Celiac disease (CD) is a chronic disorder caused by an inflammatory T-cell response to the storage proteins in wheat (gliadin), rye (secalin), and barley (hordein), which are collectively called “gluten” and characterized by the presence of typical autoantibodies and histological alterations of the small bowel mucosa. Genetic, immunological, and environmental factors are necessary for the expression of the disease. Ingestion of gluten by genetically predisposed people precipitates an uncontrolled T-cell-driven inflammatory response that leads to disruption of the structural and functional integrity of the small bowel mucosa. CD is treated with a gluten-free diet (GFD), which leads to resolution of the clinical disease and restoration of the histological abnormalities. CD was once thought to be a rare condition, but at the present time it is accepted that CD is the most common form of food hypersensitivity in children and adults.

The first description of CD is attributed to Aretaeus the Cappadocian, who lived in the second century AD. He noted the characteristic stool and chronic nature of the condition and observed that children could also be affected by the disease. In 1888, Samuel Gee, a physician working at the St. Bartholomew Hospital in London, provided a thorough description of the clinical features of childhood CD. During the first half of the past century, it was generally agreed that the treatment for CD was rest and diet. In 1924 Sidney Haas described his treatment of childhood CD with a banana diet, but there was hardly any form of diet not frequently discussed at that time as a treatment for the disease. However, the relationship between gluten ingestion and the symptoms of CD was discovered by the Dutch pediatrician Willem-Karel Dicke (1905-1962). He became the medical director of the Juliana Children’s Hospital in The Hague (The Netherlands) at the age of 31. Long before the start of the Second World War (1934-1936) he started experiments with wheat-free diets. At the end of World War II, during the 1944-1945 winter of starvation, the delivery of normal food such as bread to his young patients in his hospital was endangered. This period and dietary studies convinced him even more that eating less cereals and more uncommon food products such as tulip bulbs improved the clinical condition of his patients and that a wheat-free diet had favorable effects on children with CD. After World War II, in collaboration with Van de Kamer, a biochemist from the Netherlands’ Central Institute for Nutritional Research TNO in Utrecht, and with Weyers, a pediatrician from the Wilhelmina Children’s Hospital in Utrecht, he extended his research and demonstrated that gliadins, ie, the alcohol-soluble fractions of gluten (wheat protein), produced fat malabsorption in patients with CD. His experiences with the wheat-free diet were at first published in “Het Nederlands Tijdschrift voor Geneeskunde” (Dutch Journal of Medicine) in 1941. In his PhD dissertation, published in 1950, he described a dietary study over a period of several years at the Juliana Children’s Hospital in patients with CD. In his PhD thesis Dicke wrote: “The starting point of this treatment (gluten-free diet) was to me an observation of M.E. van Dusseldorp and H. A. Stheemann, during the treatment of a celiac patient” (chapter 3: treatment with a diet free of corn). Dicke refers to a child with CD who went through three attacks of “gastrointestinal catarrh” after eating corn-containing products during a stay in the hospital. This observation was presented by Dr. Stheemann (the supervisor of Dicke in The Hague) in The Medical Society of The Hague in 1932. Van Dusseldorp would
succeed Dicke as one of the first women directors of a Hospital in The Netherlands.

A few years after Dicke’s discovery, the advent of the peroral intestinal mucosal biopsy led to confirmation of the characteristic intestinal histopathology of CD.8

Clinical Spectrum and the Iceberg of CD

CD occurs largely in Caucasians. The disease has been well documented in Asians from India, Pakistan, and Iran,9 but it is rare or nonexistent among native Africans, Japanese, and Chinese. Using simple serological tests, it has gradually become clear that the prevalence of CD in different countries in the Middle East, North Africa, and India where wheat has been the major staple food for many centuries is almost the same as that in Western countries. Clinical studies showed that presentation with nonspecific symptoms or no symptoms is as common in the Middle East as it is in Europe. A high index of suspicion for CD should be maintained in all developing countries for patients who present with chronic diarrhea or iron-deficiency anemia.10

CD is a common, but frequently unrecognized, disease. The disease is more frequent among females, with a female-to-male ratio of 2-3:1. Screening studies have shown that CD is severely underdiagnosed, with a prevalence of 0.5 to 1% among the white population,11 both in adults12,13 and in children.14-16 Assuming a conservative prevalence of 0.5%, this corresponds to about 2.5 million CD cases in Europe. Approximately 85% of these cases are unrecognized and thus also untreated. Findings from mass screening studies in the USA show a prevalence of the disease similar to that reported in Europe and suggest that CD is a much greater problem in the United States than has previously been appreciated.17 CD is also a frequent condition in South America, as shown by the prevalence of undiagnosed CD of 1:681 among apparently healthy blood donors in Brazil18 and of 1:167 among the general urban population in Argentina, presenting with a heterogeneous clinical picture and a predominance of asymptomatic cases.19

CD is frequently unrecognized by physicians, in part because of its variable clinical presentation and symptoms.20 CD is easily diagnosed in children with a symptomatic malabsorption syndrome, but most of the children with CD do not have malabsorption and the clinical picture at presentation is very variable. Not all CD patients are equal. While some develop CD very early in life, others may eat gluten for many years before the disease becomes apparent. The clinical picture of CD is very heterogeneous with a broad spectrum of symptoms, from malabsorption, chronic diarrhea, and failure to thrive (the classic “triad”) to abdominal pain, lassitude, iron-deficiency anemia, delayed puberty, nonspecific arthritis, depression, ataxia, low bone mineral density, or dental enamel hypoplasia without gastrointestinal complaints.11,20 This heterogeneity in the clinical presentation is one of the causes of poor diagnosis of the disease. At present it is not known what causes these differences in the clinical expression of CD, but there is some evidence that both genetic and environmental factors may be involved.21,22 The relationship between the different HLA-DR and -DQ haplotypes of the children with CD and their clinical presentation has been thoroughly investigated. Some researchers have found a significant relationship between the gene dose effect and the heterogeneity of the clinical disease,21-23 but others have not noted an association.24 Congia and coworkers22 found that a double dose of DQ2 (α*0501, β1*0201) predisposes for an early onset and more severe disease manifestations. The differences in outcome can be partially explained by the fact that, for statistical analysis in this latter study, the groups were divided in double-, single-, or no-dose HLA-DQ2, and the authors also limited the phenotypic distribution to fully expressed disease versus mono-/oligosymptomatic. We have recently shown that children with the DR3DQ2-DR5DQ7 and DR5DQ7-DR7DQ2 genotype are presented with CD at an earlier age and have a more severe clinical picture, which suggests a link between the genotype and phenotype. A correlation between disease severity and the HLA-DQ2 gene dose was not observed (Vermeulen B, Hogen Esch C, Yuksel Z, et al., unpublished data). It is possible that other, non-HLA genetic factors also play a role in the different phenotypic expression of CD.

