Celiac Disease: Epidemiology, Pathogenesis, Diagnosis, and Nutritional Management

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■ **ABSTRACT**

Celiac disease (CD) is an inflammatory small intestinal disorder that can lead to severe villous atrophy, malabsorption, and malignancy. It is triggered by the gluten proteins of wheat, barley, and rye. All patients express the antigen-presenting molecules human leukocyte antigen-DQ2 (HLA-DQ2) and/or HLA-DQ8, which bind gluten peptides and thus activate destructive intestinal T cells. Patients with untreated CD have circulating IgA autoantibodies to the enzyme tissue transglutaminase (tTG), a component of endomysium. Testing for serum IgA tTG has a high predictive value. Therapy of CD is a lifelong gluten-free diet. Counseling by an expert dietitian and association with a celiac support group are important in helping the patient embark on a healthy gluten-free diet. Current research focuses on non-dietary therapies and treatment of refractory (diet-unresponsive) CD. *Nutr Clin Care.* 2005;8: 54–69 ■

KEY WORDS: autoantibody, autoantigen, celiac disease, cytokine, DQ2, DQ8, gene dose, gluten, gliadin, human leukocyte antigen, HLA, interferon, matrix metalloproteinase, MMP, pathogenesis, transforming growth factor-beta, TGF-beta, tumor necrosis factor-alpha, TNF-alpha, T cell, therapy, tissue transglutaminase

HISTORY AND EPIDEMIOLOGY

Classical celiac disease (CD) is a small intestinal inflammatory disease that is characterized by global malabsorption of nutrients, minerals, and vitamins. Histologically, it is characterized by a predominant T-cell infiltration in the epithelium and the lamina propria of the intestine, which can lead to complete destruction of the villi, through which nutrient resorption occurs.[1-5] CD was fatal in 12% of affected children in a retrospective study in 1939,[6] and its cause remained elusive until the Dutch pediatrician Willem Dicke recognized an association between the consumption of wheat products and the relapsing diarrhea of CD. During periods of food shortage in the second World War, the illness lessened in his patients when bread was replaced by non-cereal-containing foods. After the war, Dicke and van de Kamer[7] confirmed this observation by performing controlled experiments exposing children with CD to defined diets followed by determination of fecal weight and fecal fat as a measure of malabsorption. These studies clearly demonstrated that wheat, barley, and rye triggered CD and that the condition could be reversed after their exclusion from the diet.[7] The major toxicity was found in the alcohol-soluble gliadin fraction of wheat gluten.[8]

The celiac lesion of mucosal inflammation, crypt hyperplasia, and villous atrophy in the proximal small intestine, although already observed by Rudolph Bennecke from Marburg, Germany in 1910, was first described in detail in 1954,[9] and its classification was refined by Marsh.[10] With the advent of serum tests such as immunoglobulin A (IgA) antibodies to gliadin,

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and especially to an autoantigen present in reticulin and endomysium (the connective tissue of soft tissues and around smooth muscle, respectively), CD could be more easily differentiated from other malabsorptive disorders that cause villous atrophy, such as tropical (microbial) sprue and bacterial overgrowth.[11] More importantly, population studies using the autoantibody tests as screening tools with subsequent small intestinal biopsy for confirmation revealed a hitherto unexpectedly high prevalence of CD in the western world, in northern Africa, the near East, and the Middle East, ranging from about 1:80 to 1:150.[12-14] In these studies, the vast majority (>80%) of screening-detected individuals presented with clinically silent or atypical forms of the disease. If and to what extent screening-detected asymptomatic or minimally symptomatic individuals may develop clinically overt CD, secondary autoimmune diseases, or even malignancy (see below) when continuing on a gluten-containing diet is still unclear.

GLUTEN: THE CAUSATIVE AGENT IN CD

Gluten comprises the storage proteins of wheat. These proteins can be separated into the ethanol-insoluble glutenins, which are responsible for the desired baking properties of this cereal, and the alcohol-soluble gliadins. Each wheat variant produces an estimated 40 to 50 gliadins, which are structurally related proteins containing 250 to 500 amino acids, and a lower number of high- and low-molecular-weight glutenins, with 650 to 800 and 270 to 320 amino acids, respectively. Both gliadins and glutenins display a high content of the amino acids glutamine (32%–56 %) and proline (15%–30%) and, due to their cysteine content, glutenins can form complex homopolymers and heteropolymers with gliadins.[15,16] Storage proteins similar to gliadins (generally termed prolamines) have been found in rye (secalins) and barley (hordeins), while the avenins of oats and especially the zeins of rice are more distantly related (Table 1). On the basis of their electrophoretic properties and primary structure, the gliadins are subdivided into the classes of α-, γ-, and ω-gliadins, which can be further resolved into distinct proteins such as α1-11, γ1-6, and ω1-5. Although the pro-inflammatory effect of all gliadin fractions has been shown in vitro,[17,18] most experimental and human studies have focused on α-gliadins, and in particular on the pro-inflammatory peptides in its amino-terminal region.[19]

Table 1.

