World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i16.1939

World J Gastroenterol 2010 April 28; 16(16): 1939-1942
ISSN 1007-9327 (print)

EDITORIAL

Effect of the timing of gluten introduction on the development of celiac disease

Marco Silano, Carlo Agostoni, Stefano Guandalini

Marco Silano, Unit of Human Nutrition and Health, Italian National Institute of Health, Rome 00161, Italy
Carlo Agostoni, Department of Maternal and Pediatric Sciences, University of Milan, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano 20122, Italy
Stefano Guandalini, Department of Pediatrics Section of Gastroenterology, Hepatology and Nutrition, University of Chicago, Chicago, IL 60637, United States
Author contributions: Silano M collected the references and drafted the manuscript; Agostoni C and Guandalini S drafted and revised the manuscript; all authors approved the final version of the manuscript.
Supported by Intramural Funding
Correspondence to: Marco Silano, MD, Unit of Human Nutrition and Health, Italian National Institute of Health, Viale Regina Elena, 299, Rome 00161, Italy. marco.silano@iss.it
Telephone: +39-6-49902589 Fax: +39-6-49387077
Received: December 22, 2009 Revised: February 4, 2010
Accepted: February 11, 2010
Published online: April 28, 2010

Abstract

Celiac disease (CD) is a permanent auto-immune enteropathy, triggered in genetically predisposed individuals by the ingestion of dietary gluten. Gluten is the alcohol-soluble protein component of the cereals wheat, rye and barley. CD is a multifactorial condition, originating from the interplay of genetic and environmental factors. The necessary environmental trigger is gluten, while the genetic predisposition has been identified in the major histocompatibility complex region on chromosome 6p21, with over 90% of CD patients expressing HLA DQ2 and the remaining celiac patients express DQ8. The fact that only about 4% of DQ2/8-positive individuals exposed to gluten develop CD, has led to the recognition that other genetic and environmental factors are also necessary. In the last few years, several epidemiological studies have suggested that the timing of the introduction of gluten, as well as the pattern of breastfeeding, may play an important role in the subsequent development of CD. Here, we present and review the most recent evidences regarding the effect of timing of gluten introduction during weaning, the amount of gluten introduced and simultaneous breast-feeding, on the development of CD.

Key words: Celiac disease; Gluten; Weaning; Breast-feeding; Prevention; Autoimmunity; Anti-transglutaminase antibody; Duodenal biopsy

Peer reviewer: Chris JJ Mulder, Professor, Department of Gastroenterology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands

Silano M, Agostoni C, Guandalini S. Effect of the timing of gluten introduction on the development of celiac disease. *World J Gastroenterol* 2010; 16(16): 1939-1942 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i16/1939.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i16.1939

INTRODUCTION

Celiac disease (CD) is a permanent auto-immune enteropathy, triggered in genetically predisposed individuals by the ingestion of dietary gluten. Gluten is the alcohol-soluble protein component of the cereals wheat, rye and barley. It is composed of 2 major protein fractions: glutenin and gliadin; most of the toxic activity exerted by gluten in CD is due to gliadin.

CD is an increasingly recognized condition; its true prevalence is, however, difficult to ascertain, because many (arguably the majority) of affected people are asymptomatic or show mild symptoms and signs[1,2].

CD is a multifactorial condition, originating from the interplay of genetic and environmental factors. The necessary environmental trigger is gluten, while the genetic predisposition has been identified in the major his-

tocompatibility complex region on chromosome 6p21, with over 90% of CD patients expressing HLA DQ2 (DQA1*05/DQB1*02) or in the trans position in HLA-DR5/DR-7 heterozygous patients. The remaining celiac patients express DQ8 (DQA1*0301/DQB1*0302). While these haplotypes confer the highest genetic risk for CD, the fact that only about 4% of DQ2/8 positive individuals exposed to gluten develop CD, has led to the recognition that other genetic factors are also necessary[3]. In the last few years, significant advances have been made leading to the identification of 6 regions that harbor genes controlling immune responses in relevant biological pathways. So far, 7 additional candidate genes have been uncovered that are considered as plausible contributors to the development of CD[4,5].

In the last few years, several epidemiological studies have suggested that the timing of the introduction of gluten into the diet, as well as the pattern of breastfeeding, may play an important role in the subsequent development of CD.

THE ROLE OF GLUTEN-WHEN

The attractive hypothesis that the age at first introduction of gluten in predisposed individuals could influence the onset of CD relies upon the fact that at some point in time during development, humans appear to lose their ability to develop oral tolerance to newly introduced antigens[6]. On the other hand, early introduction of solid foods (i.e. before the intestinal immune system reaches a certain level of maturation) may lead to development of intolerance[7].

