

Celiac Disease

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Celiac disease (CD) is an immune-mediated enteropathy secondary to permanent sensitivity to wheat gluten and related proteins in rye and barley. It results in characteristic histologic changes consisting of inflammation, crypt hyperplasia, and villous atrophy of the small intestine in genetically susceptible individuals. Significant variability in the clinical presentation of CD in the pediatric population complicates recognition of the disease in many patients. Treatment for CD consists of a lifelong strict gluten-free diet (GFD). Adherence to this diet is associated with resolution of most related signs and symptoms and a decreased risk of related complications. With an explosion of new knowledge over the span of two decades, our understanding of CD has changed dramatically. CD has gone from a rare condition causing gastrointestinal symptoms in children of European origin to a common disorder causing symptoms that affect multiple organ systems in all ages virtually worldwide.¹

The overall prevalence of CD is similar in Europe and North America affecting up to 1% of the population.^{2,3} A large multicenter study in the United States, using serologic screening with biopsy confirmation to identify cases of CD, showed a prevalence of CD of 1:133 in individuals with no evident risk factors. Prevalence of CD in symptomatic patients was 1:56. The prevalence of diagnosed CD is much lower, especially in the United States. This reflects under-recognition and underdiagnosis related to the wide clinical spectrum of disease and the presence of silent disease.⁴ In the United States, the prevalence of CD in people of non-European descent is not known. Limited studies suggest that, in the United States, Hispanic and African-American populations have a lower prevalence of CD than non-Hispanic Caucasians. For example, a study in Colorado showed that the incidence of positive serology in Hispanic children was three times lower than in non-Hispanic Whites.⁵ African-Americans also represent a small number of patients currently diagnosed with CD. A large center in New York City reported that African-Americans comprised 1.3% of their patients with biopsy-proven CD.⁶ This is likely partially because of genetic differences in these populations. However, given the increasing recognition of CD in non-Caucasian populations internationally, serious consideration should be

given to the possibility of underdiagnosis in minority populations in the United States.

CD is being increasingly diagnosed in other parts of the world, involving populations that were not traditionally thought to be affected by the disease. Reports from Mexico, South America, North India, the Middle East, Turkey, and North Africa have changed previous assumptions that CD is a European affliction.⁷⁻¹⁵ CD is rare in people of Japanese, Chinese, and purely African-Caribbean descent.¹⁶

CD is associated with several autoimmune conditions and genetic disorders and often presents atypically or silently in these populations. In children, it is associated with autoimmune thyroid disease and with type I diabetes mellitus with a 7.8 and 4.5% prevalence of CD in affected children.^{17,18} Up to 7% of patients with a selective IgA deficiency also have CD.¹⁹ Patients with Trisomy 21, Turner syndrome, and Williams syndrome have also been found to be at higher risk of CD than the general population.¹⁹⁻²²

PATHOGENESIS

Environmental, immunologic, and genetic factors are all important contributors to the pathogenesis of CD. Clearly, enteric exposure to specific proteins in wheat, rye, and barley are essential to disease activation in a genetically susceptible person. Wheat, rye, and barley have common ancestry and are all derived from the Triticeae tribe of the grass family. Broadly termed “gluten,” the specific

proline- and glutamine-rich proteins that activate disease are gliadins in wheat, secalins in rye, and hordeins in barley. Gluten, the second major protein fraction of wheat gluten, is likely involved to a lesser degree. Multiple toxic antigenic epitopes have been described (Figure 1).

These peptides activate immune cells causing a chain of events that result in tissue damage. The mechanisms for this activation are incompletely understood and are likely a combination of adaptive and innate immunity. Partially because of their high proline content, these large cereal peptides are resistant to digestion by intestinal proteases and pass through the epithelium and into the lamina propria in an intact state. The mechanisms of this passage through the intestinal barrier are not well understood. Tissue transglutaminase deamidates these peptides in the lamina propria causing them to become negatively charged as the glutamine residues are converted to glutamic acid. Deamidated peptides bind with far greater affinity to specific positively charged residues on the peptide-binding groove of HLA-DQ2 or HLA-DQ8 major histocompatibility complex (MHC) Class II molecules. These peptides are then presented by HLA-DQ2 or HLA-DQ8 to activate gliadin-specific CD4+ T cells thereby activating an intestinal inflammatory response leading to the characteristic histopathologic changes of CD. Intraepithelial lymphocytes, T cells that are markedly increased in the intestinal biopsies of patients with active CD, are also likely involved. It is now evident that gluten can

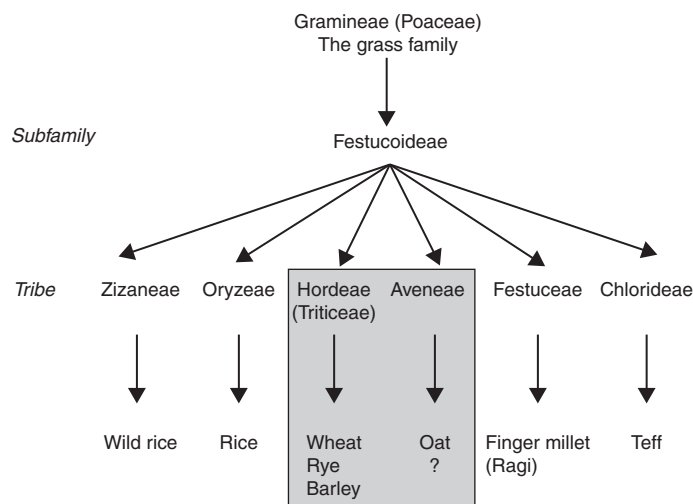


Figure 1 The grass family: Grains in the tribe *Triticeae* mediate celiac disease. Species of interest in the *Festucoideae* subfamily of the grass family are depicted. It seems likely that, for most patients with celiac disease, only grains in the tribe *Triticeae* mediate celiac disease. (Adapted from reference 23.)