Cereal	Prolamines	Composition	"Toxicity"
Wheat	gliadins	36% Q, 17%–23% P	+++
Barley	hordeins	36% Q, 17%–23% P	++
Rye	secalins	36% Q, 17%–23% P	++
Oats	avenins	high Q, low P	(+)
Maize	zeins	low Q, high A,L	–
Millet	?	low Q, high A,L	–
Rice	?	low Q, high A,L	–

THE GENETIC COMPONENT AND ASSOCIATED AUTOIMMUNITY

The genetic component of CD is more evident than that of most other inherited diseases. Transmission is autosomal dominant with incomplete penetrance, resulting in a disease prevalence of about 15% in first-degree relatives[20-22] and reaching a concordance rate of 75% in monozygotic twins.[23] CD is tightly associated with the human leukocyte antigen (HLA) class II antigens DQ2 and DQ8, which are located on chromosome 6p21.[21-22] Between 85% and 95% of patients with CD carry DQ2, and virtually all remaining patients express DQ8.[24] DQ2 is a heterodimer encoded by the alleles DQA1*05 (α) and DQB1*02 (β), which are associated with the DR3-DQ2 haplotype (when encoded on the same allele in cis) or with the DR5/DR7-DQ2 haplotype (when encoded on both alleles in trans) (Figure 1).[21-22] DQ8 is a heterodimer encoded by DQA1*0301 and DQB1*0302. DQ2 or DQ8 are necessary but not sufficient for the development of CD, since 25% to 30% and 5% to 15% of healthy controls in the susceptible populations are carriers of DQ2 and DQ8, respectively. Large studies searching for additional predisposing genes have identified loci on chromosome 5q31-33, which encodes a cluster of cytokine genes[25-27], and on chromosome 2q33, which harbors immune regulatory genes such as CTLA-4, ICOS-1, and CD28[28,29] and the DR3-linked genes MICA-A4, MICA-A5.1, MICB-CA24, and MIB-350.[30,31]

An early and massive gluten exposure appears to favor CD manifestation, which may explain the 5- to 10-fold higher prevalence in the 1970s of classical CD in children from Sweden compared with Denmark, two otherwise genetically similar populations.[32] Furthermore, patients can express two copies, instead of only a single copy, of HLA-DQ2 (DQ8), which dramatically increases the likelihood of effective antigen presentation and disease manifestation (Figure 2).[33-36]

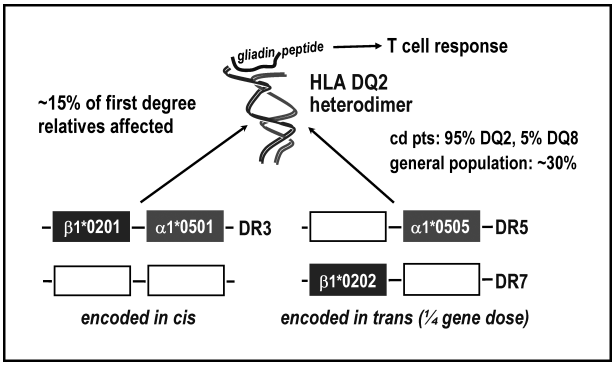

Figure 1. HLA-DQ2 (DQ8) and presentation of gluten peptides to T cells. HLA-DQ2 (DQ8) is a heterodimer of an α- and a β-chain that is necessary to present (modified) gluten peptides to gluten-reactive T cells. In most populations, more than 90% of celiac patients express DQ2 and a minority express DQ8. The two DQ2 chains can be encoded on a single allele (in cis) in association with DR3 or on the two alleles in association with DR5 and DR7 (in trans). In the case of the trans configuration, only one out of the four possible heterodimers that can form contains the correct chains, while in the case of homozygosity, the cis configuration can lead to four out of four heterodimers with the right chain composition. Homozygosity for DQ2 in cis underlies the observed gene dose effect described in Figure 2.

CD is associated with other, classical autoimmune diseases such as type 1 diabetes, autoimmune thyroiditis, connective tissue diseases, idiopathic cardiomyopathy, and autoimmune hepatitis, with prevalences ranging from 3% to 15%.[37-47] A cross-sectional report suggested that the duration of gluten exposure correlated with the occurrence of these autoimmune diseases, ranging from 5.1% to 23.6%, with age at diagnosis from less than 2 years to over 10 years, respectively.[37] However, a subsequent study demonstrated that susceptibility to secondary autoimmunity was mainly related to the age of the celiac patient.[38] It is therefore likely that a higher age and a shared genetic predisposition, such as DR4, HLA-DQ8, and genes on chromosomes 2q33 and 15q26 for type 1 diabetes[36-38] and HLA-DQ2/DQ8 and CTLA-4 polymorphisms for autoimmune thyroiditis,[41,47] underlie this association, while a causative role of gluten ingestion in the context of CD may be of minor importance.

TISSUE TRANSGLUTAMINASE: THE CD AUTOANTIGEN

Patients with untreated CD have circulating IgA autoantibodies against endomysium (the connective tissue around smooth muscle) or reticulin (delicate, extracellular fibrils). These autoantibodies are a valuable tool for diagnosis and population screening due to their high positive and negative predictive value for CD, ranging between 90% and 100%.[11] In 1997, this autoantigen was identified as the enzyme tissue transglutaminase (tTG),[48] which is expressed by almost all cell types and is usually retained intracellularly in an inactive form. When cells are under mechanical or inflammatory stress, tTG is released into the extracellular space, which explains its association with endomysium or reticulin.[49,50] tTG belongs to a family of at least eight calcium-dependent transamidating enzymes that catalyze the covalent and irreversible cross-linking of a protein with a glutamine residue (glutamine donor) to a second protein with a lysine residue (glutamine acceptor), resulting in the formation of an ε-(γ-glutamyl)-lysine isopeptide bond.[49-51]

tTG displays high specificity for only certain protein-bound glutamine residues as glutamine donor substrates, whereas lysine-containing glutamine acceptor substrates are numerous. The enzyme is only active in the presence of high calcium concentrations, as are found in the extracellular space, where it contributes to the stabilization of the extracellular matrix.[52] tTG and tTG-derived cross-linking are necessary for regulated apoptosis and play a role in neurodegen-