In reality, the results of most older studies had suggested that the age at first introduction of gluten would not affect the development of CD, while it would modify the onset of symptoms[8].

A decrease of the incidence of biopsy-proven CD following a change in weaning practices was first reported at the end of 1970s among the pediatric population of West Somerset, England[9]. The authors noticed that the incidence of CD declined from 1:1228 to 1:4168 following the recommendations to avoid both the addition of cereals to bottle feeds and the introduction of gluten before 4 mo of age. The cohort of children considered in this study was quite small and it was a retrospective analysis; additionally, the overall incidence of CD reported appears markedly low compared to the present knowledge of the epidemiology of CD. In spite of these limitations, that work gave the first support to the role of age at first exposure to gluten in the development of CD.

Much stronger epidemiological evidence about the role of timing of solid introduction on the development of CD came from a recent 10-year observational study that investigated the age at first introduction (before 3 mo of age, between 3 and 7 mo and at 7 mo or later) of gluten-containing cereals in a group of 1560 children at risk of CD or type 1 diabetes (positivity to HLA-DR3, -DR4 or a first-degree relative with type 1 diabetes) in relation to the subsequent risk of developing CD autoimmunity (CDA)[10]. CDA was defined as positive tissue transglutaminase antibody (tTG Ab) on 2 or more consecutive visits or a positive tTG Ab and a small bowel biopsy consistent with CD. The results, generated as part of a larger effort within the so-called DAISY project, showed that, out of 51 children who developed CDA, those exposed to gluten in the first 3 mo of age had a 5-fold increased risk of CDA compared to those exposed at 4 to 6 mo [hazard ratio (HR), 5.17; 95% confidence interval (CI): 1.44-18.57]; and those who received gluten for the first time at 7 mo of age or after showed a slightly increased hazard ratio compared with those exposed at 4-6 mo (HR, 1.87; 95% CI: 0.97-3.60). These results seem to confirm the existence of a "window" period, during which the first exposure to gluten should occur in order to minimize the risk of subsequent development of CD. Perhaps the biggest limitation of the DAISY study is the lack of data on the amount of gluten ingested. Although the authors speculated that the children that received gluten after 7 mo consumed a higher amount of gluten on its introduction, this remains speculative.

THE ROLE OF GLUTEN-HOW MUCH

The epidemic of CD among Swedish children observed in the mid 80s suggests that the amount of gluten ingested during weaning can play a pivotal role in the development of CD. After 1982, Sweden experienced a quite unique epidemic of CD in children under 2 years of age, with the annual incidence increasing 4-fold to 200-240 cases/100 000 inhabitants per year, followed from 1995 by a sharp decline to the previous level of 50-60 cases[11,12]. Such a trend was not observed in nearby countries (i.e. Denmark and England), where, in contrast, a decline in the incidence of CD was noticed in the same period. This epidemic pattern was later related to new dietetic guidelines (later changed for this reason) that resulted in gluten being introduced to infants after they had been weaned from the breast, and in addition (due to concomitant, unrelated reasons) larger amounts of gluten were also given at that time.

To make the story even more complex, came the observation from analysis of the data of the Swedish CD epidemic, that the overall prevalence of CD diagnosed by serological screening (EMA) was not different in the group of children born in 1996-1997 compared with those born in 1992-1993[13]. This finding indicated that the amount of gluten introduced during weaning might affect the development of symptomatic CD, but does not protect the children from being affected by subclinical or silent forms of the disease.

Finally, follow-up studies of that same cohort of children born during the epidemic[14] showed that the increased risk of developing CD carries on with time, as the prevalence of this condition in 12-year-old children

(thus born during the epidemic) has been reported to be as high as 3%[14].

The regional differences in the epidemiology of CD in India also give support to the hypothesis that the amount of gluten plays an important role in the onset of CD. CD is reported frequently in high wheat-consuming states in Northern India and quite rarely in the Southern States, where rice is the staple food[15].

THE ROLE OF BREASTFEEDING

The protective effect of breastfeeding on the development of food allergy has been long suspected. Indeed, the majority of the studies on the specific protective effect of breastfeeding on the development of CD, although having very different methodologies and population selection, found a negative correlation between the duration of breastfeeding and the development of CD[16-18]. A rigorous meta-analysis reviewed all the observational epidemiological studies dealing with the effect of breastfeeding on development of CD and found that children being breastfed at the time of gluten introduction had a 52% reduction in risk of developing CD, compared to their peers who were not breastfed at the time of gluten introduction [pooled odds ratio (OR), 0.48; 95% CI: 0.40-0.59][19].