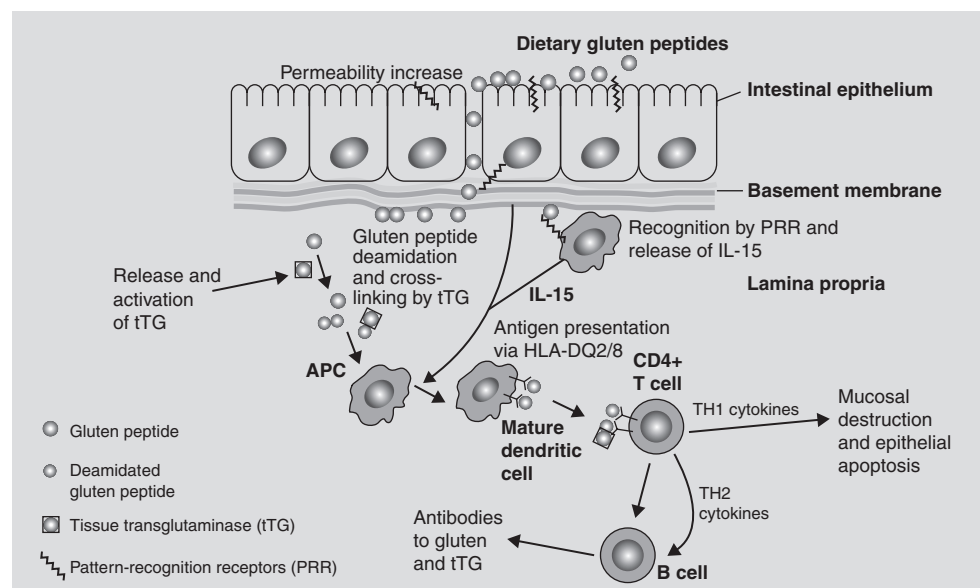


Figure 2 Adaptive and innate immune system responses in celiac disease. Cross-linking of gluten by tTG potentiates presentation of peptides by antigen-presenting cells (APC); deamidation of gluten improves binding to HLA-DQ2 or HLA-DQ8, triggering adaptive T-cell responses (inflammation and tissue remodeling (Th1) or antibody production (Th2)). Cells of the innate system recognize gluten peptides directly via pattern recognition receptors, and release cytokines (IL-15) that drive adaptive responses. Dendritic and T cells circulate to mesenteric lymph nodes (where they encounter T cells) and back to lamina propria. (Adapted from reference 26.)

stimulate interleukin-15 production, leading to the transformation of some T cells into natural killer cells and ultimately to enterocyte destruction (Figure 2).^{1,24,25}

Genetics are clearly a factor in the development of CD. Among monozygous twins, there is a 70 to 75% CD concordance rate and first-degree relatives have a 10% risk of disease.^{27,28} CD is strongly associated with HLA class II genes that map to the DQ locus. The HLA-DQ2 heterodimer is expressed in up to 95% of celiac patients with most of the remaining 5% expressing HLA-DQ8 heterodimer. These HLA types are present in 30% of the general population. Additionally, CD is concordant in only 30 to 40% of HLA-matched siblings. Clearly, these HLA types are necessary but not sufficient for CD to develop and other genes are likely to be involved. Candidate susceptibility genes include MYO9B (myosin IXB) and regions of chromosome 5, 6, 11, and 19.^{1,29} Investigation in this area is ongoing.

CLINICAL PRESENTATION

Traditionally, CD was thought to present primarily with gastrointestinal symptoms in the young. This “classical” presentation consists of poor growth, chronic diarrhea, abdominal distention, muscle wasting, poor appetite, and irritability typically seen in patients 6 to 24 months of age. Edema, pallor, and emesis are also seen. Rarely, children can present in celiac crisis with copious watery diarrhea, marked abdominal distention, dehydration, electrolyte imbalances, hypotension, and lethargy.³⁰ As serologic testing and our understanding of CD have improved, “nonclassical” or “atypical” presentations of CD are being increasingly recognized. In pediatric patients, this

form of presentation is characterized by delayed onset with gastrointestinal complaints, such as nausea, bloating, recurrent abdominal pain, or constipation.¹⁹ Many patients have no gastrointestinal complaints but have extraintestinal manifestations such as short stature, osteopenia, joint pains, pubertal delay, iron-deficiency anemia, dental enamel defects, neurologic disorders, or elevated transaminases. Some patients, with classic histologic changes on intestinal biopsy, are entirely asymptomatic and are described as having “silent” CD.^{16,30}

CD is being increasingly diagnosed in adults. In fact, the mean age of diagnosis is now in

midadult life (circa 45 years of age).¹ Many of these patients have likely had CD since childhood. Adults can present with gastrointestinal symptoms such as diarrhea, flatulence, abdominal bloating, and discomfort but often present with extraintestinal manifestations such as iron-deficiency anemia, macrocytic anemia, osteopenia, malaise, infertility, obstetrical complications, and neurologic conditions. Dermatitis herpetiformis, a pruritic blistering skin disorder, is also seen with CD but rarely occurs in pediatric patients (Table 1 and Figure 3).^{16,30}