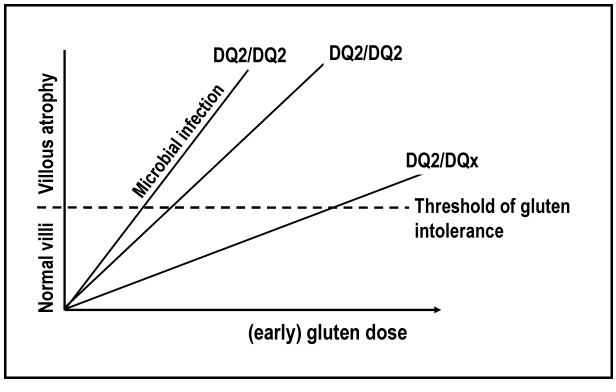

Figure 2. DQ2 gene dose and gluten load. DQ2 gene dose and extent of (early) gluten exposure determine the manifestation and severity of celiac disease (CD). While a low gene dose of DQ2 (see Figure 1) and a careful introduction of gluten in the diet can keep intestinal inflammation subliminal, a high gene dose (and thus surface expression) of DQ2, coupled with early and massive gluten ingestion, can spark off overt CD. Additional triggers are probably mechanical irritation and inflammation by chemicals or microbes that lead to enhanced intestinal permeability and increase the level of intestinal tTG and pro-inflammatory cytokines.

erative disorders such as Alzheimer's and Huntington's disease.[53,54] Intracellularly and at low pH, tTG merely deamidates a target glutamine in the substrate protein, transforming the neutral glutamine to a negatively charged glutamic acid residue (Figure 3).[55]

TISSUE TRANSGLUTAMINASE AND CD: A MISSING LINK

The existence of gluten-specific T cells remained hypothetical until 1993, when such T cells were indeed isolated from patients and found to be absent in healthy controls.[22] HLA-DQ molecules harbor a peptide-binding groove that accommodates peptides of 9 to 11 amino acids in length that must contain negatively charged amino acids at so-called anchor positions (DQ2: P4, P6 and P7, or proline in P6; DQ8: P1 and P9, and hydrophobic residues in P4, P6, and P7).[56-58] Although such acidic peptides do not occur in the gluten molecules, tTG, the target autoantigen of CD, can deamidate certain glutamines in these peptides, which introduces the negative charges required for binding to HLA-DQ-molecules (Figure 4). Thus, ingested gluten molecules are degraded to peptides by gastrointestinal enzymes, modified by tTG, bind to HLA-DQ2 or HLA-DQ8, and trigger an inflammatory T-cell response.

Extensive work has revealed the identity of a series of (deamidated) gluten peptides that can trigger such T-cell responses both in vitro and ex vivo in cultures of biopsies derived from celiac patients.[59-66] Nonetheless, many T-cell clones derived from pediatric patients and some from adult patients respond primarily to non-deamidated gliadins and glutenins, indicating that the early immune response in CD is directed to several unmodified gluten peptides, whereas long-standing disease favors a few immunodominant and preferentially deamidated peptides.[65]

The peptide PQPQLPY (proline-glutamine-proline-glutamine-leucine-proline-tyrosine) from α-gliadin,

