Federation of International Societies of Pediatric Gastroenterology, Hepatology, and Nutrition Consensus Report on Celiac Disease

Celiac Disease Working Group: *A. Fasano, †M. Araya, ‡S. Bhatnagar, §D. Cameron, *C. Catassi, ‖M. Dirks, **M.L. Mearin, ††L. Ortigosa, and ‡‡A. Phillips

*Mucosal Biology Research Center and Center for Celiac Research, University of Maryland School of Medicine, Baltimore, MD, †Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile, ‡Centre for Diarrheal Disease and Nutrition Research, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India, §Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia, ‖Division of Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, Hopital Sainte-Justine, University of Montreal, Montreal, Canada, **Departments of Pediatrics, Leiden University Medical Center and Free University Medical Center, Amsterdam, the Netherlands, ††Pediatric Gastroenterology and Nutrition Unit, Ntra Sra de Candelaria University Hospital School of Medicine, University of La Laguna, Tenerife, Spain, and ‡‡Centre for Paediatric Gastroenterology, Royal Free and University College Medical School, London, UK

Celiac disease (CD) is a gluten-sensitive, immune-mediated chronic enteropathy with a wide range of manifestations of variable severity. It is triggered by the ingestion of gliadin fractions of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible subjects. The subsequent immune reaction leads to small bowel inflammation and villous atrophy. Adherence to a gluten-free diet (GFD) is followed by amelioration or normalization of the villous architecture. CD represents a "unique" autoimmune disease in that the environmental factor triggering the immune response (gluten) is known. CD not only affects the gut but is also a systemic disease that may cause injury to extraintestinal organs as well. Human leukocyte antigen (HLA) status appears to be the strongest genetic determinant of risk for celiac autoimmunity, because of the role that specific HLA class II alleles play in the presentation of gluten to T cells. Of the affected individuals, 95% have either DQ2 (HLA-DQA1*05-DQB1*02) or DQ8 (HLA-DQA1*03-DQB1*0302), in comparison with the general population in which about 30% to 35% have either DQ2 or DQ8 (1,2). Besides HLA II class genes, there is evidence for involvement of other genes located on chromosomes 2 (2q33), 5 (5q31-q33), and 19 (19p13.1), and in the region harboring interleukin-2 (IL-2) and IL-21 (3–6).

The true prevalence of CD is difficult to estimate because of its variable clinical presentation, and many patients can have few or no symptoms. With a better appreciation of its clinical complexity and the availability of sensitive and specific screening tests, CD is now considered a public health problem worldwide. CD affects as much as 0.5% to 1.0% of European or European ancestry populations, but most cases remain undiagnosed (7–11).

CONTROVERSIAL ISSUES

Diagnosis

Serology Tests

The tissue transglutaminase antibody (tTG) enzyme-linked immunoassay is the universally recommended screening test for CD (3,4). The occurrence of both immunoglobulin (Ig)A deficiency and CD in the same individual varies between 2% and 10%; thus, measurement of total serum IgA is necessary to interpret low tTG-IgA. In cases of IgA deficiency, testing with tTG-IgG is recommended to detect CD. Because the inferior accuracy of the antigliadin assays, the use of this test no longer is routinely recommended. The use of deamidated gliadin to increase specificity of the antigliadin assay awaits confirmation by large-scale validation.

Point of Contact (POC) Tests

Point of contact (POC) tests are in vitro diagnostic devices used outside the laboratory close to the site of

patient care. The demand for POC testing is increasing, because of advances in technology and the need for rapid tests. Three rapid methods are currently available for detection of serum or whole blood tTGA with good sensitivity and specificity (12–14). These tests can be performed on a drop of whole blood, allow a visual reading of the result after a few minutes (15), and represent a valuable alternative to the traditional serological tests for CD. However, the risk that POC tests can lead to self-diagnosis and implantation of a GFD without an intestinal biopsy confirmation needs to be scrutinized in future research.