DIAGNOSIS

While the pathogenesis of CD and the genetic factors involved are being still elucidated, the resulting inflammation and tissue damage causes characteristic and well-recognized histopathologic changes. Small intestinal biopsy histology remains the gold standard in the diagnosis of CD. The spectrum of histopathologic changes in CD have been classified by Marsh with additional more recent modifications.³¹ Marsh I lesions, an early but often nonspecific finding, are characterized by increased intraepithelial lymphocytes (>30 IEL per 100 enterocytes) and normal villous architecture. Marsh II lesions consist of crypt hyperplasia in the setting of increased numbers of intraepithelial lymphocytes (>30 per 100 epithelial cells). Marsh III lesions, type a–c, are characterized by partial to total villous atrophy in addition to crypt hyperplasia and increased numbers of intraepithelial lymphocytes. To avoid misinterpretation, biopsies are best reviewed by an experienced gastrointestinal pathologist. Because of patchy distribution of these histopathologic changes, multiple biopsies taken from the duodenal mucosa are indicated (Figure 4).³²

Table 1 Clinical Manifestation of Celiac Disease in Children

Manifestations Secondary to Untreated CD	Associated Diseases (or Diseases Secondary to Untreated CD)
CD with classic symptoms	Autoimmune diseases
–Abdominal distension	–Type 1 diabetes
–Anorexia	–Thyroiditis
–Chronic or recurrent diarrhea	–Sjogren’s syndrome
–Failure to thrive/weight loss	Neurologic and psychologic disturbances
–Irritability	–Ataxia
–Muscle wasting	–Depression
–Celiac crisis (rare)	–Epilepsy with intracranial calcifications
CD with nonclassic symptoms	Other disorders
–Arthritis	–IgA nephropathy
–Aphthous stomatitis	–Osteopenia/osteoporosis
–Constipation	Genetic disorders
–Dental enamel defects	–Down syndrome
–Dermatitis herpetiformis	–Turner syndrome
–Hepatitis	–Williams syndrome
–Iron-deficient anemia	–IgA deficiency
–Pubertal delay	
–Recurrent abdominal pain	
–Short stature	
–Vomiting	

Adapted from reference 30.

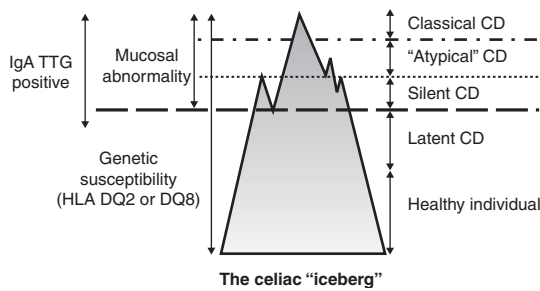


Figure 3 Clinical manifestations of celiac disease—the celiac iceberg. Celiac disease (CD) presents with a wide range of symptoms. Classical CD with prominent diarrhea and malabsorption is now less common than atypical CD presenting with iron-deficiency anemia or other disease manifestations with mild or absent gastrointestinal symptoms. Many individuals have silent CD with no symptoms or disease manifestations despite positive tTG serology and abnormal small bowel histology. Only a subset of individuals with CD has been diagnosed. This subgroup is often referred to as the “tip of the celiac iceberg.” Most individuals with genetic susceptibility (HLA DQ2 or DQ8 positive) do not develop CD.

The development of accurate serologic markers has markedly improved our ability to identify patients with untreated CD and to monitor them after diagnosis. Serologic testing, coupled with clinical assessment and histopathologic confirmation, has become a cornerstone of diagnosis. IgA endomysial antibodies (EMA IgA) can be detected by indirect immunofluorescence using human umbilical cord or monkey esophagus. In pediatric patients, the sensitivity ranges from 89 to 94% and the specificity ranges from 99 to 100%.^{33,34} However, this test is expensive and heavily operator dependent. IgA tissue transglutaminase (TTG IgA) is a less expensive, less operator-dependent assay. Its sensitivity ranges from 84.6 to 100% and specificity ranges from 76 to 97.4% in the pediatric population.^{33,35,36} These tests perform less well in pediatric patients compared to adults, especially in patients under the age of 2 years. False negatives can also occur in the setting of mild

enteropathy and in patients with IgA deficiency. TTG IgA and EMA IgA have largely replaced the older IgA and IgG anti gliadin antibody tests. Anti gliadin antibodies have poorer test performance, with low specificity in all but the youngest patients. However, in patients under 2 years of age, they may still be useful. Serologic markers also have a role in monitoring disease control once a GFD has been initiated. TTG IgA gradually normalizes within 3 to 12 months on a GFD depending upon the initial antibody concentration. TTG IgA has greater sensitivity than EMA IgA in monitoring for continued gluten intake but may not be sensitive enough to detect occasional or minor dietary errors.^{33,37}

Positive TTG or EMA serology and/or resolution of symptoms on a GFD are not sufficient to make a definitive diagnosis of CD and do not replace the need for duodenal biopsies to make the initial diagnosis. However, repeat biopsies are no longer routinely recommended. Historically, repeat intestinal biopsies were used to confirm diagnosis and to monitor disease control. However, the availability of more accurate serologic markers has greatly reduced the use of repeat biopsies in patients with CD. A second biopsy is now limited to patients with poor clinical response to a strict GFD. Gluten rechallenge, once a mainstay of diagnosis, has also largely fallen by the wayside, especially in the pediatric population. Rechallenge is now indicated only in patients on a GFD in whom the diagnosis remains in doubt (Figure 5).¹⁶

First-degree relatives of people with CD have a 10% risk of disease. In family members, symptoms may be subtle or differ significantly from those in the affected child. It is controversial whether or not to perform serologic screening of all symptomless family members. However, case finding by a careful review of symptoms or signs of possible CD in first-degree relatives should be sought routinely when a child or adolescent is diagnosed with CD.