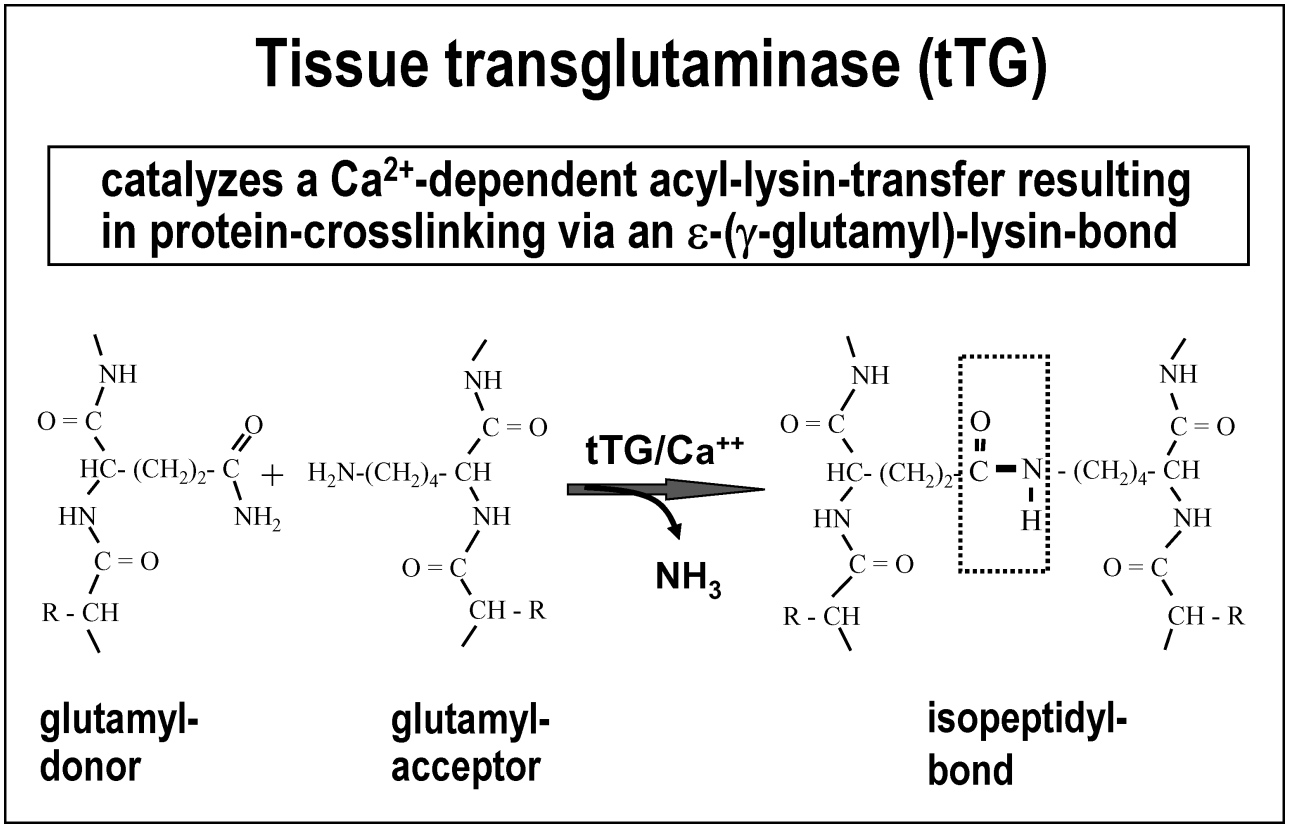

Figure 3. Protein cross-linking by tTG. Tissue transglutaminase catalyzes the cross-linking of a protein-bound glutamine residue (glutamine donor) with the lysine residue of a second protein (glutamine acceptor). The reaction is calcium dependent and results in the formation of an irreversible isopeptidyl bond. In the absence of available glutamine acceptors or at low pH, deamidation of the glutamine donor protein is favored over cross-linking, resulting in the creation of deamidated peptides.

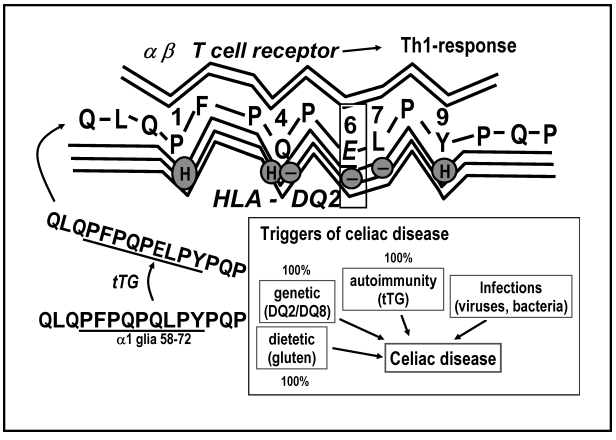

Figure 4. Triggers of celiac disease and their interplay. Celiac disease is driven by gluten in subjects carrying the predisposing genes HLA-DQ2 (DQ8) and is tightly associated with the autoantigen tTG. These three factors are present in essentially 100% of patients. An additional role of mechanical or microbial triggers that lead to the manifestation of subliminal CD is suspected. tTG can deamidate gliadin peptides, such as the immunodominant peptide α1(58-72) with the core DQ2-binding sequence PFPQPQLPY (proline-phenylalanine-proline-glutamine-proline-glutamine-leucine-proline-tyrosine), leading to the generation of a negatively charged glutamine (E) residue. Since negatively charged residues are preferred in positions 4, 6, and 7 of the antigen-binding groove of DQ2, the deamidated peptide binds more strongly to DQ2, serving as a more potent stimulator of gliadin-specific T cells.

which can be deamidated to PQPELPY (E = glutamic acid), was identified as an immunodominant epitope,[62] and a 33-mer peptide from α2-gliadin, which contains three partly overlapping stretches of this epitope, is fairly resistant to digestion by intestinal proteases.[67,70] Clinical trials using bacterial endopeptidase, which degrades this and related peptides, are currently being conducted.

Synthetic peptide libraries were used to define the primary sequence requirements for those glutamine residues that are substrates for tTG. These studies showed that the relative positions of proline to glutamine residues are crucial. Thus, only the sequences QXP and QXX (X representing a hydrophobic amino acid), but not QP or QXXP, are targeted by tTG.[63,64,67,70] Based on these sequence motifs, algorithms were designed and used to screen the available databases of cereal proteins for preferred tTG recognition sequences, leading to the detection of about 50 T-cell epitopes in wheat gliadins and similar epitopes in the phylogenetically related hordeins from barley and secalins from rye.[67,70] T-cell stimulatory sequences were also found in the structurally unrelated wheat glutenins, confirming prior observations with glutenin-reactive T-cell clones.[71] The lack of optimal tTG recognition sequences and thus ineffective deamidation by tTG in the avenins of oats,[67,72] which have a high glutamine but a low proline content (Table 1), support the clinical observation that pure oats are safe for celiac patients.[73,74] However, a recent study described three individuals with CD who were intolerant to oats and from whom avenin-reactive T-cell clones could be isolated,[75] indicating that in rare patients, oats may drive CD.

REFRACTORY SPRUE AND INTESTINAL LYMPHOMA

Refractory sprue can develop in up to 5% of adults with long-standing (and often undetected) CD who do not respond to or relapse while on a strictly gluten-free diet. The diagnosis can only be made when other causes such as tropical sprue, bacterial overgrowth, radiation damage, and food allergies have been excluded. Small bowel involvement is often extensive, and there is growth of monoclonal intestinal T-cell populations that can be detected by PCR for T-cell receptors from biopsies. Refractory sprue type I is responsive to steroids and immunosuppressants, while refractory sprue type II evolves into overt T-cell lymphoma.[76-78]

Intestinal lymphoma is an initially intraepithelial, enteropathy-associated T-cell lymphoma that appears to develop from refractory sprue[76,77]; treatment of this kind of lymphoma (and refractory sprue type II) is frustrating, but novel therapies may emerge, such as blocking interleukin-15, which is a crucial growth factor for the abnormal lymphocytes.[79]

