of gluten introduction and CD**. *Does BF at the time of gluten introduction reduce the risk of developing CD?*
(3) **Timing of gluten introduction**. *Is the age of gluten introduction important to the risk of developing CD?* The following age groups were assessed:
   (a) Gluten at 4 to 6 months compared with gluten at >6 months.
   (b) Gluten at 6 months compared with gluten at 12 months.
   (c) Gluten at <3 to 4 months compared with gluten at 4 to 6 months.
   (d) Gluten at <3 to 4 months compared with gluten at >6 months.
   (e) Gluten at <6 months compared with gluten at >6 months.
(4) **Amount of gluten at the time of gluten introduction (and later) and CD**. *Is the amount of gluten ingested an independent risk factor for the development of CD during early childhood?*
(5) **Type of gluten**. *Does the type of cereal at gluten introduction influence CD risk?*

In addition, during the process of the development of these recommendations, some members of the group considered that gluten introduction in children with first-degree relatives with CD needs to be addressed separately. Although there was a majority agreement that this is an important issue, there was no consensus within the group regarding how to interpret the limited evidence available. Thus, the majority of the group voted to discuss the issue of families with first-degree relatives having CD, but not to formulate specific recommendations for these families.

EVIDENCE SUMMARIES

GRADE evidence summaries, which were part of the PreventCD systematic review and meta-analysis (10), were considered. For assessing the quality of evidence for outcomes reported in the included studies identified through the systematic review, the GRADE methodology and GRADEProfiler software (version 3.6, 2011) were used (11). In brief, the GRADE system offers 4 categories of the quality of the evidence (high, moderate, low, and very low). The quality of evidence was *downgraded* if there was any of the following problems: methodological limitations, important inconsistencies among studies, uncertainty with regard to the directness of the evidence (ie, the generalisability of the findings to the population of interest), sparse or imprecise data, or a high probability of reporting bias. The quality of evidence was *upgraded* if there was a large effect size (eg, relative risk <0.5 or >2).

METHODOLOGY FOR GRADING RECOMMENDATIONS

To grade the recommendations, the GRADE system, developed by the Grading of Recommendations, Assessment,

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Development and Evaluations Working Group, was used. In brief, the GRADE system offers 2 categories of the strength of recommendation (strong or conditional). The strength of a recommendation was graded as *strong* when the evidence showed that the benefit of the intervention clearly outweighed the undesirable effects. The strength of a recommendation was graded as *conditional* when the trade-offs were less certain (either because of the low quality of evidence or because the evidence suggested that desirable and undesirable effects were closely balanced). The highest grade of recommendation does not always correspond to the highest evidence level.

The recommendations were drafted first by 2 members of the group (H.S., R.S.). Then, all members of the group reviewed and discussed the evidence, reviewed the drafted recommendations, and reached a consensus on the strength of each recommendation. In addition to the quality of evidence, desirable as well as undesirable effects of each specific recommendation, values, and preferences related to the recommendation in different settings were considered (see Table S2, *http://links.lww.com/MPG/A604*).

DOCUMENT REVIEW

As part of the guideline development process, the preliminary conclusions and draft recommendations were presented at the 48th Annual Meeting of ESPGHAN in Amsterdam (6–9 May, 2015). In addition, we invited a number of external reviewers based on their expertise in the area of CD and/or nutrition to review the statements and recommendations, and vote on them. These reviewers included members of ESPGHAN bodies such as the Committee on Nutrition, Gastroenterology Committee, the Special Interest Group on Coeliac Disease, and the Association of European Coeliac Societies. For both evidence statements and recommendations, a record of the vote count (for, against, recusal) was made. The ideal was 100% consensus, but a 2/3 majority was considered acceptable. For all statements and recommendations, a 2/3 consensus majority was reached in the initial vote (for details and the list of individuals who agreed to take part in the voting process and agreed that their names will be shown, see Table S3, *http://links.lww.com/MPG/A604*), and thus, a second vote was not necessary. All of the comments were considered and the revisions were made in response to peer review comments. A finalised document was submitted to the ESPGHAN Council for peer review before publication.