EFFECT OF CD ON GROWTH AND BODY COMPOSITION

Short stature is a common presenting sign of CD, especially in the pediatric population. It may be the only manifestation.^{39–43} The pathophysiology of CD growth retardation is not fully defined but is traditionally thought to be secondary to associated malnutrition. With the initiation of a GFD and nutritional rehabilitation, children with CD undergo significant growth acceleration. This catch-up growth appears to be most evident during the first year on a GFD.⁴⁴ There is some evidence that, even when diagnosed early, monitored closely, and kept on a strict GFD, many children do not catch up completely and remain slightly below average height for age and skeletal age into adolescence.^{45,46} New evidence suggests overlap of CD with growth hormone deficiency.^{47,48} When catch-up growth on a GFD is not observed, further evaluation and possible growth hormone replacement is warranted.

In addition to linear growth, body composition is also significantly affected by CD. Longitudinal study of children and adolescents with newly diagnosed CD has shown significantly decreased weight, fat mass, and muscle mass compared to controls.⁴⁹ Decreased fat mass has also been described in children presenting with asymptomatic disease.⁵⁰ Similar findings have also been described in the adult population.⁵¹ After 1 year on a GFD, affected children have been found to have complete restoration of body composition with no significant differences in weight, fat mass, or lean mass of the limbs compared to healthy controls. This restoration appears to occur faster and more completely when the GFD is initiated in childhood or adolescence compared to adulthood. It also appears to be a lasting effect, as body composition in young adults who had initiated a GFD in childhood or adolescence was entirely normal.⁴⁹ Even without strict adherence, long-term

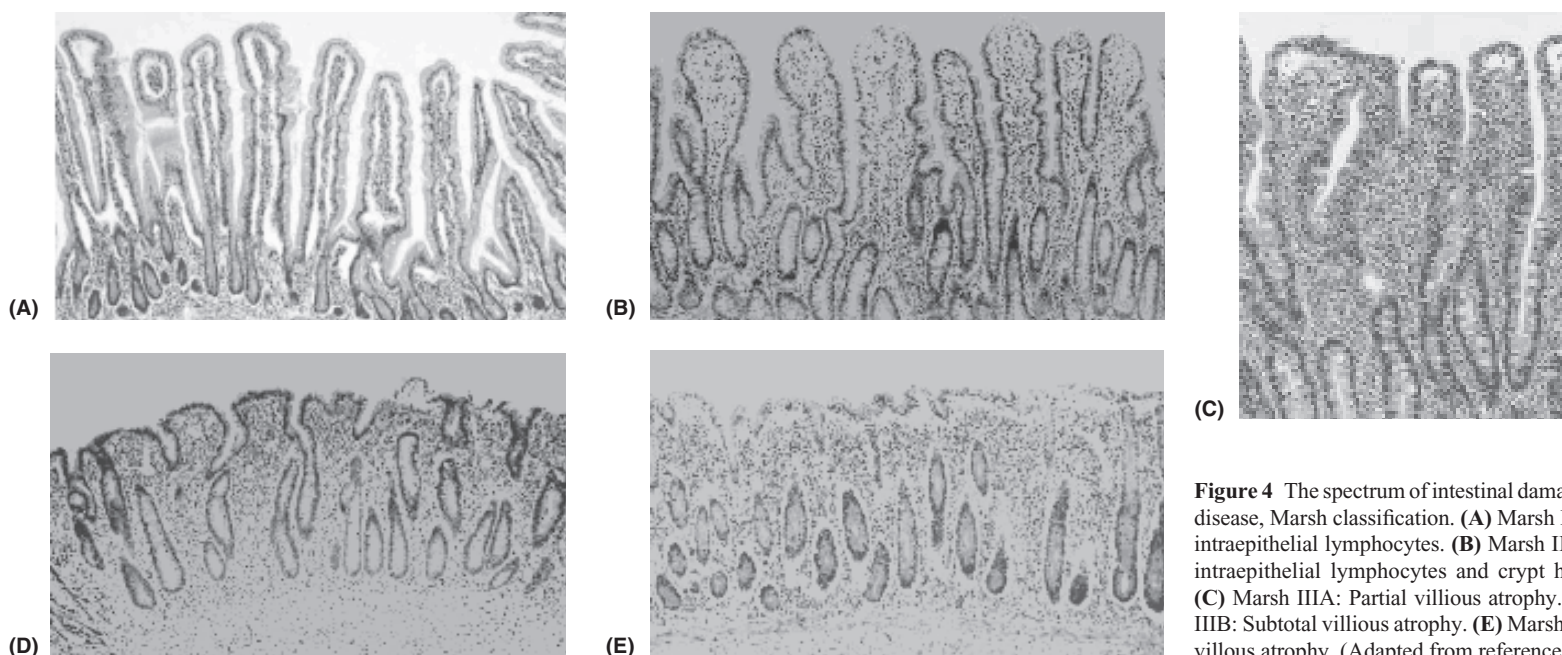


Figure 4 The spectrum of intestinal damage in celiac disease, Marsh classification. (A) Marsh I: Increased intraepithelial lymphocytes. (B) Marsh II: Increased intraepithelial lymphocytes and crypt hyperplasia. (C) Marsh IIIA: Partial villous atrophy. (D) Marsh IIIB: Subtotal villous atrophy. (E) Marsh IIIC: Total villous atrophy. (Adapted from reference 119.)