DIAGNOSIS OF CD

Small intestinal biopsy histology (usually two to four biopsies from different parts of the descending duodenum) remains the gold standard for the diagnosis of CD, usually revealing significant villous atrophy (lesions of Marsh stage II and especially III). In screening of normal populations, IgA and IgG anti-gliadin antibodies display sensitivities of 82% and 89% and specificities of 90% and 66%, respectively.[11] Specificity of elevated IgG anti-gliadin antibodies is unacceptably low, but the IgA anti-gliadin antibody test is somewhat

better. However, for IgA anti-gliadin antibodies, there will still be 10 times as many positives (up to 10% of the adult population) as there are biopsy-proven patients with CD, especially in the age group above 50 years.[80] Only long-term positivity of IgA anti-gliadin antibodies indicates the presence of CD with higher specificity.[81] IgA autoantibodies to endomysium, which are detected by indirect immunofluorescence on sections of esophagus, umbilical cord, or liver, are a sensitive and the most specific serological test to screen for CD. The sensitivity reported from reference laboratories in Europe is 93% to 87% and specificity is 99% to 99.7%.[11] However, lower sensitivities have been observed in the United States,[5] apparently as a result of poor standardization. In a CD reference center in the Netherlands,[82] IgA anti-endomysial antibodies were only associated with more severe intestinal lesions (Marsh IIIc > IIIb > IIIa), but were not found in patients with mild lesions (Marsh II). Furthermore, it remains difficult to determine the absolute sensitivities and specificities in a population screen, since duodenal biopsy, the supposed gold standard, is not feasible in all subjects tested.

With the identification of tTG as the target CD autoantigen recognized by endomysial autoantibodies,[48] the development of ELISA tests, which are easy to perform and observer independent, has become possible. This autoantigen has a particular link to CD pathogenesis, as described above. For population screening, the IgA autoantibodies to tTG serve as an excellent tool to predict CD with a sensitivity and specificity of 94% and 97%, respectively, when optimized assays based on human recombinant tTG are used. The original assay versions were based on guinea pig tTG extracted from liver and should not be used because, despite similar sensitivity, their specificity is lower (93%) due to contamination and thus cross-reactivity with liver antigens. In contrast to endomysial autoantibody testing, which largely depends on the expertise of the laboratory, it is the quality of the commercially available human recombinant tTG assays that determine diagnostic accuracy, making selection of a good assay supplier essential.[11]

NON-DIETARY THERAPIES

Due to tremendous recent advances, CD is considered the best-understood HLA-linked disorder. The disease is driven by a defined external (nutritional) trigger, namely gluten proteins from wheat, rye, and barley. It develops on the background of a genetic association with HLA-DQ2/DQ8 and involves tTG as an autoantigen that plays a key role in disease pathogenesis, namely antigenic potentiation of gluten peptides. In addition, the amount of gluten ingested, the gene dose of HLA-DQ2 (DQ8), and the local expression of tTG appear to be important determinants of CD manifestation and severity. A sizable number of immunodominant gluten peptides have been identified, part of them resisting degradation by intestinal peptidases and thus reaching the intestinal mucosa intact, where reactive T cells are recruited. Th1 cytokines released from these activated, gluten-specific T cells or from intraepithelial lymphocytes cause the typical mucosal damage of CD.

Effective therapy of CD requires adherence to a strictly gluten-free diet, which is a burden for most patients. Therefore, alternative treatments are being explored.[83] These include degradation of immunodominant gliadin peptides that resist intestinal proteases by use of exogenous bacterial prolyl endopeptidases[66,69]; inhibition of intestinal tTG activity by specific inhibitors[84]; inhibition of CD-specific T-cell stimulation by peptides that bind to HLA-DQ2 or -DQ8 but not to the gluten peptide-specific T cell receptors[85]; and modulation of the intestinal cytokine milieu, e.g. by immunomodulatory cytokines or by cytokine antagonists.[83] Apart from benefiting patients with CD, such novel therapies may provide a template for the treatment of other autoimmune diseases.

NUTRITIONAL THERAPY

Nutritional therapy for CD is a lifelong gluten-free diet. Early referral to, and counseling by, an expert dietitian is enormously important in helping the patient to make the challenging adjustments needed to embark on a gluten-free lifestyle. The patient's participation in an established celiac support group that provides updated product information, resources, and social and emotional support is also extremely helpful.

The National Institutes of Health (NIH) held a landmark consensus conference in June 2004, culminating in concise guidelines regarding the diagnosis and management of CD, as well as recommendations for future research.[86] According to the consensus conference statement, the six key elements in the manage-

ment of CD are: 1) consultation with a skilled dietitian, 2) education about the disease, 3) lifelong adherence to the gluten-free diet, 4) identification and treatment of nutritional deficiencies, 5) access to a support group, and 6) continuous long-term follow-up by a multidisciplinary team.

Guidelines for Nutritional Assessment

The initial counseling session should include a complete nutritional assessment (Table 2) and a thorough gluten-free diet education, including the provision of educational resources to the patient (Table 3). Con-

Table 2. Nutrition Assessment Standards of Care for Celiac Disease/Gluten-Sensitive Enteropathy