The iceberg is a model frequently used to explain the clinical spectrum of CD (Fig 1).

- The tip of the iceberg is formed by the children with clinically diagnosed CD, among others, those with clear gastrointestinal symptoms such as chronic diarrhea and malabsorption (Table 1), those with so-called “classic CD.” The symptoms
start typically after the introduction of gluten into the diet of babies or toddlers, but they may also present later in life. The severe clinical condition in young children, known as “celiac-crisis,” accompanied by skin bleeding, hypocalcemic tetany, hypoalbuminemia, and edema is nowadays very rare.

In the Netherlands, as in most countries, the majority of CD diagnoses are in children with the “classic” symptoms. However, the results of a prospective national study of all the newly diagnosed cases of CD throughout the country from 1993 to 2000 show that the recognition of childhood CD in the Netherlands has increased significantly during the last few years (Fig 2), and that the clinical picture has changed as well with a decrease in the frequency of “classic” symptoms (Fig 3). The overall crude incidence rate of CD for 1993 to 2000 was 0.81/1000 live births. We found a significant linear increase of the crude incidence rate from 0.55 per 1000 live births in 1993 to 1.10 per 1000 live births in 2000. From 1996 onward, there was a greater increase in incidence of CD among children older than 2 years than among the younger children.

This increasing frequency of diagnosis seems to be true worldwide, including the USA. An open question is whether the increase in diagnosed childhood CD is due to more children developing CD or whether it reflects a greater awareness of the disease among the physicians who increasingly recognize more subtle expressions of the disease.

Under the water level in the CD iceberg, we find the children with unrecognized or nondiagnosed CD. These children have the typical CD histological alterations in their small bowel mucosa and they may or may not have health complaints or symptoms. In the Netherlands, for every child with diagnosed CD, there are at least seven children with unrecognized CD. Identification of these children
after mass screening programs in the general population in different countries has shown that about 0.5 to 1% of the children have CD14-16 and that CD is the most common form of food intolerance in children, adolescents, and adults. Children with unrecognized CD may be asymptomatic, but they frequently have symptoms such as chronic abdominal pain or lassitude that is frequently a cause of consultation with a pediatrician. CD may also be unrecognized if it is associated with other, frequently autoimmune diseases such as type 1 diabetes mellitus, anemia, arthritis, and osteoporosis even in the absence of gastrointestinal symptoms11 (Table 2). A link between CD and asthma has been supported by some studies but not by others. Greco and coworkers found no difference in the prevalence of atopy in cases affected by CD and their relatives compared with controls and their relatives.28 On the other hand, an important study on the Finnish Medical Birth Register data of the whole 1987 birth cohort (n = 60,254 births) showed a significant increased cumulative incidence of asthma in children with CD (24.6%) than in children without CD (3.4%) during the first 7 years of life, indicating that TH1 and TH2 immunological mediated diseases can coexist and may have a common environmental denominator.29 Another associated disease is idiopathic pulmonary hemosiderosis, a rare condition of unknown autoimmune etiology mainly affecting children and adolescents, in which a GFD may be very effective for the regression of the pulmonary hemosiderosis.30

- An important associated disease is dermatitis herpetiformis, a dermatology disease also known as “CD of the skin,” with a high frequency of CD in adults,31 but with a much lower frequency in childhood CD.32 Down syndrome is strongly associated with CD,33 and to a lesser degree, Turner’s syndrome is associated with the disease.34 Under-diagnosis is common in children with Down syndrome and we found only two cases of Down syndrome among 225 children with CD diagnosed in the Netherlands between 1975 and 1990, while CD was identified by screening in 7% of the children with Down syndrome in the same area.35 The health complaints present in children with Down syndrome and CD are frequently and repeatedly attributed to Down syndrome, but in most of the children the health status improves after a GFD. Another possible manifestation of CD is short stature. In two British population-based studies on short stature, where CD was not specifically inves-
tigated, the prevalence of CD was 2:180 and 0:149, respectively. In children with short stature and no gastrointestinal symptoms investigated for CD, the prevalence increases to 2 to 8%. When other (endocrine) causes for short stature are excluded, the prevalence could rise to 59%. CD may be asymptomatic both above and below the water level of the CD iceberg, for example, among family members of CD patients (approximately 3 to 10% asymptomatic) and among young children with CD identified by mass screening (approximately 50% asymptomatic). Normal growth does not exclude CD in children as it was demonstrated in a mass screening program in the Netherlands: all the children from the general population identified with CD had normal growth for both weight and height. The bottom of the CD iceberg is formed by the children with the genetic predisposition for CD who may or may not develop CD during their lives.

Complications of CD

CD is an important health problem for the individual and the community, because of its high prevalence, association with nonspecific morbidity, and long-term complications. The health burden of CD is considerable. CD is an immune-mediated disease that can affect any organ. The broad spectrum of symptoms varies considerably between children and within a single child over time, often resulting in delayed or missed diagnosis. Many undiagnosed children accept a chronic state of vague ill health as normal. Paradoxical constipation and symptoms more typical of peptic or reflux disease are common. Health problems due to untreated CD include anemia, delayed puberty, elevated serum transaminases, depression, epilepsy with cerebral calcifications, low bone mineral density, and dental enamel hypoplasia. CD subjects also have an increased risk for other autoimmune diseases, depending on the duration of gluten exposure.

Two severe eventual complications of CD are malignancy and osteoporosis. **CD and Malignancy.** In adults, CD has been considered a premalignant condition, which could progress to lymphoma. Evidence that treatment of CD with a GFD might reduce the risk of malignancy was established by Holmes and coworkers. In adults, increased frequency for lymphoma (6%), small bowel adenocarcinomas, and esophageal and oropharyngeal squamous carcinomas have been described. However, these prevalence figures represent probably an overestimation of the frequency of malignancy in CD since the studies were performed in centers for CD. Recent population-based studies indicate that the increased risk of malignancy associated with CD is less than previously thought with an odds ratios (OR) for non-Hodgkin lymphoma of 2.6 to 6.3. There is a form of cancer, the enteropathy-associated T-cell lymphoma (EATL), with a very high association with CD, but this in general is a rare condition with an absolute risk of only 1:1000 based on the local prevalence of CD. Small bowel lymphoma and EATL are very rare diseases, but CD is the most important risk factor for these conditions.