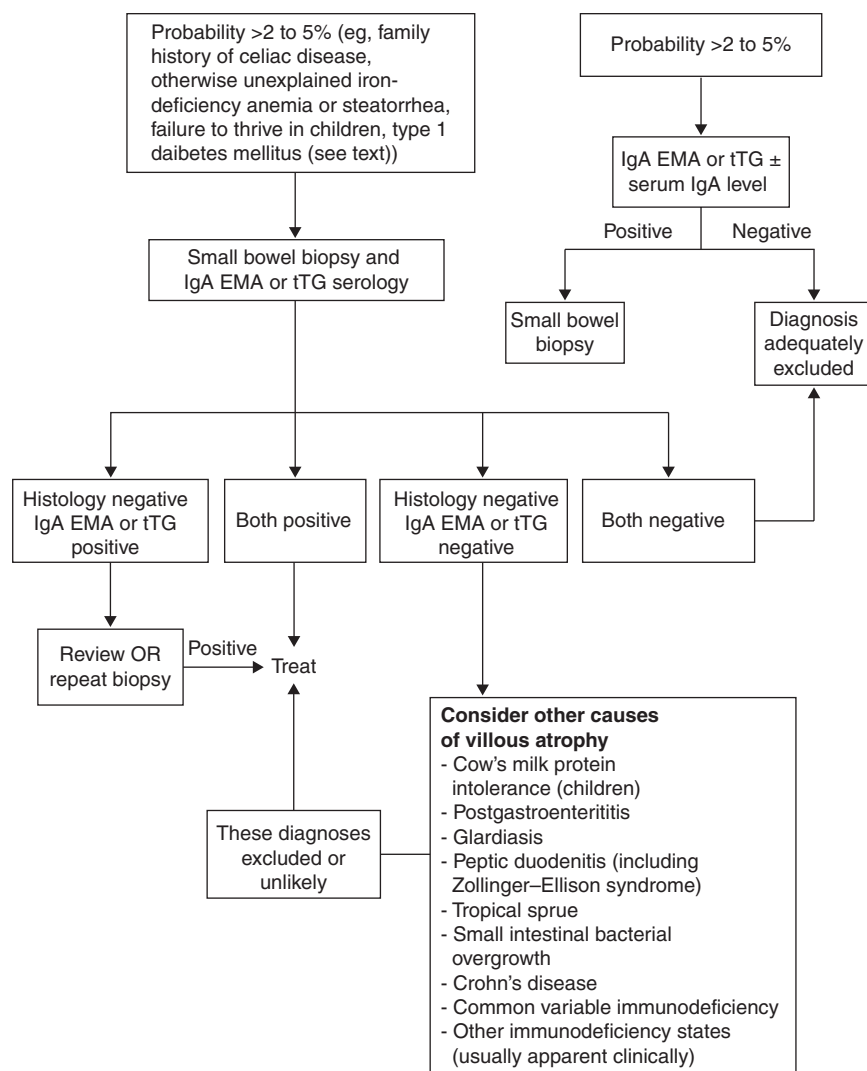


Figure 5 Making the diagnosis of celiac disease. (Adapted from reference 38.)

maintenance of the diet through adolescence was associated with improvements in body composition.⁵² As nonclassical forms of CD are being increasingly recognized, these characteristic changes in body composition may not be found consistently. A recent analysis of adults with CD in the United States showed that only 18% were underweight at the time of diagnosis with 21% meeting criteria of being either overweight or obese (specifically defined as a BMI > 25).⁵³ This has not yet been demonstrated in the pediatric population (Figures 6 and 7).

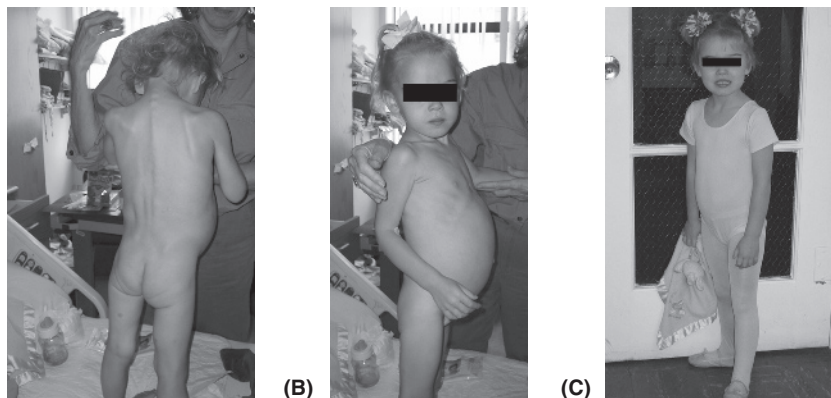


Figure 6 A toddler with “classic” presentation of celiac disease: (A) at the time of diagnosis (1); (B) at the time of diagnosis (2); (C) 1 year on a gluten-free diet.