UPDATING

The group will monitor new publications and evidence made available and decide whether and when it is necessary to update the recommendations. The recommendations will be updated once important new information is available.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The risk of inducing CD through a gluten-containing diet exclusively concerns persons carrying at least one of the coeliac risk alleles. This applies to 30% to 40% of the general population in Europe and, to ~75% to 80% of the offspring of families in which at least one first degree relative (father, mother, sibling) is affected by CD (5,6). Because the genetic risk alleles are generally not known in an infant at the time of solid food introduction, we propose that the following recommendations are applicable to all infants, although accepting that they may not be of importance to approximately two-thirds of the population without a genetic predisposition.

Breast-feeding Compared With No Breast-feeding

STATEMENT: BF compared with no BF has not been shown to reduce the risk of developing CD during childhood. [100% agreement]

Summary of evidence. The systematic review (10) of the effect of BF compared with no BF included observational data from 7 studies (5,6,12–16). The 7 studies found no effect of any BF compared with no BF on the risk of developing CD during childhood. Caution is, however, needed when interpreting these results. Randomisation to BF or no BF groups is unfeasible and unethical. Therefore, none of these studies was designed to address directly the effect of BF on CD. In some of the studies, the sample sizes of the non–breast-fed groups were small. The pooled results of 5 studies (12–16) found that any BF compared with no BF had no effect on the risk of developing CD; however, considerable heterogeneity across the studies was found. The overall quality of the available evidence for the effect of any BF compared with no BF on CD risk was considered to be low.

RECOMMENDATION. Recommendations on BF should not be modified because of considerations regarding prevention of CD (*conditional recommendation; low quality of evidence).* [97% agreement]

Breast-feeding at the Time of Gluten Introduction

STATEMENT: BF at the time of gluten introduction, as compared to gluten introduction after weaning (ie, cessation of BF), has not been shown to reduce the risk of developing CD during childhood. [97% agreement]

Summary of evidence. The systematic review of the effect of BF at the time of gluten introduction compared with no BF included evidence from 9 studies (5,6,17–23); among them were observational data from 2 randomised interventional trials (5,6), 4 case-control studies (17,18,19,23), and 3 cohort studies (20–22). Of note, some of these studies were observations of the entire population (17–19,22,23), and some were observations of populations at high risk of developing CD (5,6,20,21).

With regard to observational data from RCTs, one found no change in the risk of developing CD (relative risk [RR] 1.31, 95% CI 0.77–2.23) (5). Similarly, another prospective study reported no protective effect of introducing gluten during BF (6). Again, caution is needed when interpreting these results, as neither of these 2 studies was designed to address directly the effect of BF at the time of gluten introduction and risk of CD.

The pooled results of all of the observational studies showed no effect on the risk of CD (OR 0.88, 95% CI 0.52–1.51; significant heterogeneity was evident, $I^2 = 89\%$) (10). Notably, there were differences when the case-control and cohort studies were evaluated separately. A meta-analysis of the 4 case-control studies found that BF at the time of gluten introduction was associated with a reduced

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risk of CD (OR 0.51, 95% CI 0.34–0.77; $I^2 = 89\%$) (10); however, a meta-analysis of the 3 cohort studies found that BF at the time of gluten introduction was associated with an increased risk of CD (OR 1.51, 95% CI 1.18–1.93; $I^2 = 0\%$) (10). The overall quality of the available evidence for the effects of gluten introduction while BF on CD manifestation was considered low.

RECOMMENDATION: Introducing gluten while the infant is being breast-fed cannot be recommended as a means of reducing the risk of developing CD (*conditional recommendation; low quality of evidence).* [100% agreement]

Timing of Gluten Introduction

The effects of various timings of gluten introduction on the risk of developing CD were studied. We summarise the evidence for various timings followed by a single recommendation on the timing of gluten introduction.