An inquiry among the members of ESPGHAN found 25 cases of children with cancer and CD, suggesting that an association between CD and cancer in childhood is not likely, but it showed also that the combination of cancer and CD in childhood is under-reported. The children described with CD and cancer were found only through a limited number of highly specialized pediatricians in Europe. Six of the 25 children reported had malignant disease localized in the small bowel [4 of them a non-Hodgkin lymphoma (NHL)], suggesting that in children and adults there is an association between CD and small bowel malignancy. However, NHL is a common cancer in childhood and small bowel localization frequently occurs. To get more data on this subject, the importance of reporting all cases of CD and cancer in children to the literature should be stressed.

The role of the pediatrician in counseling the parents of a child with CD regarding the long-term risks of cancer should be to reassure them, since, in the big series of CD complicated by cancer, there were no patients in whom CD has been diagnosed during childhood CD, suggesting that the association of childhood CD with cancer may be very low.

**Osteoporosis.** Osteoporosis is characterized by a low bone mass with an increase in bone fragility and susceptibility to fracture. Intestinal malabsorption may cause loss of bone mass and mineral metabolism alteration. In CD the main mechanisms of osteoporosis are malabsorption and the production of proinflammatory cytokines, activating osteoclasts. Osteoporosis may complicate CD, in both adults and children and it is mostly present in patients with overt malabsorption at diagnosis, but it may also be present in subclinical or in asymptomatic CD. However, the
risk of bone fracture in CD seems to be lower that previously presumed. Bone density improves after following a GFD, but in adult CD this improvement does not reach the normal sex- and age-matched values for the control population. In contrast, in childhood CD with a very early treatment, gluten exclusion prevents bone loss and most children reach a normal bone mass. This discrepancy can be explained by the fact that bone loss has an irreversible component (disappearance of trabeculae and thinning of the cortex) and a reversible component (increased intracortical tunneling, thinning of trabeculae). While late treatment in adulthood may revert only the reversible bone loss, very early treatment during infancy could prevent both the irreversible and the reversible bone loss. Consequently, there is no need to perform bone mass measurement in children if fully compliant with GFD. The question is weather bone mass should be assessed at diagnosis in cases of subclinical or silent disease in older children. Following the advice for adult CD, the evaluation of bone mass after the first year of strict adherence to GFD seems to be of more clinical use, since the treatment with mineral-active drugs may be started on the basis of the results of gluten exclusion. Risk factors for fractures have not been specifically identified in CD, but are likely to include, in addition to noncompliance with GFD, steroid treatment, untreated hypogonadism, age, low body mass index, and previous fragility fracture. The role of lifestyle factors should be not underestimated in the prevention of osteoporosis and adolescent patients with CD should be encouraged to follow a calcium-rich diet, to maintain a high level of exercise, and to stop smoking.

### Genetics, Gluten, and Immunology

CD is a familial disorder: first-degree relatives of CD patients have an increased risk of 5 to 10% of developing the disease. Twin studies are very useful to assess the genetic and environmental components to disease susceptibility. Both monozygotic and dizygotic twin pairs share the same environmental factors, but differ by sharing 100 and 50% of genetic variability, respectively. In CD the concordance in monozygotic twins is approximately 83% and this is only 17% in dizygotic twins. By way of comparison monozygotic concordance rates are 25% in multiple sclerosis, 36% in type I diabetes, and in 33% in Crohn’s disease, showing that CD has one of the highest concordance rates of the complex multifactorial diseases. The sibling relative risk (RR, defined as the risk for CD to a sibling of a CD patient divided by the risk for CD in the general population) is also useful to measure the heritability of CD. Population studies estimate sibling RR for CD between 30 and 48, also suggesting a stronger genetic component in CD than in many other complex diseases.

#### The Human Leukocyte Antigen (HLA) Complex

CD is strongly associated with genetic factors coded by the HLA complex, which occupies a 4-Mb region on chromosome 6p21 and contains some 200 genes of which over half are known to have immunological function. Around 95% of patients with CD express HLA-DQ2 (\(\alpha 1^*0501/\beta 1^*0201\)), either in the cis- (encoded by HLA-DRB1*03-DQA1*05-DQB1*03) or in the trans- (encoded by HLA-DRB1*11/12-DQA1*05-DQB1*03/DRB1*07-DQA1*0201-DQB1*02) configuration and most of the remainder express HLA-DQ8 (\(\alpha 1^*0301/\beta 1^*0302\)) encoded by HLA-DRB1*04-DQA1*03-DQB1*0302, showing that the chance to develop CD in absence of HLA-DQ2 and/or HLA-DQ8 is very small (Table 3). However, HLA-DQ2 and DQ8 are frequently present in the white population (approximately 30%), implying that HLA-DQ2 and DQ8 are very important, but not enough, to explain the genetics of CD. This knowledge has triggered the search for other non-HLA genetic variants predisposing to CD, but currently no other genetic variants have been found that exert a major influence similar to the HLA. The primary function of the HLA-DQ molecules is to present exogenous peptide antigens (in CD gluten peptides) to helper T-cells. The strong relationship between the HLA genetic factors and CD is illustrated by the impact of the HLA-DQ2 gene dose on the chance of disease development: HLA-DQ2 homozygous individuals have an at least five times higher risk of disease development compared with HLA-DQ2 heterozygous individuals. It is likely that the large HLA effect size is related to the essential permissive role of DQ2 peptide presentation in disease pathogenesis. The level of HLA-DQ2 expression influences the magnitude of the gluten-specific T-cell response: it has been demonstrated that gluten presentation by HLA-DQ2 ho-
mozygous antigen-presenting cells is superior to presentation by HLA-DQ2/non-DQ2 heterozygous antigen-presenting cells and this correlates with the risk of disease development. The question is if there may be additional alleles in the HLA region in addition to DQ2 and DQ8 that confer risk for CD. Although the association between CD and another HLA gene, such as and TNF and MICA, may be explained by the linkage disequilibrium across the HLA; at the moment there is no evidence for additional HLA risk factors.

**Genome-Wide Linkage Studies**

Several genome-wide searches have been performed in CD. Genome-wide linkage studies aim to identify broad genomic regions that contain disease-predisposing variants and are successful to identify loci for monogenic disorders (e.g., cystic fibrosis, hemochromatosis), but they are less useful to identify loci in the more common polygenic diseases.