The same author proceeded to estimate how many cases of CD could be prevented in the UK by assuming higher rates of breastfeeding, to conclude that if all babies were breastfed at the time of gluten introduction, this would result in the prevention of more than 2500 cases of CD per year[20]!

The observation of the Swedish experience also gave some clues about the protective role of breastfeeding on CD. The Swedish children that were breastfed at the first exposure to gluten, even with high amounts, showed a lower risk of developing CD than those who were formula fed (OR, 0.59; 95% CI: 0.42-0.83), and the risk was reduced further if they continued to be breastfed afterwards (OR, 0.36; 95% CI: 0.26-0.51)[21,22].

Surprisingly, the data generated in the context of the DAISY project previously mentioned[8] did not provide evidence on the protective role of prolonged breastfeeding. The authors themselves pointed out this discrepancy, ascribing it to the different methodology - the DAISY study was prospective and focused on high risk children, whereas all the previous studies were retrospective and included the general pediatric population.

In spite of all the evidence outlined, some crucial issues remain unanswered: (1) Does breastfeeding at the first exposure to gluten offer a permanent protection against CD or does it only delay its appearance? (2) Are those children breastfed during the introduction of gluten more likely to develop extraintestinal ("atypical") CD? A series of 162 celiac children enrolled at the University of Chicago showed that children breastfed at the time of gluten introduction were just as likely to develop intestinal as extra-intestinal symptoms, whereas children who were not breastfed when weaned with gluten had a much higher chance of showing intestinal symptoms[6]; and (3) What is the mechanism underlying the protective role of breastfeeding towards the development of CD? Presently one can only speculate on 4 possible ways: (a) breast milk contains substances with immunomodulatory activity on the intestinal mucosa, within the idiotypic network; (b) children that are breastfed at gluten introduction during weaning receive lower amounts of gluten, even on a pro/kg body weight basis; (c) breastfeeding prevents gastrointestinal infections, a known contributing factor in the pathogenesis of CD; or (d) the absence of possible multiple contemporary associations with other solids and nutrients.

ESPGHAN RECOMMENDATIONS

On the basis of the above described epidemiological data, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee recommended avoidance of both early (< 4 mo) and late (> 7 mo) introduction of gluten and introduction of small amounts of gluten gradually while the child is still breastfed[23]. This temporary window allows the possibility of modulating the mucosal immune response, with progressively decreasing breastfeeding and maturation of the gastro-intestinal system[22].

CONCLUSION

There remain several open questions about the role of early feeding practices on the development of CD, including the role of additional genetic factors, the type of gluten introduced, and, certainly not least, the role played by the microbiota. It appears that celiac children, even in remission, have a composition of microflora that differs from healthy controls[24]. It is likely that CD may be the end result of an intricate interplay by all of these factors. The challenge is for us to tease out their roles and understand the specific mechanisms that ultimately lead to CD, in order to achieve the ambitious goal of its prevention.

REFERENCES

1 **Jabri B**, Kasarda DD, Green PH. Innate and adaptive immunity: the yin and yang of celiac disease. *Immunol Rev* 2005; **206**: 219-231

2 **Setty M**, Hormaza L, Guandalini S. Celiac disease: risk assessment, diagnosis, and monitoring. *Mol Diagn Ther* 2008; **12**: 289-298

3 **Sollid LM**. Coeliac disease: dissecting a complex inflammatory disorder. *Nat Rev Immunol* 2002; **2**: 647-655

4 **van Heel DA**, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, Wapenaar MC, Barnardo MC, Bethel G, Holmes GK, Feighery C, Jewell D, Kelleher D, Kumar P, Travis S, Walters JR, Sanders DS, Howdle P, Swift J, Playford RJ, McLaren WM, Mearin ML, Mulder CJ, McManus R, McGinnis R, Cardon LR, Deloukas P, Wijmenga C. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet* 2007; **39**: 827-829

5 **Hunt KA**, Zhernakova A, Turner G, Heap GA, Franke L, Bruinenberg M, Romanos J, Dinesen LC, Ryan AW, Panesar D, Gwilliam R, Takeuchi F, McLaren WM, Holmes GK, Howdle PD, Walters JR, Sanders DS, Playford RJ, Trynka G, Mulder CJ, Mearin ML, Verbeek WH, Trimble V, Stevens FM, O'Morain C, Kennedy NP, Kelleher D, Pennington DJ, Strachan DP, McArdle WL, Mein CA, Wapenaar MC, Deloukas P, McGinnis R, McManus R, Wijmenga C, van Heel DA. Newly identified genetic risk variants for celiac disease related to the immune response. *Nat Genet* 2008; **40**: 395-402