Osteoporosis, rickets, and osteomalacia are all seen with CD. The specific mechanism of bone disease associated with CD is unclear but is likely related to malabsorption of calcium and vitamin D, and a possible effect of increased interleukins and other inflammatory mediators. Decreased bone mineral density is frequently seen in patients with CD, even in patients with clinically silent CD.⁵⁴ In untreated adult celiac patients, the reported prevalence of decreased bone mineral content is 22 to 80%. In children and adolescents with CD, bone mineral density

is often decreased at the time of diagnosis (3 to 39% prevalence).⁵⁵ However, after 1 year on a strict GFD, the bone mineral density of children and adolescents with CD appears to normalize and reach the level of healthy controls. After 4 years of a GFD, these patients continue to have normal values.^{54,56} Again, this restoration appears to be most consistent in the setting of early recognition and treatment.⁵⁷ Interestingly, patients who are poorly compliant did not appear to achieve peak bone mineralization.⁵⁶ The effect of the GFD on bone mineral density in adult studies has shown conflicting results. Some studies report improvement of bone mineral density on the diet and others show no such effect.^{51,58–60} The age at diagnosis and initiation of the GFD seems to be a determining factor in bone restoration perhaps because of the increased activity of bone metabolism in childhood and adolescence.⁶¹ There are conflicting data, however, on whether fracture risk is increased in adult patients with CD so the clinical significance of this osteoporosis is not clear.^{62,63}

Another characteristic change associated with celiac disease involves dentition. Dental enamel defects of permanent teeth involving symmetric and chronologic distribution are well recognized in CD affecting up to 96% of children with CD and 83% of adults.⁶⁴

NUTRITIONAL DEFICIENCIES

Nutritional deficiencies associated with CD are well recognized and should be an important consideration at the time of diagnosis and in continued management. Abnormal folate, iron, and vitamin B₁₂ levels are found in children, adolescents, and adults with newly diagnosed or untreated CD. This appears to be true in patients with clinically silent disease as well as those with more “classic” manifestations. A study of screening-detected adolescent cases of CD in Finland (30% asymptomatic) found that 1 of 3 had abnormal folate or iron status.⁶⁵ European studies in adults have shown decreased levels of vitamin B₁₂ in 11 to 41% of patients with CD.^{66,67} Additionally, there is some evidence that untreated adult patients with CD have reduced endogenous pools of zinc.⁶⁸ Children with active gastrointestinal CD have also been shown to have lower serum zinc levels than healthy controls and children with celiac on the GFD.⁶⁹ Fat-soluble vitamins such as vitamin E, vitamin D, and vitamin K levels may also be low.

Iron-deficiency anemia is the most common clinical presentation of CD in adults but is also seen in children.^{70,71} This is likely secondary to decreased absorption of iron in the proximal small bowel but may also be related to inadequate dietary intake as a result of CD-associated anorexia or chronic inflammation. Megoblastic anemia due to folate or vitamin B₁₂ deficiency is also seen. Thrombocytopenia, leukopenia, and prolonged coagulation have also been reported in the pediatric population.⁷² Notably, these abnormalities appear