Outside the HLA region there are at least three genomic areas related to CD: CELIAC2 on 5q31 to 33, CELIAC3 on 2q33, and CELIAC4 on 19p13. From two of these regions the responsible genes have been identified: CTLA4 on 2q65 and Myosin IXB on 19p, but their mode of action is unclear.

Chromosome 6q21-22 (distinct from the HLA) has been reported to be related to CD in type I diabetes, rheumatoid arthritis, and multiple sclerosis and it is possible that a common variant at this locus might predispose to autoimmune diseases in general (as demonstrated by the HLA A1-B8-DR3-DQ2 haplotype).

Newer methods including gene expression analysis will provide further insight in the genetic susceptibility for CD.

**Gluten**

Gluten, the antigenic protein mixture for CD patients, present in wheat and related cereals, is the water-insoluble material in wheat flour that gives dough its elasticity. The major components are the glutenins and the gliadins, both representing complex families of proteins (Koning F, Mearin ML. Manuscript submitted for publication, 2006). In a single wheat variety dozens of distinct gluten proteins are found. Gluten contains a high amount of the amino acid proline, which renders gluten resistant to degradation in the gastrointestinal tract. Together with the fact that gluten is a very much used protein in the food industry—the daily consumption of gluten is estimated to be between 10 and 15 g—this indicates that gluten exposure is high and continuous.

**Immunology**

In celiac patients, gliadin and glutenin peptides are presented by HLA-DQ2 or -DQ8 expressed on antigen-presenting cells to gluten-specific CD4+ T-cells. This generates a mixed Th0 and Th1 response. Antigenic protein fractions (peptides) binding to HLA is in part mediated by interactions between particular amino acids in the bound peptide and pockets in the HLA molecule. In the case of HLA-DQ2 and -DQ8 it is well established that negatively charged amino acids are required for these interactions. As gluten contains very few negatively charged amino acids, gluten peptides were therefore predicted to poorly bind

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**TABLE 3.** Comparison of the distribution of the HLA-DR/DQ genotypes in Dutch children with celiac disease (CD) and in the Dutch general population

<table>
<thead>
<tr>
<th>Risk for CD</th>
<th>DR</th>
<th>DQ</th>
<th>CD (n = 149) (%)</th>
<th>General population (n = 2307) (%)</th>
<th>Relative risk RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Homozygote DR3 DQ2</td>
<td>DR3 DQ2/DR7 DQ2</td>
<td>40</td>
<td>5</td>
<td>8.0 (6.1-10.5)*</td>
</tr>
<tr>
<td>Medium</td>
<td>DR3 DQ2/DR5 DQ7</td>
<td>DR5 DQ7/DR7 DQ2</td>
<td>15</td>
<td>5</td>
<td>3.1 (2.1-4.7)*</td>
</tr>
<tr>
<td>Medium</td>
<td>DR3 DQ2/DRX DQX**</td>
<td>DR3 DQ2/DR4 DQ8</td>
<td>36</td>
<td>18</td>
<td>2.0 (1.6-2.6)*</td>
</tr>
<tr>
<td>Low</td>
<td>DR7 DQ2/DRY DQY**</td>
<td>DR4 DQ8/DRZ DQZ**</td>
<td>9</td>
<td>72</td>
<td>0.1 (0.07-0.2)*</td>
</tr>
</tbody>
</table>

*P < 0.05.
**DRX DQX = not DR3DQ2, DR4DQ8, DR5DQ7, or DR7DQ2. DRY = DR7DQ2 of DRXDQX. DRZ DQZ = DR4DQ8 or DRXDQX.
to HLA-DQ2 and -DQ8. This paradox was solved by the observation that the enzyme tissue transglutaminase (tTG) can convert the amino acid glutamine in gluten into glutamic acid, which introduces the negative charge(s) required for strong binding to HLA-DQ2/8.70,71

Several studies have investigated the specificity of the gluten-specific T-cell response in CD and revealed that polyclonal T-cell responses to multiple gluten peptides are almost invariably found in patients.72,73 Most responses are specific for tTG-modified gluten peptides. These peptides can be derived from all types of gliadins as well as glutenins. However, some peptides are immunodominant; in particular, a proline-rich stretch in alpha-gliadin is found in the large majority of patients, while other peptides are less frequently recognized.74,75 Similar peptides are found in the gluten-like molecules in barley and rye and T-cells specific for gluten peptides can cross-react with those homologous peptides in these other cereals.76

However, it is clear that HLA-DQ2/8 and tTG are not the only factors that contribute to disease development since the physiological role of tTG is tissue repair and approximately 40% of the white population expresses HLA-DQ2 and/or -DQ8 and only 1% develop CD. Therefore, it is possible that, although enhanced by tTG modification, gluten is in itself immunogenic. One proposed model for the pathogenesis of CD states that tTG drives the diversification of the gluten-specific T-cell response: once a gluten-specific T-cell response is initiated, the accompanying tissue damage will lead to the release of intracellular tTG which, in turn, allows the generation of additional gluten peptides that can trigger T-cell responses, more tissue damage, more T-cell activation, etc. A vicious circle is initiated that is driven by gluten intake.76

In a healthy situation the role of the intestinal mucosal immune system is the maintenance of tolerance and, even though HLA-DQ2 and/or -DQ8-positive individuals are prone to the development of gluten-specific T-cell responses, such responses will generally be suppressed. However, stress situations, like, for example, intestinal infections, would force the immune system to raise an inflammatory response accompanied by the production of IFNγ. This would increase the HLA-DQ expression and, combined with the fact that due to the high gluten intake gluten peptides are almost continuously present in the intestine, and that inflammation can raise tTG levels, this may lead to a situation where gluten specific T-cell responses are initiated instead of suppressed.66

In addition, it has also been shown that gluten activates the innate immune system. A particular α-gliadin peptide, p31-43, which is not known to bind to HLA-DQ2/8 and stimulate T-cells, has been shown to upregulate natural killer cells (NKG2D) and induce MICA expression in biopsies of patients.77,78 The cytokine IL-15 appears to be a key factor in the inflammatory intestinal response in CD. IL-15 promotes the maturation of intestinal dendritic cells and might stimulate the recognition of gluten-peptide-derived T-cell epitopes by lamina propria CD4+ T-cells.79 In addition, IL-15 stimulates the effector properties of intra epithelial lymphocytes (IEL), their synthesis of γ-interferon, and their cytotoxicity and can license IEL to kill enterocytes by signaling delivered by their NKG2D receptor and by inducing the epithelial target of this receptor on enterocytes, the MHC Ib molecule MICA.78-81