Gluten at 4 to 6 Months Compared With Gluten at >6 Months of Age

STATEMENT: Gluten introduction at 4 to 6 months compared with gluten introduction at >6 months of age does not reduce the cumulative incidence of CDA or CD during childhood. [100% agreement]

Summary of evidence. The systematic review (10) identified 1 double-blind, placebo-controlled RCT (n = 944) that compared the administration of small amounts of gluten (100 mg of immunologically active gluten daily) between 16 and 24 weeks of age compared with placebo. After the intervention, parents in both the groups were advised to introduce gluten gradually using regular food products and standardised recommendations (mg/day: 250, 500, 1000, and 1500 at months 6, 7, 8, and 9, respectively) (5). This RCT reported a similar risk of CD autoimmunity (CDA) at 3 years of age (RR 0.81, 95% CI 0.49–1.32), as well as a similar risk of CD at 3 years of age (RR 1.21, 95% CI 0.79–1.84).

The pooled results of 3 observational studies found no difference in the risk of developing CDA (13,20,21) or CD (21,22,25) in children exposed to gluten at the age of 4 to 6 months compared with first exposure at 6 months or later (OR 0.82, 95% CI 0.43–1.56 and OR 1.14, 95% CI 0.75–1.75, respectively) (10).

One cross-sectional study (24) comparing 2 birth cohorts of 12-year-olds found a significant difference in the total prevalence of CD when it was recommended to introduce gluten from ages 4 to 6 months compared with children born when gluten was recommended to be introduced from 6 months of age (OR 0.75, 95% CI 0.6–0.93). It cannot, however, be ruled out that other factors may have been changed as well in the 2 birth cohorts.

Gluten at 6 Months Compared With Gluten at 12 Months of Age

STATEMENT: In children at high risk for CD, gluten introduction at 6 months compared with gluten introduction at 12 months of age does not reduce the cumulative incidence of CDA or CD, but it leads to an earlier manifestation of CD. [97% agreement]

Summary of evidence. One large RCT (6) found that the nonblinded introduction of gluten at 6 months of age compared with the introduction at 12 months of age increased the risks for CDA and CD at 2 years of age (n = 536, RR 2.25, 95% CI 1.34–3.79, and RR 2.36, 95% CI 1.27–4.36, respectively), but it had no significant effect on the cumulative incidences of CDA and CD at 5 years of age (the primary outcome) (n = 451, RR 1.06, 95% CI 0.74–1.52, and RR 1.02, 95% CI 0.67–1.56, respectively) and at 10 years of age; however, at the latter age, the number of children was small (n = 89).

Based on the findings of the systematic review (10), the pooled results of 2 RCTs reported that the introduction of gluten at 6 months of age compared with the introduction at 12 months of age increased the risk of CDA at 2 years of age (n = 566, RR 2.25, 95% CI 1.35–3.76). No difference in the risk of CDA, however, was found at 3 years of age (2 RCTs, n = 180, RR 1.43, 95% CI 0.6–3.41), at 5 years of age (1 RCT, n = 451, RR 1.06, 95% CI 0.74–1.52), or at 13 years of age (1 RCT, n = 150, RR 1.66, 95% CI 0.74–3.72).

Gluten at <3 to 4 Months Compared With Gluten at 4 to 6 Months of Age

STATEMENT: It remains unclear whether gluten introduction at <3 to 4 months compared with gluten introduction at 4 to 6 months of age has an effect on the risk of developing CDA or CD. [87.5% agreement]

Summary of evidence. The pooled results for observational studies showed no significant difference in the risk of CD in children exposed to gluten at the age of <3 to 4 months compared with first exposure at 4 to 6 months (3 studies (21,22,25), OR 0.82, 95% CI 0.46–1.49), as well as in the risk of CDA (4 studies (20–22,25), OR 1.10, 95% CI 0.80–1.52).