Tools	Assessment	Interventions
Diet history/food record	Look for adequate: ● Calories ● Protein ● Calcium ● Iron ● B-complex ● Iron ● Intake of fruits/vegetables Eating and shopping behaviors: ● Cultural/religious preferences ● Cooking experience ● Willingness/time to cook ● Use of prepared vs. whole foods ● Eating at restaurants vs. home ● Favorite foods/preferences	General diet recommendations: ● 1–2 g protein/kg BW ● 35–40 calories/kg BW ● Possibly low fiber at first, gradually increasing ● Possibly lactose-free ● Possibly fat-restricted ● Use food record and suggest ways to correct nutrient deficits; include recipe modification and snacks as ways to increase nutrient intake; add fruits and vegetables if intake is inadequate
Physical	● Height ● Weight ● BMI ● Growth chart (children) ● Skin, hair, nails	General recommendations: ● Calcium supplement ○ Children: 500 mg/d ○ Adults: 1000–1500 mg/d ● Multivitamin if needed ○ Children: standard 1/d ○ Adults 18–55 ■ Male 1/d ■ Female prenatal w/moderate vitamin A ○ Adults 56+: senior formula ● Iron supplementation if needed ● Modify diet for any other medical conditions (e.g., diabetes, HTN) ● Check meds for possible gluten or food/medicine interactions
Tests/labs	● Bone density/endoscopy results ● Any other tests ● Albumin, cholesterol, HDL, LDL ● Hgb, Hct, iron, transferrin, TTBC, B_{12} ● Na^+, K^+, Ca^+	
Medical	● Family history ● Associated symptoms or related illnesses ● Medications/supplements	
Social/emotional assessment	● Query response to diagnosis and diet ● Family support ● Literacy level	● Referral to social services if needed ● Positive reinforcement of health benefits of gluten-free diet ● Include family in nutrition education
Symptoms review	● Bloating/gas ● Diarrhea ● Constipation	● Trial of lactose-free diet ● If already lactose-free, highlight non-dairy sources of calcium and stress adequate protein ● Use lactose enzyme tablets or drops when using dairy products ● Use soluble fiber from fruits, vegetables, and grains to resolve diarrhea/constipation ● Encourage adequate fluid intake ● Use 3 small meals and 3 snack pattern, include protein at each ● If fat tolerance is diminished, digestive or pancreatic enzymes may be helpful

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Table 3. Nutrition Education for Celiac Disease/Gluten-Sensitive Enteropathy

Consultation	Information Required	Topics Covered/Resources Given to Patient
Initial consultation (90 min)	• Antibody results • Upper endoscopy biopsy results • Routine blood work • Bone density report • List of medications • List of supplements/herbs • Three-day food intake record • Copies of growth chart (pediatric patients)	Topics • What is celiac disease? • How does it affect nutritional status? • How does the GI tract work? • What areas are affected by celiac disease? • Simplified gluten-free diet ○ Grains allowed ○ Grains to avoid • Review of food record, using it as a teaching tool to correct any other nutritional deficiencies or to highlight areas that comply with the gluten-free diet and those requiring change Additional Handouts • Kitchen survival guide • Label reading, highlighting hidden sources of gluten • List of manufacturers of gluten-free food • List of local stores that carry gluten-free food Supplements • Possibly add multivitamin
First follow-up (60 min) 3–4 weeks after initial consultation	• Three-day food intake record (include daily activity and any change in symptoms) • Reports/tests done subsequent to initial visit	• Review food record, focusing on compliance with gluten-free diet and corrections of prior nutritional discrepancies • Review any new results • Use food record as a teaching tool, emphasizing positive steps made • Cover: ○ List of local restaurants that are helpful with gluten-free requests ○ Dining out strategies ○ Travel tips ○ School lunch and social gathering strategies • Weigh patient ○ Discuss changes in weight ○ Discuss weight goals • Review benefits of routine exercise/activity • Add, if not previously done, multivitamin and calcium supplements
Second follow-up (30–40 min)	• Three-day food intake record (include daily activity and any change in symptoms) • Reports/tests done since last visit	• Weigh patient ○ Discuss changes in weight ○ Discuss weight goals • Review label reading, school lunch, dining out, and travel • Review preplanning strategies for above • Review deficiencies of gluten-free diet with strategies to compensate • Review alternate grain information and preparation tips • Emphasize healthy lifestyle issues: activity, relaxation, balanced intake

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sideration of the patient's cultural preferences, eating and shopping behaviors, and social/emotional mindset is also critical for effective education.[87] Finally, incorporation of additional dietary adaptations may be needed for co-existing medical conditions such as diabetes, iron deficiency, or lactose intolerance.

The Gluten-Free Diet

All varieties of wheat (spelt, kamut, triticale, etc.), in addition to any derivatives of wheat, as well as rye and barley, must be strictly avoided on the gluten-free diet (Table 4). Other grains, such as rice, soy, corn, tapioca and potato flours, sorghum, Indian rice grass, amaranth, quinoa, buckwheat, millet, and teff are gluten free and vary in their nutritional profiles. Patients are taught that plain meats, fish, poultry, nuts, seeds, eggs, legumes, milk, cheese, fruits, and vegetables are naturally gluten free (Table 5).

The Oats Issue

Based on numerous studies conducted with adults and children in Europe and the United States, it appears that the majority of people with CD can tolerate oats.[72,73,88-93] However, due to the potential for cross-contamination with gluten-containing grains during harvesting, milling, or processing, it is still recommended that individuals with CD avoid oats at this time. Furthermore, a very minor subpopulation of patients with CD has a sensitivity to certain amino acid sequences in oats (see above).[75,88-93] In consultation with their doctors, individuals must determine for themselves whether to incorporate oats into their gluten-free diets. If, despite the risks and controversy, an individual with CD chooses to eat oats, the safest approach is to limit consumption to amounts found safe in several studies (50–70 g of dry, whole-grain rolled oats per day), to choose oats that have been tested and deemed free of contamination,[93] and to continue to be closely monitored by a physician.

Table 4. Grains, Starches, and Flours "Toxic" to Patients with Celiac Disease

- Barley
- Bran
- Bulgur
- Couscous
- Durum flour
- Einkorn*
- Emmer*
- Farro*
- Farina
- Gluten, gluten flour
- Graham flour
- Kamut*
- Malt, malt extract, malt flavoring
- Oats, oat bran, oat syrup†
- Orzo
- Rye
- Semolina (durum wheat)
- Spelt
- Triticale
- Wheat germ, wheat starch, wheat bran, any item with wheat in its name

*Types of wheat

†Although many studies have indicated that a moderate amount of oats can safely be eaten by people with celiac disease, there is concern over the contamination of oats by wheat and barley.