**Diagnosis**

In 1970 the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) established the criteria for the diagnosis of CD in childhood, based on the recovery of the characteristic histological alterations of the small intestinal mucosa after following a GFD and on the histological relapse following a gluten-challenge (the reintroduction of gluten into the diet).82 At least three small intestine biopsies (SIB) were necessary to diagnose CD. Currently SIB is still the gold standard for the diagnosis of CD. SIB can be taken blindly with peroral suction biopsy tubes or at the time of upper endoscopy from descending duodenum83: both techniques are considered relatively safe.84 Because the intestinal lesions in CD may be patchy, it is recommended that multiple biopsy specimens be obtained. In 1990 a working group of the ESPGHAN published revised criteria for the diagnosis of childhood CD based on a retrospective study of the diagnosis procedure in a large group of celiac children.85 According to the revised criteria, gluten-challenge should only be necessary in those children who were younger than 2 years when the first SIB was performed. In this group of young children a number of diseases other than CD may produce histological small intestinal alterations similar to the typical CD lesions (Table 4). However, in some cases
gluten-challenge may be needed to prove the necessity of continuing lifelong GFD or to confirm the diagnosis in those patients on a GFD who did not have a diagnostic SIB.

The typical histological lesion of the SIB of a celiac child eating gluten is the subtotal villous atrophy with elongated and hypertrophic crypts and a chronic inflammatory infiltration in the mucosa (Fig. 4). The lamina propria contains an increased number of lymphocytes, plasma cells, and some eosinophils and histiocytes. The crypts contain an increased number of cells in mitosis, Paneth cells, and argentaffin cells. There is a reduction in the number of goblet cells and an increased number of intraepithelial gamma/delta T-lymphocytes. There is a reduction in the number of goblet cells and an increased number of intraepithelial gamma/delta T-lymphocytes. A widely used classification of the histological alterations in CD was introduced by Marsh in 1992 and it ranges from type 0 (Marsh 0) to Marsh type 4:

- Type 0 concerns the normal stage of the small bowel mucosa.
- Marsh type 1 or infiltrative lesion comprises normal mucosal architecture in which the villous epithelium is infiltrated by small, nonmitotic intraepithelial lymphocytes and it is characteristically present in first-degree relatives of children with celiac disease.
- Type 2, or hyperplasic lesion, consists of a type 1 lesion with enlarged crypts.
- Marsh type 3 or destructive lesion is synonymous with the typical flat mucosa of CD and it is subclassified according to the different degrees of villous atrophy present: Marsh type 3a, with partial villous atrophy; Marsh type 3b, in the presence of subtotal villous atrophy; and Marsh type 3c, when total villous atrophy is present.
- Marsh type 4 or hypoplastic lesion (total villous atrophy with crypt hypoplasia) represents the extreme end of the gluten-sensitivity spectrum and an irreversible lesion is present in some adult CD patients whose small bowel mucosa is unresponsive to gluten withdrawal: the so-called refractory CD.

Marsh type 3 is accepted as a clear feature of CD, but whether the hyperplasic changes of Marsh type 2 lesions should be considered as distinctive for CD is still controversial.

In addition to the small intestine alterations, a lymphocytic gastritis has been described in CD.

Serology Tests in the Diagnosis of CD

For more than 25 years it has been possible to use serological markers to identify CD with high sensitivity and specificity. The most useful are the IgA antibodies to endomysium (EMA) and to human tissue transglutaminase (tTGA). The EMA is an immunofluorescence test that requires expertise in the subjective interpretation of the results and the use of monkey’s primate esophagus or human umbilical cord as substrate. According to the evidence Report/Technology Assessment performed by the Agency for Healthcare Research and Quality in 2004, the determination of EMA has a high sensitivity for CD of approximately 90% and a very high specificity approaching 100%. The titer of EMA correlates with the degree of mucosal damage; accordingly, the sensitivity increases with higher prevalence of subtotal villous atrophy in the CD population studied.

The recognition of the enzyme tTG as the substrate for the EMA formed the basis for the development of an enzyme-linked immunoassay (ELISA) for the determination of tTGA. Assays using human tTG, either recombinant or derived from human red cells, have better results than those using guinea pig tTG. The sensitivity of tTGA is greater than 90%, but the specificity is lower than the one of the EMA. It has been shown that TGA results may be positive in other diseases different from CD, such as in type 1 diabetes, chronic liver disease, or rheumatoid arthritis, although small bowel biopsy was not always performed to exclude CD in the cases described. A controlled European multicenter study performed in biopsy-proven CD cases and control with other diseases different from CD controls to evaluate the value of IgA antibody measurement to human recombinant tTG in comparison to IgA-EMA in the diagnosis of CD found that tTGA measurement were effective and at least as good as EMA in the case-finding of CD.
the tTGA ELISA method, and its lower price, it is likely that, of all serological screening tests, tTGA determination will be the first choice.

Selective IgA deficiency (SIgAD) occurs more frequently in children with CD than in the general population. These patients with CD lack IgA-EMA and IgA-tTG. To avoid missing CD in children with SIgAD, it is advisable to determine the total IgA level in serum when testing for CD. Children with already known SIgAD should be tested with an IgG antibody-based tTG test, the IgG-tTG.

Figure 5 shows the scheme that is usually followed in the clinical diagnosis of CD in children.

Who Should Be Tested for Celiac Disease?

The availability of such sensitive and specific serological tests to identify CD, together with the increasing knowledge of the heterogeneous character of the clinical picture, opens the question about who should be tested for CD. Nowadays, these serological tests are advised for active case-finding, among children who seek medical advice for health problems that suggest CD (Table 1). Targeted screening is also widespread, aiming at high-risk groups such as relatives of CD patients or individuals with associated conditions like type I diabetes mellitus or Down syndrome (Table 2).

According to the official recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition on the diagnosis and treatment of CD in children and adolescents, CD should be considered early in the differential diagnosis of children with failure to thrive and persistent diarrhea. In addition, it is recommended that CD be considered in the differential diagnosis of children with other persistent gastrointestinal symptoms, including recurrent abdominal pain, constipation, and vomiting. Testing is recommended for children with nongastrointestinal symptoms of CD (dermatitis her-
petiformis, dental enamel hypoplasia of permanent teeth, osteoporosis, short stature, delayed puberty, and iron-deficient anemia resistant to oral iron). Testing is also recommended for asymptomatic children who have conditions associated with CD (type 1 diabetes mellitus, autoimmune thyroiditis, Down syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and first-degree relatives of celiac patients). It is recommended that testing of asymptomatic children who belong to groups at risk begin around 3 years of age provided they have had an adequate gluten-containing diet for at least 1 year before testing.  