Genetic Tests

CD patients lacking HLA-DQ2 or DQ8 are exceptional, and the lack of both haplotypes strongly argues against the diagnosis of CD (3). HLA typing for DQ2/DQ8 has a high sensitivity but low specificity for CD, indicating a poor positive predictive value, but a high negative predictive value for the disease. If in the future the ''CD cluster'' of predisposed genes is identified, this may form a useful tool to detect CD. Determining whether specific genotypes can affect type and/or age of onset of symptoms and possible associated complications would be an important objective for future research.

Intestinal Biopsy

Small bowel biopsy has remained the confirmatory cornerstone test for CD (16). Esophagogastroduodenoscopy is the preferred diagnostic technique, allowing multiple intestinal biopsies (4–6). Interpretation of the biopsy requires an expert pathologist to score the most severely affected biopsy (17). Marsh type 1 alterations, or increased intraepithelial lymphocytes (>25/100 enterocytes), are nonspecific in children, especially in children from developing countries (18), but in the setting of positive tTGA and symptoms a trial of GFD may be warranted. Both pediatric and adult studies have suggested algorithms for the detection of CD without a biopsy (19,20) in those with typical gastrointestinal symptoms and high titer of tTGA. These findings need to be confirmed by larger population studies to be validated as routine clinical practice.

Screening

Targeted Screening of High-risk Groups

There is evidence that CD should be tested in children with persistent gastrointestinal symptoms such as diarrhea, recurrent abdominal pain, constipation, and vomiting, as well as in children with nongastrointestinal symptoms of CD such as dermatitis herpetiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty, and iron-deficient anemia

(14). CD testing also is recommended for asymptomatic children who have conditions associated with CD such as type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency, as well as first-degree relatives with CD. Testing of asymptomatic children who belong to groups at risk should begin at around 3 to 4 years of age, provided they have had an adequate gluten-containing diet for at least 1 year before testing (21).

Mass Screening

The prevalence of CD exceeds by far that of a number of diseases for which mass screening programs are in place (22). CD has a broad spectrum of symptoms and the disease is difficult to identify on clinical grounds alone, often resulting in delayed or missed diagnosis. Health consequences of untreated CD include anemia, delayed puberty, growth impairment, hypertransaminasemia, neuropsychiatric disturbance, depression, epilepsy with cerebral calcifications, low bone mineral density and dental enamel hypoplasia, and autoimmune diseases, depending on the duration of gluten exposure (23). Two severe late complications of CD are malignancy and osteoporosis. CD has an accepted treatment, the GFD. Mass screening of the general population is 1 way to identify people with CD at an early stage. However, despite fulfilling many of the general screening criteria, mass screening for CD includes several controversial factors that keep a debate ongoing (24,25).

CELIAC DISEASE IN THE DEVELOPING WORLD

CD Causal Factors Show a Worldwide Distribution

The principal genetic (HLA DQ2 and DQ8) and environmental (gluten) factors responsible for the development of CD show a worldwide distribution (26). A variable frequency of either high (eg, DQ2 in homozygosity) or low/moderate risk (eg, DQ8) genotypes could explain the variable prevalence of CD that has been reported in different parts of the world.

CD Is Increasingly Reported From the Developing World

Epidemiological studies have shown that CD is common in many developing countries (27). The presence of CD is long established in many South American countries that are mostly populated by individuals of European origin (10,28).