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Common Concerns about Following a Gluten-Free Diet

Cost

Gluten-free commercial foods tend to be more expensive than their gluten-containing counterparts. A single loaf of gluten-free bread can cost two to three times more than regular bread. Patients can reduce the shopping bill by purchasing longer-lasting produce (e.g., root vegetables such as potatoes, carrots, and parsnips) and seasonal produce; using beans, split peas and lentils; baking their own breads and baked goods; buying foods in large quantities with friends or support group members; and cooking from basic ingredients. Individuals with CD may claim the gluten-free diet as a medical expense deduction on their US income taxes if the net amount of reimbursements exceeds 7.5% of adjusted gross income.

Accessibility

Each region of the country has different grocery stores and health food markets that offer a variety of gluten-free products, some more than others. Patients can request that their neighborhood food store order certain products, or they can shop online or via mail-order.

Wheat-free versus Gluten-free

Products listed as "wheat-free" are not necessarily "gluten-free." Wheat-free products may contain spelt, kamut, or barley, which are toxic to patients with CD and should be avoided.

Table 5. Getting Started: A Basic Gluten-Free Diet

MILK PRODUCTS
- Milk, cream, most ice cream, buttermilk, plain yogurt, cheese, cream cheese, processed cheese, processed cheese foods, cottage cheese

GRAIN PRODUCTS
- Breads: bread and baked products containing amaranth, arrowroot, buckwheat, corn bran, corn flour, cornmeal, cornstarch, flax, legume flours (bean, garbanzo, or chickpea, garfava, lentil, pea), millet, Montina® flour (Indian rice grass), potato flour, potato starch, quinoa, rice bran, rice flours (white, brown, sweet), sago, sorghum flour, soy flour, sweet potato flour, tapioca, and teff
- Hot cereals: puffed amaranth, cornmeal, cream of buckwheat, cream of rice (brown, white), hominy grits, rice flakes, quinoa flakes, soy flakes, and soy grits
- Cold cereals: puffed amaranth, puffed buckwheat, puffed corn, puffed millet, puffed rice, rice flakes, and soy cereals
- Pastas: macaroni, spaghetti, and noodles from beans, corn, pea, potato, quinoa, rice, soy, and wild rice
- Miscellaneous: corn tacos, corn tortillas

MEATS AND ALTERNATIVES
- Meat, fish, and poultry: fresh
- Eggs
- Miscellaneous: lentils, chickpeas (garbanzo beans), peas, beans, nuts, seeds, tofu

FRUITS AND VEGETABLES
- Fruits: fresh, frozen, and canned fruits and juices
- Vegetables: fresh, frozen, and canned vegetables and juices

SOUPS
- Homemade broth, gluten-free bouillon cubes, cream soups and stocks made from allowed ingredients

FATS
- Butter, margarine, lard, vegetable oil, cream, shortening, homemade salad dressing with allowed ingredients

DESSERTS
- Ice cream, sherbet, whipped toppings, egg custards, gelatin desserts; cakes, cookies, pastries made with allowed ingredients, gluten-free ice cream cones, wafers and waffles

MISCELLANEOUS
- Beverages: tea, instant or ground coffee (regular or decaffeinated), cocoa, soft drinks, cider; distilled alcoholic beverages such as rum, gin, whiskey, vodka, wines and pure liqueurs; some soy, rice and nut beverages
- Sweets: honey, jam, jelly, marmalade, corn syrup, maple syrup, molasses, sugar (brown and white), icing sugar (confectioner's)
- Snack foods: plain popcorn, nuts, and soy nuts
- Condiments: plain pickles, relish, olives, ketchup, mustard, tomato paste, pure herbs and spices, pure black pepper, vinegars (apple or cider, distilled white, grape or wine, spirit), gluten-free soy sauce
- Other: sauces and gravies made with ingredients allowed, pure cocoa, pure baking chocolate, carob chips and powder, chocolate chips, monosodium glutamate (MSG), cream of tartar, baking soda, yeast, brewer's yeast, aspartame, coconut, vanilla, and gluten-free communion wafers

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Cross-contamination

Significant effort should be made to avoid cross-contamination at home, when shopping, and when dining out. In the kitchen, individuals can take a few necessary precautions, such as cleaning cutting boards, microwave walls, and countertops frequently, using separate condiments to avoid contamination with gluten-containing grains, isolating cooking utensils to which gluten may congeal (e.g., colanders), and using separate toasters for gluten-free products.[94] Shoppers can purchase from bulk bins that hold only gluten-free products. Products from dedicated facilities that only produce gluten-free products offer the least risk of cross-contamination; however, it may be economically unrealistic to buy food from these venues alone. In restaurants or at friends' homes, individuals can question the ingredients of each dish (Does the sauce or gravy contain wheat flour? Has the fish or chicken been dusted with flour? Has the gluten-free food item been fried in the same fryer with flour-coated items?). Restaurant cards listing safe and unsafe ingredients are available in several languages from several sources (e.g., www.livingwithout.com and www.gluten.net) and can be helpful in communicating dietary restrictions to restaurant staff.

Hidden Gluten

While gluten is easily identified in bread, pasta, cookies, cakes, crackers, and cereals, it can also be found in many other products, including salad dressings, luncheon meats, communion wafers, vitamin and herbal supplements, and medications. Gluten may also be a hidden ingredient in modified food starch, seasonings, and flavorings. Barley is commonly used as a flavoring agent in malt form and may only be listed as "flavoring or natural flavoring," making it difficult to determine the origin.[95] It is prudent for patients to routinely check the ingredient list before purchasing any product, as ingredients may change at any time without notice. The dietitian can carefully review a food log and help identify hidden gluten in