The Use of HLA-DQ Typing in the Diagnosis of CD

Because CD is very unusual in the absence of HLA-DQ2 or HLA-DQ8, the determination of these haplotypes may be used in the identification of CD, among others, in high-risk groups for CD whose members may develop the disease at a certain moment in their lives, but in whom it is not known how often CD should be tested. This is especially the case among first-degree relatives of CD children: in these families there is frequently anxiety to know who may or may not develop CD. However, HLA-DQ2 and -DQ8 are not specific for CD since they are present in about 40% of the general white population, and their contribution to the identification of the disease resides in their high negative-predictive factor. Using HLA-DQ typing, a two-step model has been proposed to identify CD in children with high risk for CD. The first step should consist of the typing for the molecularly defined HLA-DQ2 and -DQ8, which has to be performed only once in life, because it does not change in time. This will help to exclude the children without HLA-DQ2 and/or HLA-DQ3 from further unnecessary tests for CD. The second step should consist of total IgA and IgA-tTGA and/or IgA EMA determinations in serum in the children selected by HLA-typing. Individuals with positive serological tests should be offered a small bowel biopsy, and in the case of histological alterations treatment with a GFD should be provided. The children with normal serological tests or normal small bowel biopsies should be further investigated for CD, for example, every 1 to 2 years.

To Screen or not to Screen?

CD is a hidden public health problem worldwide. Many studies have shown that CD affects about 1.0% of children of white ancestry, but most cases remain undiagnosed. The prevalence of CD thus exceeds by far that of a number of diseases for which screening programs are currently applied such as congenital hearing loss (1/1000), congenital hypothyroidism (1/3400), and phenylketonuria (1/18,000). Mass screening is the only way to identify the majority of people with CD.

Mass screening for CD, ie, screening of the general population, is a controversial issue. To decide whether mass-screening programs for CD would be performed, the principles for early disease detection as elaborated by Wilson and Jungner should be taken into account. These principles are as follows: (1) The condition should be an important health problem; (2) There should be an accepted treatment for the disease; (3) Facilities for diagnosis and treatment should be available; (4) There should be a recognizable latent or early symptomatic stage; (5) There should be a suitable test for disease detection; (6) The test should be acceptable for the population; (7) The natural history of the condition, including development from latent to declared disease, should be understood; (8) There should be an agreed policy of whom to treat as a patient; (9) The Costs of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole; and (10) Case-finding should be a continuous process. Nine of the 10 principles for mass-screening are met by CD, but the natural history of CD is not well known and it is not clear if the children with none of subtle symptoms of CD identified by mass screening have the same health risks and long-term complications that the children with clinical diagnosed CD. Assuming a standardized mortality ratio of 1.5 or higher for untreated CD patients, mass screening for CD has been shown to be cost-effective in populations with a relatively high prevalence of CD over a wide range of ages at screening.

To answer this question, limited screening programs in well-defined regions should be initiated with continuous and prospective evaluation of their costs and benefits in comparison with control populations.

Treatment

A lifelong strict GFD with exclusion of gluten from wheat, rye, and barley is the treatment of CD. Wheat, rye, and barley are the predominant grains containing
the peptides known to cause CD. Triticale (a combination of wheat and rye), kamut, and spelt are also known to be harmful. Other forms of wheat are semolina (durum wheat), farina, einkorn, bulgur, and couscous. Malt is also harmful because it is a partial hydrolysate of barley prolamins. In general, any ingredient with malt in its name (barley malt, malt syrup, malt extract, malt flavorings) is made from barley. The ingestion of very small amounts of gluten, even without the accompaniment of clinical or serological responses, induces changes that are detectable at the small bowel level.

The clinical response of children with CD after starting a GFD may be observed within days or weeks. The histological recovery of the small bowel mucosa after GFD takes longer, but the recovery in children is much quicker and complete than in adults and 95% of the children show histological recovery after 2 years on a GFD.

Initially, oats were considered to be harmful for CD patients, but more recently it has been shown that, in general, oats are safe both for adults and for children with CD. One concern about oats consumption in a GFD is the frequent contamination of oats with gluten during the harvesting and milling process. In addition, some CD patients have avenin-reactive mucosal T-cells that can cause mucosal inflammation and clinical follow-up of CD patients eating oats is advisable.

Recently, in vitro experiments showing the absence of gluten-derived T-cell epitopes in tef, suggest that this cereal may be suitable for use in the diet of patients with CD. Tef (Eragrostis tef), a cereal traditionally grown in Ethiopia and used to make flat bread, can substitute for wheat flour in almost all applications and has a nutritional value similar to that of wheat. Studies on tef consumption by patients with CD are needed to determine whether tef is safe for these patients.

In principle, a GFD appears simple; in practice, it represents a challenge to children and their families, dieticians, and physicians, since wheat products are added to many processed foods in the Western diet. Several helpful books distributed by the National Celiac Societies provide excellent dietary instructions and gluten-free recipes.

Adherence to the GFD diets is difficult, because sources of unintentional gluten intake are so numerous; among others:

1. Contamination with wheat flour of foods that are “naturally” gluten-free,
2. Residual gluten in gluten-free wheat starch used for bread mixes,
3. Mislabelling of foods

Lists of gluten-free food are available for patients. General awareness should be promoted to keep these lists updated.

The Codex Alimentarius Committee on Nutrition and Food for Special Dietary Uses (CCNFSDU) in 1982 set the limit of gluten allowed in raw materials to produce gluten-free food to 0.05 g nitrogen per 100 g dry matter. Recently an R5 ELISA method for gluten/gliadin determination in food has become available based on a monoclonal antibody reacting with the specific gliadin pentapeptide glutamine-glutamine-proline-phenylalanine-proline (QQPFP) with a sensitivity and limit of detection (1.5 ppm gliadin), which is superior to older methods of detection. At the moment a provisional level of [20 ppm] gluten for food gluten-free by nature and [200 ppm] for food rendered gluten-free has been accepted (Draft Revised Standard for Gluten-free Foods (ALINORM 04/27/26) CCNFSDU). The problem is that this standard refers to the amount contained in a food and not to the amount of food that can be taken by a person who is sensitive to it. Patients with CD need careful support to provide them with up-to-date facts about a GFD. This may in part be given by the many Celiac Patients Societies around the world, among others the Association of European Celiac Societies (www.aoecs.org) and the American Celiac Sprue Association (www.csaceliacs.org).