6 **Strobel S**. Immunity induced after a feed of antigen during early life: oral tolerance v. sensitisation. *Proc Nutr Soc* 2001; **60**: 437-442

7 **Cummins AG**, Thompson FM. Effect of breast milk and weaning on epithelial growth of the small intestine in humans. *Gut* 2002; **51**: 748-754

8 **Guandalini S**. The influence of gluten: weaning recommendations for healthy children and children at risk for celiac disease. *Nestle Nutr Workshop Ser Pediatr Program* 2007; **60**: 139-151; discussion 151-155

9 **Challacombe DN**, Mecrow IK, Elliott K, Clarke FJ, Wheeler EE. Changing infant feeding practices and declining incidence of coeliac disease in West Somerset. *Arch Dis Child* 1997; **77**: 206-209

10 **Norris JM**, Barriga K, Hoffenberg EJ, Taki I, Miao D, Haas JE, Emery LM, Sokol RJ, Erlich HA, Eisenbarth GS, Rewers M. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA* 2005; **293**: 2343-2351

11 **Ivarsson A**, Persson LA, Nyström L, Ascher H, Cavell B, Danielsson L, Dannaeus A, Lindberg T, Lindquist B, Stenhammar L, Hernell O. Epidemic of coeliac disease in Swedish children. *Acta Paediatr* 2000; **89**: 165-171

12 **Ivarsson A**. The Swedish epidemic of coeliac disease explored using an epidemiological approach--some lessons to be learnt. *Best Pract Res Clin Gastroenterol* 2005; **19**: 425-440

13 **Carlsson A**, Agardh D, Borulf S, Grodzinsky E, Axelsson I, Ivarsson SA. Prevalence of celiac disease: before and after a national change in feeding recommendations. *Scand J Gastroenterol* 2006; **41**: 553-558

14 **Myléus A**, Ivarsson A, Webb C, Danielsson L, Hernell O, Högberg L, Karlsson E, Lagerqvist C, Norström F, Rosén A, Sandström O, Stenhammar L, Stenlund H, Wall S, Carlsson A. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr* 2009; **49**: 170-176

15 **Gupta R**, Reddy DN, Makharia GK, Sood A, Ramakrishna BS, Yachha SK, Thapa BR, Banerjee R, Anuradha S, Dutta U, Puri AS, Jain AK, Mulder CJ, Kumar A, Boindala S. Indian task force for celiac disease: current status. *World J Gastroenterol* 2009; **15**: 6028-6033

16 **Auricchio S**, Follo D, de Ritis G, Giunta A, Marzorati D, Prampolini L, Ansaldi N, Levi P, Dall'Olio D, Bossi A. Does breast feeding protect against the development of clinical symptoms of celiac disease in children? *J Pediatr Gastroenterol Nutr* 1983; **2**: 428-433

17 **Greco L**, Auricchio S, Mayer M, Grimaldi M. Case control study on nutritional risk factors in celiac disease. *J Pediatr Gastroenterol Nutr* 1988; **7**: 395-399

18 **Peters U**, Schneeweiss S, Trautwein EA, Erbersdobler HF. A case-control study of the effect of infant feeding on celiac disease. *Ann Nutr Metab* 2001; **45**: 135-142

19 **Akobeng AK**, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. *Arch Dis Child* 2006; **91**: 39-43

20 **Akobeng AK**, Heller RF. Assessing the population impact of low rates of breast feeding on asthma, coeliac disease and obesity: the use of a new statistical method. *Arch Dis Child* 2007; **92**: 483-485

21 **Persson LA**, Ivarsson A, Hernell O. Breast-feeding protects against celiac disease in childhood--epidemiological evidence. *Adv Exp Med Biol* 2002; **503**: 115-123

22 **Agostoni C**, Shamir R. Can a change in policy of complementary infant feeding reduce the risk for type 1 diabetes and celiac disease? *Pediatr Endocrinol Rev* 2008; **6**: 2-4

23 **Agostoni C**, Decsi T, Fewtrell M, Goulet O, Kolacek S, Koletzko B, Michaelsen KF, Moreno L, Puntis J, Rigo J, Shamir R, Szajewska H, Turck D, van Goudoever J. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008; **46**: 99-110

24 **Collado MC**, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. *J Clin Pathol* 2009; **62**: 264-269

S- Editor Wang YR **L- Editor** Cant MR **E- Editor** Zheng XM