Although the frequency of CD in many parts of Africa is still unknown, it is clear that this condition is present in the African continent. The highest CD prevalence in the world (5.6%) occurs in an African population originally

living in western Sahara, the Saharawi, of Arab-Berber origin (29). The reasons for this may be related to the high level of consanguinity and the high frequency of HLA-DQ2 and-DQ8 in the Saharawi population (30). Gluten consumption is also high. CD also is a common and usually undiagnosed disorder among Egyptian children (31). In a recent mass screening for CD on 6284 children in Tunisia, a prevalence of 1:157 was found (32). Indirect evidence suggests that CD is not a rare disorder in other northern African countries (33,34). CD is a frequent disorder also in the Middle East (35). In studies from Iran, Iraq, Saudi Arabia, and Kuwait, CD accounted for 20% and 18.5% of cases with chronic diarrhea in adults and children, respectively. In a study from Jordan, the high incidence of CD was related to the large wheat consumption of the population (135 kg/head/year) (36). The overall prevalence of CD in India is not known, but is likely to be high in a part of northern India where wheat is a staple food (26). There are only anecdotal reports of CD in Far East countries. Given the low prevalence of HLA predisposing genes DQ2/DQ8 and the low/absent gluten consumption, reduced disease prevalence should be expected in those populations.

The burden of disease caused by CD in developing countries is largely underestimated. Reasons for this include the belief that CD does not exist in developing countries; poor awareness of the clinical variability of CD; scarcity of diagnostic facilities; and more emphasis on other causes of small intestinal damage, such as intestinal tuberculosis and environmental enteropathy (26). It also is possible that the prevalence of CD is increasing in some developing countries because of increasing consumption of gluten-containing cereals.

CD Clinical Spectrum in Developing Countries

The typical child with CD in developing countries may resemble the picture of chronic protein-energy malnutrition known as kwashiorkor. The predominant clinical manifestations of CD among Saharawi children are chronic diarrhea, abdominal distension, growth failure, depressed mood, and loss of appetite (29). In children affected with CD from India, the majority (84%) presented with diarrhea; other features were failure to thrive in 91%, anemia in 84%, wasting in 87%, and stunting in 60% of cases.

Although symptomatic forms seem to be more common in developing countries, serological screening studies in these regions have shown many cases present with mild complaints or no symptoms at all.

Reliability of Diagnostic Tools

Studies in South America, the Middle East, and India have shown that both the endomysium antibodies and tTG are highly specific markers of celiac autoimmunity in subjects living in areas with high rate of infectious and/or parasitic diarrhea. The recent introduction of a quick test for POC determination of IgA class anti-tTG could overcome, at least in part, problems related to the scarcity of sophisticated diagnostic equipment (12).

Treatment Strategies

To be effective, implementation of a GFD has to take local dietary habits into account by using naturally gluten-free products that are locally available, such as millet (Africa), manioc (South America), and rice. To avoid cross-contamination with gluten, dedicated machinery needs to be used to mill these grains. The treatment strategy also should include education for doctors, nurses, dieticians, school personnel, affected families, and the general population. Finally, creation of patient support groups can provide psychological support, a valuable source of information.

Treatment Alternatives to the Gluten-free Diet

A GFD is effective and safe and at present is the only available treatment for CD. Any alternative treatment in the future must have a safety and effective profile equivalent to that of the GFD, but with the advantage of increased compliance, quality of life, and feasibility in developing countries in which implementation of a GFD is complicated by formidable economical, cultural, and distribution difficulties.

Enzyme Therapy

Gluten peptides are resistant to digestion by pancreatic and brush border proteases (37). Enzyme supplement therapy with bacterial prolyl endopeptidases has been proposed to promote digestion of cereal proteins and thus destroy T cell multipotent epitopes. It remains to be assessed to what extent such intraluminal digestion is effective in practice. An alternative approach is based on a pretreatment of gluten-containing food with bacterial-derived peptidase (38). CD patients tolerated breads produced with sourdough (lactobacillus digested) better than those with Baker's yeast (39). Another approach to produce nontoxic, wheat-based products is transamidation of gluten peptides by tTG, because it has been shown that these peptides inhibit interferon gamma expression in intestinal T-cell lines (40).