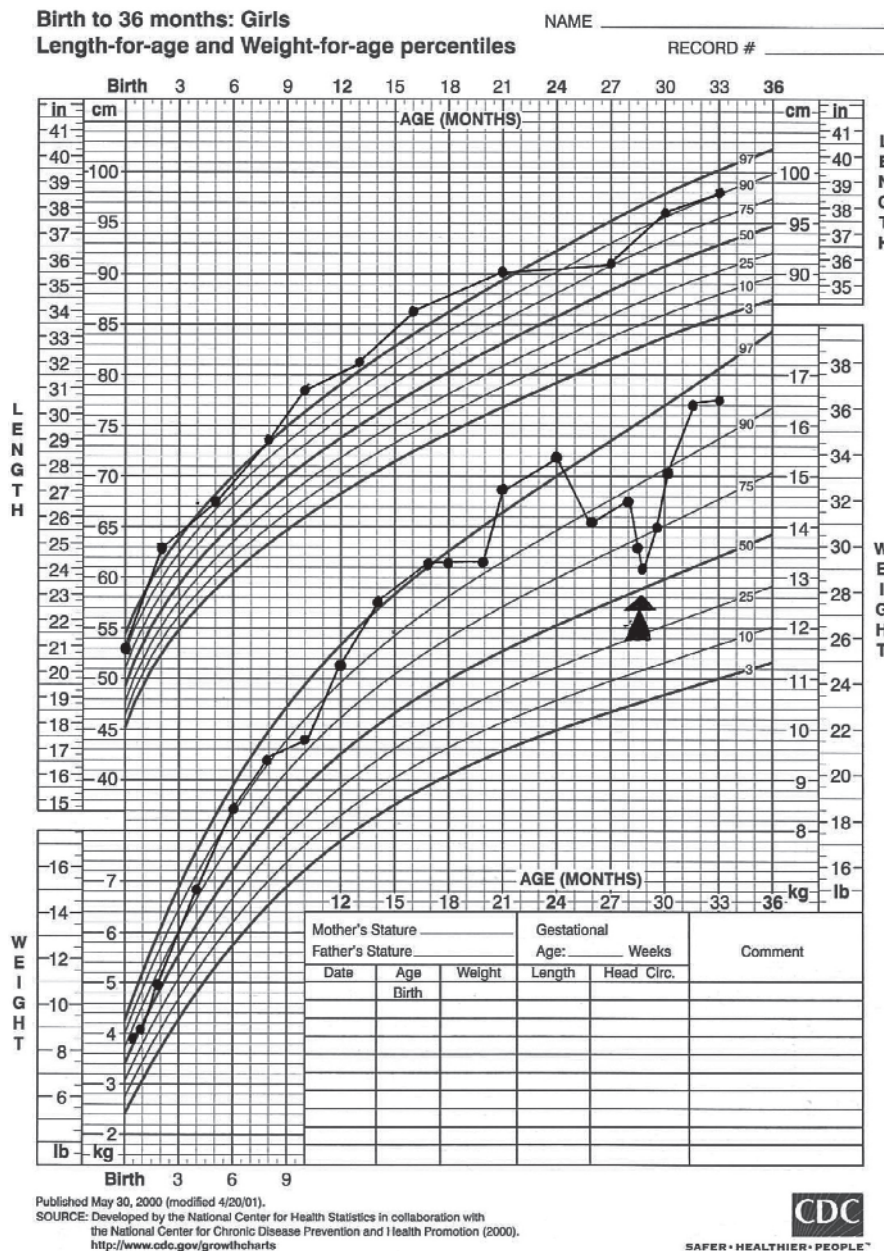


Figure 7 Growth chart of a classically presenting toddler with celiac disease. The arrow indicates time of diagnosis and initiation of a gluten-free diet.

to resolve with treatment. For example, up to 95% of patients have correction of their anemia after 1 year on the GFD.⁷³

OTHER EXTRAINTestinal MANIFESTATIONS

Hepatic involvement is seen in adult and pediatric patients with CD. In a European study of 114 consecutive pediatric patients with CD, mild hypertransaminasemia was observed in 32% of patients at the time of diagnosis. In 5 patients (4.3%), it was the only manifestation of CD. In these children, aminotransferases normalized within 1 year of initiating a GFD either before or at the same time as serologic marker normalization. Hypertransaminasemia does not seem to be related to malnutrition in these patients and the mechanism of hepatic injury is not clear.⁷⁴ Similar findings have been reported in the adult celiac population.⁷⁵ Severe liver disease that

resolved with a GFD has also been reported in adults with CD.⁷⁶

Pubertal delay can occur in both boys and girls with CD. Hypogonadism, infertility, and sexual dysfunction have all been described in the literature. Boys have been found to have an abnormal pattern of androgen resistance. Girls with untreated CD have been shown to have delayed menarche compared to their mothers and to girls with CD who are on a GFD.^{77,78} Increased risk for recurrent miscarriage, premature delivery, and lower birth weight babies have each been reported in women with untreated CD.^{79–81}

Neurologic complications are a rare but recognized manifestation of CD. In fact, there are a growing number of reports linking neurologic symptoms with CD, sometimes as the presenting manifestation. Cerebellar ataxia, peripheral neuropathy, and epilepsy have been described primarily in the adult celiac population. Depression and anxiety have also been described to affect up

to a third of patients with CD.^{82–84} The syndrome of bilateral occipital cerebral calcifications and seizures, also known as CD, epilepsy, and cerebral calcifications (CEC syndrome), has been well described in association with CD. It presents primarily in childhood.⁸⁵

There are limited studies on other neurologic complications of CD in pediatrics. Headache appears to be the most common neurologic complaint in children affecting almost a third of patients. Neurologic disorders such as hypotonia, developmental delay, learning disabilities, attention deficit hyperactivity disorder, headache, and ataxia have been described in up to 52% of patients with CD diagnosed in childhood which was significantly higher than a healthy control group. Epilepsy unrelated to CEC syndrome was not strongly associated with CD in children. There is no increase in the incidence of tics in patients with CD.⁸⁶ Despite previous reports to the contrary an association between CD and autism has not been confirmed.^{30,84,87}

The spectrum of neurologic complications responds variably to a GFD. Up to half of children experiencing headaches improved on the diet. High rates of response in transient infantile hypotonia associated with classical early onset CD have also been reported, perhaps because of resolution of nutritional deficiencies.⁸⁶ In cases of epilepsy, improved seizure control has been reported but not seizure resolution. Depressive symptoms and anxiety may improve with a GFD in some patients but depression remains common in the treated celiac population. A few reports describe improvement of neuropathy and ataxia on a GFD but for most patients these neurologic problems persist or progress despite gluten avoidance.⁸⁴

NATURAL HISTORY

Overall mortality in patients with CD has been described as two times that of the general population. The risk of increased mortality appears higher in patients with malabsorptive symptoms with no increased risk in patients with minor or no symptoms. Increased mortality has also been observed in association with delayed diagnosis and with poor adherence to the GFD.^{88,89}

Specifically, an increased risk of malignancy has been associated with CD since the 1960s. Patients with CD appear to be at increased risk for non-Hodgkin lymphoma, especially small-intestinal T-cell lymphoma, small-intestinal adenocarcinoma, squamous cell carcinomas of the esophagus, mouth, and pharynx, and other gastrointestinal tract tumors. However, the absolute risk for malignancy remains small and recent data suggest that the risk while present is less than previously estimated and is low in patients with clinically silent CD.^{89,90–93} The mechanism for this increased risk of cancer is not well understood but is perhaps related to chronic inflammation, increased exposure to environmental carcinogens secondary to intestinal permeability, immune surveillance abnormalities, or nutritional deficits.