Nonadherence to the GFD may lead to complications such as diarrhea, abdominal pain, anemia, and osteoporosis. For many patients adherence to the diet may be difficult to achieve. This seems to be particularly true among adolescent patients with CD, with a reported compliance with the GFD between 52 and 81%. Determination of celiac antibodies in serum has been reported as a reliable way to monitor the compliance with the GFD. However, in a study among young celiacs in the Netherlands we did not find a correlation between the self-reported compliance with the diet and the results of the celiac antibodies in serum. Neither did we find a relation between the amount of gluten consumed and the level of antibodies (EMA, iTGA). It is also possible that the determination of the antibodies in serum is not an
adequate method to detect adherence to the GFD, both in adults and in adolescents, as it has been suggested by others.\textsuperscript{124-126} In addition, adherence to a GFD may have negative nutritional consequences.\textsuperscript{127,128} Mariani and coworkers\textsuperscript{121} reported overweight and an unbalanced diet rich in fat and protein, poor in carbohydrate, and deficient in calcium, iron, and fiber in 72% of the Italian CD adolescents adhering strictly to the GFD. In a prospective study performed in Dutch adolescents and young adults, we found a high dietary compliance (75%) with a median gluten intake of 44 mg per day (2-6382 mg). The nutritional state was adequate, with normal scores for height and body mass index, but the nutrient intake was not adequate. The fiber and iron intake were significantly lower, and the saturated fat intake was significantly higher than recommended, but comparable with the general population. Most of the patients (61%) found the diet easy to follow. Regular medical controls were reported by 86%, but regular dietary controls were reported by only 7% of the patients.\textsuperscript{122} Better medical and dietary support is necessary to prevent long-term complications and to achieve an ongoing satisfying management in this group of young patients with a chronic disorder. Most young patients with CD thought that avoiding cancer was the most important reason to adhere to the GFD. It has been found that when patients with CD adhere to a GFD for five consecutive years or more, their risk of malignancy is not increased compared with that of the general population.\textsuperscript{42,129} On the other hand, over the last few years it has become clear that, although CD patients have a higher risk of developing cancer than the general population, the risk is much lower than previously presumed.\textsuperscript{45-47} At present the GFD is the only effective treatment for CD and it is prudent to recommend strict adherence to the diet to all celiac patients. However, the fear of developing malignancy is not necessarily the most important reason for designing a strict diet to CD patients.\textsuperscript{48} Physicians should mainly stress the advantages of the diet with regard to the prevention of other complications of CD, such as osteoporosis\textsuperscript{49} and autoimmune disorders.\textsuperscript{42} They should also point out the relation between adherence to the GFD and improvement of fertility and birth outcomes.\textsuperscript{50,130,131}

**Quality-of-Life**

Decreased quality-of-life (QOL) has been described in adults with CD, especially in females.\textsuperscript{128} Having a chronic illness like CD may reduce a child’s QOL. Not only can physical function be affected, but also a child’s emotional and social world may change. The illness can therefore be an important factor in the evaluation of QOL of a child.\textsuperscript{132} Health-related QOL (HRQOL) is a multidimensional concept containing physical, emotional, social, and cognitive domains, variable over time, and is getting increasing attention in medical and health care settings.\textsuperscript{133} What matters in HRQOL is the way patients feel about their functioning, not their functioning itself.\textsuperscript{134} HRQOL can be measured by generic, disease-generic, and disease-specific instruments. These instruments can be seen as having a pyramid structure, with, at the bottom, the generic QOL questionnaires such as the DUX25\textsuperscript{135} and the TACQOL.\textsuperscript{136} In the second layer of the pyramid, disease-generic questionnaires are found, which can be administered to children with any disease, including chronic diseases. Finally, disease-specific questionnaires complete the top layer. These questionnaires can be given to children, healthy and ill. Generic HRQOL instruments offer specific possibilities in the assessment of the QOL of patients with a particular disease: they allow comparison with normative data and across disease populations. Most QOL instruments are designed as top-down instruments. This means that they are developed by researchers and physicians who used their own experience as guidelines. In the last few years there has been an increasing interest in the development of generic and disease-specific HRQOL instruments developed from the bottom-up approach such as the KIDSCREEN and DISABKIDS questionnaires. These questionnaires used a focus group based bottom-up approach.\textsuperscript{137} A bottom-up approach allows us to perceive the situation from the child’s point of view. It can be seen as a child-centered methodology, designed to ensure that the children, rather than their parents or health care professionals, generate, prioritize, and explain the issues of interest to them. It can produce data that adult investigators and even parents have never considered.

The HRQOL of children with CD has been previously assessed, making use of the TACQOLCD, a questionnaire especially designed for CD and based on the generic instrument TACQOL, in which the child’s well-being was estimated by the researchers and attending physicians.\textsuperscript{138} The TAQOLCD did not provide information about the children’s view, nor that of their parents, and it contained only symptomatic questions mainly useful for the investigation of physical
complaints. In the absence of complaints, thanks to compliance with the GFD or to coping with the disease, the results gave an optimal score which may not give an accurate view of the HRQOL. Recently, together with the Dutch foundation Doctors for Children, a foundation that works for the improvement of the QOL of children with chronic illness, an improved questionnaire developed from the bottom up, to assess the QOL of children with CD has been developed (van Doorn RK, Winkler LMF, Zwinderman KH, Mearin ML, Hendrik M, Koopman HM. Manuscript submitted for publication.): the Celiac Disease DUX (CDDUX). Using the CDDUX children with CD appears to have a lower QOL than the healthy reference group. Children with a better health status have a higher score on the CDDUX questionnaire. The new disease-specific questionnaire CDDUX provides information about how children with CD think and feel about their illness. The use of a similar questionnaire enables researchers and clinicians to determine the consequences of CD on the daily living of the children. In this context the results of an important study aimed to evaluate the impact of the GFD on the 5240 members of the Canadian Celiac Association shows that the QOL in those with CD could be increased with early diagnosis, increased availability of gluten-free foods, improved food labeling, and better dietary instruction. Education of physicians and dieticians about CD and its treatment is essential.