Engineered Grains and Inhibitory Gliadin Peptides

Breeding programs and/or transgenic technology may lead to production of wheat that is devoid of biologically active peptide sequences. Site-directed mutagenesis of wheat, which would not affect the baking properties, also has been proposed, although the number and the repetition of such sequences in wheat render this approach difficult.

Immunomodulatory Strategies

The autoantigenic tTG is mainly expressed in the lamina propria and catalyzes transamidation of gluten peptides (glutamine to glutamic acid), increasing their rate of phagocytosis by antigen-presenting cells (41). Selective inhibition of tTG in the small intestine may represent a useful therapeutic strategy in CD.

Correction of the Intestinal Barrier Defect

The barrier function and ability to regulate the trafficking of macromolecules between the environment and the host is an important function of the small bowel. Together with the gut-associated lymphoid tissue and the neuro-endocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non–self-antigens (42). The correction of the intestinal barrier defects may represent an innovative therapeutic alternative in CD, because small intestinal permeability abnormalities are seen in untreated CD patients, which return to normal on a GFD (43). The use of the zonulin inhibitor AT1001 to correct intestinal barrier defects already has been successfully explored in an animal model of autoimmunity (44). Recently, AT1001 has been shown to be well tolerated and to reduce gluten-induced intestinal barrier dysfunction, proinflammatory cytokine production, and gastrointestinal symptoms in celiac patients (45).

RESEARCH AGENDA

In 2007 the European platform on CD CDEUSSA– formed by 103 key stakeholders from 27 countries, representing among others research, food industry, and public health and patient organizations–identified 4 CD topics (clinical aspects, treatment, prevention, and public health) in need of investigation during the next few years. These research areas and related topics have been proposed to the European Community as high priority research to improve the health status of the European population and are presented in Table 1 (46). The overall research goal should be to improve the quality of life of the population by implementing primary prevention strategies, early diagnosis, and improved treatments for CD. Strategies for effective case-finding, and even mass screening efforts, should be explored to decrease the large proportion of undiagnosed and untreated CD subjects. Such efforts should include evaluation of short- and long-term consequences both for participating individuals and society, also considering health economic aspects, particularly in developing countries. The magnitude of the CD problem worldwide and trends over time should be established. New treatment strategies need to be developed. Expected results are the identification of nutritional, immunomodulatory, and biochemical strategies useful to successfully treat CD subjects. The option of primary prevention should be fully explored, which requires combined epidemiological, clinical, and basic science research efforts. Such studies also should consider the importance of gene–environment interactions in the development of CD. To achieve these goals, and have a significant impact on the public health problem of CD, a collaboration of the stakeholders is fundamental, including research and patient organizations as well as industries within both diagnostics and food production.

CONSENSUS GUIDELINES

- CD is an immune-mediated enteropathy that can affect any system or organ and that can present itself with a wide range of clinical manifestations of variable severity
- CD represents a unique autoimmune disease in that the environmental factor triggering the immune response (gluten) is known
- CD is a complex genetic disorder and HLA status appears to be the strongest genetic determinant of risk for celiac autoimmunity
- The diagnosis of CD is based on specific and sensitive screening tests (particularly in at-risk populations) and an intestinal biopsy as a confirmatory test
- CD is not confined to whites of European origin. Rather, CD is extremely frequent in any area of the world where both genetic determinants (HLA class II genes) and environmental trigger (gluten) are present
- CD is one of the most frequent genetic disorders of humankind, affecting 0.5% to 1% of the general population
- Nevertheless, CD remains highly underestimated, particularly in developing countries, where its clinical presentation can be mistaken for pathologies (infections, malnutrition, etc) that have been considered more prevalent
- The best approach to search for CD patients (mass screening vs case-finding) remains controversial; however, cost-benefit analyses and issues related to treatment compliance suggest that case-finding is the most appropriate approach
- The implementation of a GFD remains the most effective treatment for CD; however, treating the disease with GFD in a developing country with limited resources can be extremely difficult or not doable at all
- Regardless of the socioeconomic realities, there are a number of drawbacks to a lifelong GFD possibly affecting the quality of life of CD patients
- New knowledge has opened the potential of new preventive and therapeutic strategies for CD that are being explored