Increased mortality and malignancy appear to be issues that primarily affect adult patients with CD. Few cases of cancer in children and adolescents with CD have been reported and increased risk of malignancy in this population has not been shown clearly.^{91,93-95} Nonetheless, prompt identification of CD and appropriate treatment likely has long-term effects into adulthood. Adult patients with CD who were diagnosed in childhood appear to have a normal mortality rate presumably a benefit of long-term adherence to a GFD.⁸⁹ Additionally, patients who adhere to a GFD appear to have decreased malignancy risk that approaches that of the general population.^{93,94}

The prevalence of autoimmune disorders is higher in adolescents and adults with CD and in their relatives as compared to the general population.⁹⁷⁻⁹⁹ This association is likely related to the common genetic background including HLA type. It has been suggested that the risk of autoimmunity is related to the duration of gluten exposure and the age of diagnosis.⁹⁷ However, other studies have disputed this theory.^{100,101}

TREATMENT

Gluten and related proteins in rye and barley are clearly implicated in the pathogenesis of CD and eliminating these proteins from the diet is currently the mainstay of treatment. Adherence to a strict GFD leads to histopathologic remission, serologic normalization, resolution of most of the related symptoms, and likely prevention of long-term complications.

However, the GFD is often challenging and sometimes overwhelming to people with CD. Wheat-based foods are a major staple of the American diet and finding palatable gluten-free alternatives can be difficult and expensive. Additionally, gluten is a hidden ingredient in many foods and medications and labeling can be confusing. The initiation of a strict GFD can have significant implications on quality of life. In fact, both adults and children with CD report negative feelings toward the diet and report difficulties with adherence especially related to eating out of the home, traveling, and social events.^{102,103} Thus it is not surprising that adherence to the GFD is a major issue in CD management. This is true across all ages but especially in adolescents and young adults. Strict adherence to a GFD in this age group has been reported to be between 45 to 65%.^{104,105} A very young age of diagnosis is associated with higher rates of adherence.¹⁰⁶ Screening detected disease, with either atypical or silent features, is associated with poorer compliance.¹⁰⁷ Patient and family education and support help the transition to a GFD and increase adherence. Intensive support is best given via a team approach with involvement of both a physician and a dietitian experienced in CD. Involvement in support groups is also helpful.^{102,103}

The role of oats in the GFD has been somewhat controversial. In Europe, they are often

included as part of a GFD. Various studies show that the inclusion of oats is safe for the majority of children and adults with CD. In some individuals, the avenin proteins in oats can trigger a response similar to gluten.¹⁰⁸⁻¹¹⁰ However, because of concerns about high levels of cross-contamination with wheat in the North American oats supply, it is not yet widely recommended in the United States. As uncontaminated sources of oats become more available, gradual introduction of oats with close clinical follow-up may be attempted in patients with well-treated CD.

Lactose intolerance is common in both children and adults with untreated CD. In fact, up to half of newly diagnosed patients are affected. Lactose intolerance in the setting of active CD is likely secondary to low lactase enzyme activity in the damaged small intestinal mucosa. Lactose-containing foods may need to be avoided initially in newly diagnosed patients with significant symptoms. Fortunately, most patients can tolerate dairy intake within 3 to 6 months after initiation of a GFD.^{111,112}

While general nutritional status improves with treatment, a lifelong GFD may not be nutritionally well balanced. Few gluten-free products in the United States are enriched and most are lower in fiber than their wheat-containing counterparts.¹⁰⁸ In fact, adult and adolescent patients on a GFD have been shown to have decreased fiber intake.^{113,114} Mean daily intakes of folate and vitamin B₁₂ were significantly lower in adults with CD on a GFD as compared to healthy controls.¹¹⁵ Children on a GFD were also found to consume only 60% of the recommended daily allowance of iron.¹¹⁶ Another nutritional study of children with CD found that those children on a strict diet were more likely to have a nutritionally unbalanced diet and were more likely to be overweight than children who were not adherent to the diet.¹¹⁷ A study in adult celiac patients after 8 to 12 years of GFD with biopsy-proven remission showed that 56% showed signs of poor vitamin status, specifically with lower plasma levels of folate, vitamin B₆, and elevated levels of homocysteine (a metabolic marker of folate, vitamin B₆, and vitamin B₁₂ deficiency).¹¹⁵ Thus the use of a daily gluten-free multivitamin supplement is often recommended.¹⁰⁸

Please refer to Chapter 71, "Special Diets," for additional information about a gluten-restricted diet and celiac resources and support groups.

BEYOND THE GFD

While highly effective, a GFD is not an ideal therapeutic option for many individuals with CD because of the challenges associated with diet adherence and the negative impact on quality of life. Developing grains, through selective breeding and transgenic technology, that have low or nontoxic peptide sequences and acceptable baking qualities is technically challenging. Fortunately, as our understanding of the pathophysiology of CD has grown, several potential targets for new

treatments have been identified. Alternatives to the GFD are currently being investigated.

Intraluminal therapies, such as endoproteolytic enzymes, may help degrade gluten peptides in the lumen thereby rendering them nontoxic. Blocking zonulin, a protein that regulates intestinal permeability, is also being explored and may act by preventing disruption of the intestinal epithelial barrier and the passage of toxic gluten peptides into the lamina propria. Other strategies target recognition and presentation of the offending gluten antigens via blockade of dendritic cells and other antigen-presenting cells, specific antagonization of HLA-DQ peptide binding or by inhibition of TTG. Interfering with the subsequent inflammatory response by cytokine therapy and selective adhesion molecule inhibition is another potential intervention that is currently being explored in other disease processes.¹¹⁸

Many of these potential new treatments, while promising, are in the early phases of investigation.

Ideally, a safe and effective treatment will be developed that can replace the GFD and allow patients with CD to eat freely. However, a more realistic goal may be to develop therapies that allow patients with CD increased flexibility with their diet. A treatment that allows individuals to tolerate small or moderate amounts of gluten in their diets would clearly have a positive impact on the lives of people with CD.

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