Gluten at <3 to 4 Months Compared With Gluten at >6 Months of Age

STATEMENT: It remains unclear whether gluten introduction at <3 to 4 months compared with gluten introduction at >6 months of age has an effect on the risk of developing CDA or CD. [91% agreement]

Summary of evidence. The pooled results of 3 observational studies (21,22,25) showed no significant difference in the risk of CD in children exposed to gluten at the age of 3 to 4 months compared with first exposure at 6 months or later (OR 0.94, 95% CI 0.69–1.30). Similarly, the pooled results of 4 observational studies (20–22,25) found no difference in the risk of CDA between groups (OR 1.15, 95% CI 0.9–1.46).

Gluten at <6 Months Compared With Gluten at >6 Months of Age

STATEMENT: It remains unclear whether gluten introduction at <6 months compared with gluten introduction at >6 months of age has an effect on the risk of developing CDA. [87.5% agreement]

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Summary of evidence. The pooled results of 5 observational studies (12,20–22,26) showed no significant difference in the risk of CDA in children exposed to gluten at <6 months compared with first exposure after 6 months (OR 0.98, 95% CI 0.73–1.32) (10).

SUMMARY RECOMMENDATION. Gluten can be introduced into the infant's diet between the ages of 4 and 12 completed months.* The age of gluten introduction in infants in this age range does not seem to influence the absolute risk of developing CDA or CD during childhood *(conditional recommendation; depending on the age, quality of evidence varies from very low to high quality of evidence).* [100% agreement]

*4 completed months = 17 weeks of age.

Type of Gluten

STATEMENT: The type of gluten at introduction was not shown to modify the risk of developing CD. [97% agreement]

Summary of evidence. The systematic review (10) identified only 1 observational study that analysed whether the risk of developing CD was affected by the type of gluten-containing food introduced (19). This study showed that the type of gluten-containing food given (solid foods such as bread, biscuits, porridge, and pasta, as well as gluten-containing follow-on formula, used exclusively or in combination with solid food) was not associated with the risk of developing CD. The quality of evidence was very low.

RECOMMENDATION: No recommendation can be made regarding the type of gluten to be used at introduction *(conditional recommendation; very low quality of evidence).* [97% agreement]

Amount of Gluten and the Risk of CD

STATEMENT: Introduction of 200 mg of vital wheat gluten (equivalent to 100 mg of immunologically active gluten) per day at 4 to 6 months of age compared to avoidance of gluten did not modify the risk of developing CDA or CD at 3 years of age. Data from observational studies indicate that consumption of large amounts of gluten at weaning and during the first 2 years of life may increase the risk of CD during childhood. [84% agreement]

Summary of evidence. One RCT (5) found that compared with placebo, the introduction at 4 to 6 months of age of 200 mg/day of vital wheat gluten, that is, a form of gluten processed from wheat flour (equivalent to 100 mg of immunologically active gluten), and followed, after the intervention, by a gradual increase in gluten consumption in both groups, had no effect on the risk of CD at 3 years of age. In the same prospective intervention study, a higher frequency of CD was observed in children with higher genetic predisposition despite the same amount of gluten consumption (5).

Data on other amounts of gluten introduced at weaning and subsequent CD development were insufficient to allow one to draw conclusions, because they rely on retrospective observational data (Table S4, *http://links.lww.com/MPG/A604*). One observational Swedish study found a modestly increased risk of developing CD in infants consuming large amounts of gluten compared with small or medium amounts of gluten at weaning (27). In that study, a large amount of gluten at 2 weeks after the introduction of gluten was defined as >16 g of flour per day (approximately 1 g of gluten), and this was a significant and independent risk factor for developing CD before 2 years of age (19). In the ETICS study (part of the larger, EU-funded, PREVENTCD project), which compared infants born during the peak of the Swedish CD ''epidemic'' with those born after the ''epidemic'' (24), the average daily flour consumption from milk- and cereal-based, follow-on formula was 38 g/child/day versus 24 g/child/day below the age of 2 years, respectively, but this calculation did not include bread, a major source of gluten. In addition, besides recall bias after 12 years, it cannot be ruled out that other factors such as additional genetic factors, gastrointestinal infections (28,29), and gut microbiota (30) may also have been involved. Taken together, the data are insufficient to permit recommendations regarding consumption of any specific amount of gluten.