TABLE 1. *Some of the most important issues in celiac disease (CD) in need of investigation in the coming years*

Clinical aspects
Elucidation of the clinical spectrum	Pathomechanisms underlying different manifestations
	Role of tissue deposited IgA anti-transglutaminase antibodies
Exploring the autoimmunity spectrum	Identification of the whole spectrum of gluten-related autoantibodies
	Gluten ingestion and risk of autoimmunity
	Infant feeding patterns and risk of autoimmunity
Definition of the natural history	Timing of appearance of CD-related autoantibodies
	Environmental factors conditioning severity of CD
Revision of diagnostic criteria	Identification of genes and risk assessment
	Immunological markers of innate and adaptive immunity
	New diagnostic approaches
	Development of new noninvasive diagnostic algorithms

Treatment
Decide on treatment criteria	Long-term health risks of silent and potential cases
	Development of gluten tolerance in CD cases
Improve health care and quality of life	Nutritional consequences of gluten-free diet and food labeling, availability of gluten-free foods, and awareness of this disease
	Strategies to implement a gluten-free diet in developing countries
Development of safe and new foods	Oats toxicity
	Threshold of tolerance to gluten
	Genomics and proteomics of different wheat cultivars and implementation of traditional or biotechnologically modified gluten-free cereal variants
Explore treatment alternatives	Enzyme supplements therapy
	Blocking of gliadin presentation such as HLA blockers and tTG inhibitors
	Cytokines and anticytokines such as ILIO, anti-IFN-γ, anti-IL-15
	Reestablishment of tolerance (modified gluten peptides, nasal tolerance)
	Reestablishment of the intestinal barrier function

Prevention
Determine role of breast-feeding	Long-term effects of breast-feeding
	Molecular basis for the protective effect
Determine role of timing and dose of gluten during introduction	Optimal age for introducing gluten
	Timing in relation to breast-feeding and infectious episodes
	Optimal dose of gluten and pattern for introduction
	Mucosal immune response at time of gluten introduction
Explore role of probiotics and prebiotics	Possibly role in oral tolerance
Explore role of lifestyle factors in children and adults	A life course approach to CD development, thus, a search for potentially contributing causes, also after infancy
Explore option of general and targeted prevention	Advice to general population vs genetically identified high-risk subjects
	Public health impact of different preventive strategies

Public health
Estimate consequences with respect to health-related quality of life	Standardized instruments for measuring health-related quality of life
	Consequences of CD and its treatment on daily life of affected people.
	Public health impact of CD.
Evaluate consequences of mass screening	Active-case finding and mass-screening strategies
	Costs and savings related to diagnosis and treatment
	Gains in health-related quality of life estimated as QALYs
	Costs per QALY gained and comparison with other health interventions
Determine global occurrence	Validation of POC tests as initial screening tools, particularly in areas in which public health facilities are scarce or difficult to reach
	Analysis of weight of environmental and genetic components in determining regional and temporal variability of CD prevalence
	Cross-sectional screening of age- and sex-representative population samples globally to facilitate health care planning
	Incidence registers for epidemiological surveillance and to be used as basis for etiologic and long-term follow-up studies

Ig = immunoglobulin; HLA = human leukocyte antigen; tTG = tissue transglutaminase; IFN = interferon; IL = interleukin; QALY = quality-adjusted life year; POC = point of contact.
Adapted from Reference 46.