Future Prospects

Prevention

There is some evidence suggesting that prevention of CD may be possible. One observation is that the level of HLA-DQ2 expression is linked to the probability of disease development: a double gene dose leads to an at least fivefold increased risk. Usually children are exposed to high levels of gluten. The question is what will happen when we lower the amount of gluten in the diet. It is conceivable that this may have a similar effect as the HLA-DQ2 gene dose: lower gluten exposure would decrease the risk to develop CD. Epidemiological studies from Sweden suggest that early nutrition patterns may have a significant impact on the later risk of developing CD. The occurrence of “epidemics” of CD after changes in the Swedish infant feeding during the 1980s and 1990s suggested that the disease may be preventable by improving early nutrition and inducing tolerance to gluten in predisposed individuals. The “Swedish epidemic of CD” started in 1983 when gluten introduction was postponed from month 4 to 6 by changed national recommendations for gluten introduction into the diet of young children. Carefully performed studies exploring the epidemic in detail suggest that the causal factors of the epidemic were whether breastfeeding was ongoing or not while gluten was introduced and also the amount of gluten then given. Thus, when introduction of gluten in 1983 was postponed, it also implied that more infants had ended breastfeeding, and that gluten was introduced by larger amounts. Moreover, the epidemic subsided in 1996 when gluten introduction was once again “allowed” from 4 months of age when more of the infants were still breastfed and gluten was introduced in smaller amounts. Thus, the Swedish studies strongly support that ongoing breastfeeding during the period of gradual introduction of gluten-containing foods into the infant diet reduces the risk of symptomatic CD. Based on an estimate of the attributable fraction, half of the CD cases during the Swedish epidemic might have been avoided if all infants had been introduced to gluten in small amounts while still being breastfed. The latter finding opens the way to possible prevention strategies.

It is possible that gradual introduction of antigens will lead to the development of oral tolerance. It is also likely that the response of the immune system to gluten may be modified by breastfeeding. Several studies have been performed in different European countries on gluten consumption and breastfeeding, but the methods used to assess gluten intake were mostly time consuming and differed from each other. An important American study has published the findings on a cohort of 1560 children who had an increased risk of developing CD or type 1 diabetes, as defined by possessing either HLA-DR3 or DR4 alleles, or having a first-degree relative with type 1 diabetes, derived from the Diabetes Autoimmunity Study in the Young project. At a mean follow-up of 4.8 years the authors concluded that (1) there is a “window of opportunity” of introducing gluten into the diet when the child is aged between 4 and 6 months with regard to the risk of developing CD; and (2) that the contribution of breastfeeding was to be disregarded in this respect. However, the authors did not make specific attempts to calculate the gluten amount ingested by the children or to correlate this important early nutrition event with the presence or absence of
breastfeeding. A systematic review and a meta-analysis of observational studies published between 1966 and June 2004 that examined the association between breastfeeding and the development of CD showed that breastfeeding seemed to protect against CD. Prospective cohort studies may shed light on the importance of the quantity of exposure to gluten in early life in the development of CD. One problem in this respect is that, until now, there were no validated instruments to quantify gluten intake by young infants. The instruments available were work intensive, time consuming, and difficult to use in population studies. Recently we have developed and validated food frequency questionnaires for this purpose, using the 2-day food record as a reference (Hopman EG, Kiefte-de Jong JC, le Cessie S, et al., unpublished data). This instrument may be used in collaborative studies to assess the role of the quantity of gluten consumption in the development of CD.

The actual guidelines for infant nutrition recommend introducing gluten into the diet no earlier than at the age of 6 months, and at this age, only a low percentage of the children, ranging from 1 to 46% in the different European countries, receive breastfeeding. On the other hand, the Swedish study only investigated the effect of the early dietary history on symptomatic CD in children. It may be that the nutritional factors only have an effect on the symptoms of CD and/or on the time of presentations of the symptoms. In addition, there is no information on the biological mechanisms involved in the effect of early nutrition in the development of CD. Prospective intervention nutritional studies in high-risk populations are necessary to provide parents with sensible advice to prevent CD in their children.

Safer Foods

Gluten is a complex mixture of proteins that contains a multitude of immunogenic peptides. This is because bread wheat and pasta wheat are hexaploid and tetraploid species, containing three and two entire wheat genomes, respectively. These wheat varieties have been selected for good crop yield and superior baking qualities. However, there are many wheat varieties and not all of those appear to be equally toxic to patients. This offers two opportunities for the generation of safer wheat strains. In addition, other cereals can be selected that do not contain harmful gluten or gluten-like molecules, like the Ethiopian cereal tef.

Novel Treatments?

A GFD is at present the only possible treatment for CD children, but there are a number of drawbacks to a lifelong diet. At present there are four options that can be explored, as follows: (1) Enzymatic degradation of gluten before it reaches the small intestine; (2) Blocking of peptide binding to HLA-DQ2/8; (3) Blocking of tTG; (4) Blocking of IL-15. Of these four options, the latter two may be dangerous. tTG is important for the maintenance of tissue integrity, while IL-15 is required for normal functioning of the immune system. Oral supplementation with a postproline cutting enzyme has therefore been proposed as a potential way to destroy gluten before it can do damage in the small intestine. Blocking HLA-DQ would also be highly selective as it would block the gluten-specific T-cell response but would leave non-HLA-DQ-mediated T-cell responses intact. These two and other possible options deserve further study.

Practice Points

- Celiac disease is a common, but frequently unrecognized disease. Consequently, celiac disease is severely underdiagnosed.
- The health burden of celiac disease is considerable. Two important complications of celiac disease are malignancy and osteoporosis.
- Recent population-based studies indicate that the increased risk of malignancy associated with celiac disease is less that previously thought.
- There is no need to perform bone mass measurement in children if fully compliant with the GFD.
- Celiac disease is strongly associated with genetic factors coded by the HLA complex. Around 95% of the patients express HLA-DQ2 and most of the remainders express HLA-DQ8. The risk of developing celiac disease in the absence of HLA-DQ2 and/or HLA-DQ8 is very small.
- It is possible to use serological markers to identify celiac disease with high sensitivity and specificity. The most useful are the IgA antibodies to EMA and to human tTGA.
- At the present time small bowel biopsy is the gold standard for the diagnosis of celiac disease.
CD should be considered early in the differential diagnosis of children with failure to thrive and persistent diarrhea and in children with other persistent gastrointestinal symptoms in children with nongastrointestinal symptoms of CD and in conditions associated with CD.

At present a GFD is the only effective treatment for celiac disease.

Better medical and dietary support is necessary to prevent long-term complications and to achieve satisfying management in children and young patients with celiac disease.

References


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