Overall, consumption of large amounts of gluten, however, may potentially result in infants and young children developing CD earlier with malabsorption and failure to thrive. This may be considered harmful in nonscreened children, but it offers the advantages of clear and early diagnosis that from a societal perspective would lead to less long-term complications that follow undiagnosed CD.

Because there is some evidence suggesting that intake of a high amount of gluten is associated with an increased risk of CD, national societies should comment on the amount of gluten in products available in individual countries, as food items and gluten content vary between populations. Based on the data regarding flour consumption in Sweden, published by Ivarsson et al (19,27), the group has calculated the approximate gluten intake taking into account differences in gluten content in the different grains and corresponding flours. Thus, accordingly, in 1 study (19), 16 g of flour was considered a high gluten intake at weaning; however, there were no data on which flours were consumed. If we consider that the majority of flour consumed was wheat, and assuming a gluten content of 8.5% in wheat flour, this would correspond to 1.36 g of gluten per day. If we assume that subjects consumed about 50% wheat flour and 50% other cereals, however, then the cut-off of 16 g of flour would correspond to 0.9 g of gluten per day. In a slice of white bread (30 g), there is about 3 g of protein, corresponding to about 2.4 g of gluten. Thus, the high dose of gluten consumed in the Swedish study corresponds to about half of a slice of white bread per day, 2 weeks after the introduction of gluten. As a comparison, infants in the PreventCD study received 0.2 g of gluten per day during the first 8 weeks after gluten introduction (5), which corresponds to less than 1/10 of a slice of white bread per day. In the second study by Ivarsson et al (27), taking into account the differences in protein and prolamin content for the different cereals (wheat, rye, barley, oats), the gluten consumption was as shown in Table S5 (*http://links.lww.com/MPG/A604*). Data on the amount of gluten in a sample of European products are available in Table S6 (*http://links.lww.com/MPG/A604*).

RECOMMENDATION: Neither the optimal amounts of gluten to be introduced at weaning nor the effects of different wheat preparations on the risks of developing CD and CDA have been established. Despite the limited evidence regarding the exact amounts and with no RCTs to support it, ESPGHAN suggests that consumption of large amounts of gluten should be discouraged during the first months after gluten introduction *(conditional recommendation; very low quality of evidence).* [87.5% agreement]

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Gluten Introduction in Children From Families With a First-Degree Relative With CD

STATEMENT: The very early development of CDA and CD (<3–5 years of age) seems to affect preferentially children carrying the very high risk of CD alleles (HLA-DQ2.5 homozygous), which are found in only 1% to 2% of the general population but in 10% to 15% of children with first-degree relatives having CD. [84% agreement]

It remains a matter of debate whether or not separate recommendations for gluten introduction should be formulated for children from families with first-degree relatives who have CD that differ from the recommendations made for the general population. Although present evidence does not support separate recommendations, highlighting the available literature is, however, essential.

The prevalence of CD is higher among persons who have first-degree relatives with CD (10%–15%) (31). In family screening, relatives (especially siblings) with DQ2- or DQ8-positive are at a higher risk of developing CD. HLA-DQ2 homozygosity is associated with a significantly increased risk of CDA and CD among first-degree relatives (31,32). Moreover, the PreventCD study showed that children who were homozygous for DR3-DQ2 had a 2.5 times higher risk of developing CD with gluten introduction at 4 months compared with gluten introduction at 6 months (5). This effect lasted until 3 to 5 years; however, not for all enrolled children, and the difference between groups reached only a borderline significance (n = 129, hazard ratio 2.55, 95% CI 0.96–6.77). Moreover, the absolute number of CD cases was higher in other HLA risk groups than in the homozygous group. Similarly, the CELIPREV study suggested that children with high-risk HLA alleles had a higher risk of developing CD at all time points with early (at 6 months) compared with later (at 12 months) gluten introduction, but the difference between groups was not significant (hazard ratio 0.7, 95% CI 0.3–1.8, $P = 0.51$) (6). Taken together, these data suggest that very early development of CDA and CD (<3–5 years of age) affects preferentially children carrying the very high risk of CD alleles (HLA-DQ2.5 homozygous) and that these infants may potentially benefit from later gluten introduction.