REFERENCES

1. Bevan S, Popat S, Braegger CP, et al. Contribution of the MHC region to the familial risk of coeliac disease. *J Med Genet* 1999;36:687–90.
2. Hogberg L, Falth-Magnusson K, Grodzinsky E, et al. Familial prevalence of coeliac disease: a twenty-year follow-up study. *Scand J Gastroenterol* 2003;38:61–5.
3. Reeves GE, Squance ML, Duggan AE, et al., and the Multicentre Coeliac Study GroupDiagnostic accuracy of celiac serological tests: a prospective study. *Eur J Gastroenterol Hepatol* 2006;18:493–501.
4. Craig D, Robins G, Howdle PD. Advances in CD. *Curr Opin Gastroenterol* 2007;23:142–8.
5. Van Heel DA, Franke L, Hunt KA, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. *Nat Genet* 2007;39:827–9.
6. Van Heel DA, Hunt K, Greco L, et al. Genetics in coeliac disease. *Best Pract Res Clin Gastroenterol* 2005;19:323–39.
7. Catassi C, Ratsch IM, Fabiani E, et al. Coeliac disease in the year 2000: exploring the iceberg. *Lancet* 1994;343:200–3.
8. Csizmadia CG, Mearin ML, von Blomberg BM, et al. An iceberg of childhood coeliac disease in the Netherlands. *Lancet* 1999;353:813.
9. Hovell CJ, Collett JA, Vautier G, et al. High prevalence of coeliac disease in a population-based study from Western Australia: a case for screening? *Med J Aust* 2001;175:247–50.
10. Gomez JC, Selvaggio G, Viola M, et al. Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. *Am J Gastroenterol* 2001;96:2700–4.
11. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;163:286–92.
12. Korponay-Sazbó IR, Raivio T, Laurila K, et al. Coeliac disease case finding and diet monitoring by point-of-care testing. *Aliment Pharmacol Ther* 2005;22:729–37.
13. Nemec G, Ventura A, Stefano M, et al. Looking for CD: diagnostic accuracy of two rapid commercial assays. *Am J Gastroenterol* 2006;101:1–4.
14. Blesa LC, Donat E, Ortigosa L, et al. Coeliac disease screening by immunochromatographic visual assays. Results of a multicentre study. *J Ped Gastroenterol Nutr* 2007;45:546–50.
15. Catassi C. Coeliac disease epidemiology is alive and kicking, especially in the developing world. *Dig Liver Dis* 2007;39:908–10.
16. Walker-Smith JA, Guandalini S, Schmitzs J, et al. Revised criteria for the diagnosis of celiac disease. Report of the working group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;65:909–11.
17. Marsh MN, Crowe PT. Morphology of the mucosal lesion in gluten sensitivity. *Baillieres Clin Gastroenterol* 1995;9:273–93.
18. Corazza GR, Villanacci V, Zambelli C, et al. Comparison of the interobserver reproducibility with different histological criteria used in celiac disease. *Clin Gastroenterol Hepatol* 2007;5:838–43.
19. Bhatnagar S, Gupta SD, Mathur M, et al. Celiac disease with mild to moderate histologic changes is a common cause of chronic diarrhea in Indian children. *J Pediatr Gastroenterol Nutr* 2005;41: 204–9.
20. Barker CC, Mitton C, Jeron G, et al. Can tissue transglutaminase antibody titres replace small bowel biopsy to diagnose celiac disease in selected pediatric populations? *Pediatrics* 2005;115: 1341–6.
21. Hill ID, Dirks MH, Liptak GS, et al., North American Society for Pediatric Gastroenterology, Hepatology, and NutritionGuideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:1–19.
22. Hopper AD, Cross SS, Huristone DP, et al. Pre-endoscopy serological testing for celiac disease: evaluation of a clinical decision tool. *BMJ* 2007;334:729–34.
23. Mearin ML. Celiac disease in children and adolescents. *Curr Probl Pediatr Adolesc Health Care* 2007;37:86–105.
24. Fasano A. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:168–9.
25. Kumar PJ. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:170–1.
26. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120:636–51.
27. Catassi C, Fasano A, Corazza GR (editors). In: *The Global Village of Celiac Disease*. AIC Press:Pisa, Italy; 2005.
28. Oliveira RP, Sdepanian VL, Barreto JA, et al. High prevalence of celiac disease in Brazilian blood donor volunteers based on screening by IgA antitissue transglutaminase antibody. *Eur J Gastroenterol Hepatol* 2007;19:43–9.
29. Catassi C, Rätsch IM, Gandolfi L, et al. Why is celiac disease endemic in the people of Sahara? *Lancet* 1999;354:647–8.
30. Catassi C, Doloretta Macis M, Rätsch IM, et al. The distribution of DQ genes in the Saharawi population provides only a partial explanation for the high celiac disease prevalence. *Tissue Antigens* 2001;58:402–6.
31. Abu-Zekry M, Diab M, Kryszak D, et al. Prevalence of celiac disease in Egyptian children disputes the East–West agriculture-dependent spreading of the disease. *J Pediatr Gastroenterol Nutr* 2008; 47:136–140.
32. Ben Hariz M, Kallel-Sellami M, Kallel L, et al. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. *Eur J Gastroenterol Hepatol* 2007;19:687–94.
33. Mediene S, Hakem S, Bard JM, et al. Serum lipoprotein profile in Algerian patients with celiac disease. *Clin Chim Acta* 1995;31:189–96.
34. Al-Tawaty AI, Elbargathy SM. Coeliac disease in north-eastern Libya. *Ann Trop Paediatr* 1998;18:27–30.
35. Shahbazkhani B, Forootan M, Merat S, et al. Coeliac disease presenting with symptoms of irritable bowel syndrome. *Aliment Pharmacol Ther* 2003;18:231–5.
36. Rawashdeh MO, Khalil B, Raweily E. Celiac disease in Arabs. *J Pediatr Gastroenterol Nutr* 1996;23:415–8.
37. Shan L, Molberg O, Parrot I, et al. Structural basis for gluten intolerance in celiac sprue. *Science* 2002;297:2275–9.
38. Di Cagno R, De Angelis M, Auricchio S, et al. Sourdough bread made from wheat and nontoxic flours and started with selected lactobacilli is tolerated in celiac sprue patients. *Appl Envison Microbiol* 2004;70:1088–96.
39. Di Cagno R, De Angelis M, Lavermicocca P, et al. Proteolysis by sourdough lactic acid bacteria: effects on wheat flour protein fractions and gliadin peptides involved in human cereal intolerance. *Appl Environ Microbiol* 2002;68:623–33.
40. Gianfrani C, Siciliano RA, Facchiano AM, et al. Transamidation of wheat flour inhibits the response to gliadin of intestinal T cells in celiac disease. *Gastroenterology* 2007;133:780–9.
41. Piacentini M, Colizzi V. Tissue transglutaminase: apoptosis versus autoimmunity. *Immunol Today* 1999;20:130–4.
42. Fasano A, Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nat Clin Pract Gastroenterol Hepatol* 2005;2:416–22.
43. Ukabam SO, Cooper BT. Small intestinal permeability as an indicator of jejunal mucosal recovery in patients with celiac sprue on a gluten-free diet. *J Clin Gastroenterol* 1985;7:232–6.
44. Watts T, Berti I, Sapone A, et al. Role of the intestinal tight junction modulator zonulin in the pathogenesis of type I diabetes in BB diabetic-prone rats. *Proc Natl Acad Sci USA* 2005;102:2916–21.
45. Paterson BM, Lammers KM, Arrieta MC, et al. The safety, tolerance, pharmacokinetic, and pharmacodynamic effects of single doses of AT-1001 in celiac disease subjects: a proof of concept study. *Aliment Pharmacol Ther* 2007;26:757–66.
46. Troncone R, Ivarsson A, Szajweska H, et al. Future research on celiac disease–a position report from the European multi-stakeholder platform on celiac disease (CDEUSSA). *Aliment Pharmacol Ther* 2008;27:1030–43.