Because of a lack of consensus within the group on how to interpret the limited evidence available, no recommendations have been formulated. This may change when more data on the outcome of these children become available with long-term follow-up (symptoms, complications, final height). On one hand, it can be argued that delaying gluten introduction toward the end of the first year may be considered in all infants from CD families to reduce the risk of very early CD manifestation with potential adverse effects on growth and development at a young age, even though delaying gluten introduction may only benefit the 10% to 15% who have the high risk alleles. An alternative approach could be intensive CD screening such as HLA typing in all children born in families with a first-degree relative with CD to assess the risk of CD by identifying infants with high risk alleles (32), and careful serological screening after gluten introduction to detect CD before deficiencies of macro- and micronutrients develop. The recommendations on screening are, however, beyond the scope of this article.

SUMMARY OF RECOMMENDATIONS

When formulating the final recommendations on gluten introduction and the risk of developing CD, present ESPGHAN position papers on BF (33) and complementary feeding (7) were included, because both address the introduction of solids to infants and, thus, are practically important (even if not the topic of this position paper).

The recommendations are based on findings in children genetically predisposed to developing CD, because the risk of inducing CD through a gluten-containing diet exclusively applies to persons carrying at least 1 of the coeliac risk alleles. Because the genetic risk alleles are generally not known in an infant at the time of solid food introduction, the following recommendations are, however, applicable to all infants, although it is recognised that they may not be relevant to approximately two thirds of the population.

Breast-feeding and CD

(1) Recommendations on BF should not be modified because of considerations regarding prevention of CD (*conditional recommendation; low quality of evidence).*

(2) Introducing gluten while the infant is being breast-fed cannot be recommended as a means of reducing the risk of developing CD (*conditional recommendation; low quality of evidence).* BF should, however, be promoted for its other well-established heath benefits.

Timing of Gluten Introduction

(1) Gluten can be introduced into the infant's diet between the ages of 4 and 12 completed months. The age of gluten introduction in infants in this age range does not seem to influence the absolute risk of developing CDA or CD during childhood *(conditional recommendation; depending on the age, quality of evidence varies from very low to high quality of evidence).*

Type of Gluten

(1) No recommendation can be made regarding the type of gluten to be used at introduction *(conditional recommendation; very low quality of evidence).*

Amount of Gluten

(1) Neither the optimal amounts of gluten to be introduced at weaning nor the effects of different wheat preparations on the risks of developing CD and CDA have been established. Despite the limited evidence regarding the exact amounts and with no RCTs to support it, ESPGHAN suggests that consumption of large amounts of gluten should be discouraged during the first months after gluten introduction *(conditional recommendation; very low quality of evidence).*

Gluten Introduction in Children From Families With a First-Degree Relative With CD

(1) No recommendation was made on gluten introduction in children from families with first-degree relatives with CD.

FUTURE RESEARCH

A number of important questions remain unanswered. Multicentre and multinational RCTs, rigorously designed and conducted, are needed to define the optimal type of gluten and amount of gluten to be used at introduction into the diet, as well as the duration of the

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gradual increase in amounts, to assess thresholds above. There are presently no data available evaluating whether delaying gluten introduction for >1 year would reduce the long-term prevalence of CD. The *pros* (avoiding early symptomatic disease that may negatively affect growth and development) and *cons* (less classical symptoms with lower chance of diagnosis if there is no serological screening) of gluten avoidance for >1 year need to be considered. In addition, easy and accurate methods of quantifying the gluten content of different types of flour should be made available. Finally, considering that CD is a health problem, and that primary prevention is not feasible, mass screening for CD remains an open question. Recommendations on screening strategies for CD in risk groups such as in children with family members affected by CD are needed.

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