Table 6. Celiac Centers and Organizations/Associations

MEDICAL CENTERS	
Celiac Center Beth Israel Deaconess Medical Center Boston, MA	Website: www.bidmc.harvard.edu/celiaccenter Phone: 617-667-1272
Celiac Disease Center Columbia University New York, NY	Website: www.cdcc.hs.columbia.edu Phone: 212-342-0251 (Nurse) Phone: 212-342-0252 (Dietitian) E-mail: celiac@columbia.edu
Celiac Disease Clinic Mayo Clinic Rochester, MN	Phone (clinicians): 507-284-2631 Phone (patients): 507-284-5255
Celiac Clinic Department of Internal Medicine University of Iowa Hospitals and Clinics Iowa City, IA	Website: www.uihealthcare.com Phone: 319-356-4060
Celiac Group Digestive Center of Excellence University of Virginia Health System Charlottesville, VA	Website: www.healthsystem.virginia.edu/internet/digestive-health/patientcare.cfm (go to "GI Nutrition" and scroll down to "Celiac Support Group") Phone: 434-243-9309
Celiac Sprue Research Foundation Palo Alto, CA	Website: www.celiacsprue.org Phone: 650-251-9865 E-mail: gpyle@celiacsprue.org
Celiac Disease Program University of Chicago Chicago, IL	Website: www.uchospitals.edu Phone: 773-702-7593
Center for Celiac Research University of Maryland School of Medicine Baltimore, MD	Website: www.celiaccenter.org Phone: 410-706-8021
ASSOCIATIONS/ORGANIZATIONS	
Gluten Intolerance Group Seattle, WA	Website: www.gluten.net Phone: 206-246-6652 E-mail: info@gluten.net
Celiac Disease Foundation Studio City, CA	Website: www.celiac.org Phone: 818-990-2354 E-mail: cdf@celiac.org
Celiac Sprue Association of the United States of America (CSA/USA, Inc) Omaha, NE	Website: www.csaceliacs.org Phone: 402-558-0600 E-mail: celiacs@csaceliacs.org
Canadian Celiac Association/L'association Canadienne de la Maladie Coeliaque Toronto, Canada	Website: www.celiac.ca Phone: 905-507-6208 or 800-363-7296 E-mail: celiac@look.ca
American Dietetic Association Chicago, IL	Website: www.eatright.org Phone: 312-899-0040

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medications, supplements, meals eaten in and away from home, body care products that enter the mouth or nose, and other potential exposure to gluten.

Intentional Gluten Ingestion

Temptations to eat gluten may loom large for anyone with CD; for those patients who are asymptomatic, the benefits of a strict, lifelong diet may be even more difficult to accept. These patients should be educated on the consequences of long-term exposure to gluten and then encouraged to comply, fortified with a variety of helpful resources such as books, magazines, and newsletters. They should also be given assistance in finding convenient gluten-free foods and should join a support group for emotional and social assistance. Table 6 lists US medical centers and North-American organizations that specialize in CD, with resources for both patients and clinicians.

IMPACT OF CD ON NUTRITIONAL STATUS

Malabsorption is common in CD due to a decrease in the absorptive mucosal area and the enterocyte brush border digestive enzymes. Studies show a 4% incidence of anemia in newly diagnosed patients with CD in the United States.[96] According to Annibale et al.,[97] recovery from anemia in adult patients can occur on a gluten-free diet alone. Research by Hallert et al.[98] indicates that even those CD patients who have been carefully treated with a gluten-free diet for several years have higher total plasma homocysteine levels and lower mean daily intakes of folate and vitamin B_{12} than control subjects, suggesting that vitamin deficiencies may occur even with a gluten-free diet; therefore, vitamin status should be reviewed annually in all adult CD patients.

Immediately after diagnosis, gluten-free vitamins and minerals in therapeutic doses may be required to correct iron, folate,[4] or any other vitamin or mineral deficiency while the mucosa heals. Depending on individual factors, including age, laboratory test results, compliance with the gluten-free diet, and overall eating habits, a standard gluten-free multivitamin and mineral supplement is likely to be indicated.[94,99] The need for iron supplementation should be evaluated on an individual basis. When prescribing medication or supplements for a patient with CD, the physician should indicate "as ordered, if gluten-free, or provide a gluten-free equivalent" on the prescription.[96]

A well-balanced, gluten-free diet can provide adequate amounts of most nutrients. Prepared gluten-free cereals and commercial grain products, however, often tend to have reduced quantities of B vitamins, iron, and fiber compared with products containing gluten.[100-102] Patients should be encouraged to include in their diet foods rich in folate (e.g., dark leafy greens, citrus fruit, dried beans and legumes, and flax seeds) and vitamin B_{12} (e.g., meat, milk, fish, and poultry), as well as foods rich in heme iron (lean meats, poultry, and seafood) and non-heme iron (nuts, seeds, and legumes, taken with a vitamin C-rich food to increase iron absorption). Amaranth, buckwheat, and quinoa are good sources of iron, fiber, and some of the B vitamins. Enriched, gluten-free commercial products should regularly be selected over refined ones.[103]

Bone Disease

Adequate calcium and vitamin D intake should be encouraged through dietary sources and supplementation, particularly for those patients with osteopenic bone disease.[12] Calcium-rich foods include milk, gluten-free yogurt, cheese, sardines or canned salmon with bones, calcium-fortified beverages such as orange or apple juice, and enriched, gluten-free soy, almond, or rice milk. Good sources of vitamin D, necessary for calcium absorption, include vitamin D-fortified milk, fatty fish and fish oils, liver, egg yolk, some gluten-free enriched beverages, and exposure to sunshine during late spring, summer, and early fall. Supplementation with calcium and vitamin D may be necessary[87] depending on age, gender, menopausal status, and other conditions. Weight-bearing exercise is also very important for bone health.

Lactose Intolerance

Bloating, gas, and diarrhea may be suggestive of lactose intolerance, a common problem in individuals with CD. If these symptoms occur, patients should avoid or limit lactose consumption for one or more months while lactase enzyme production recovers.[101]

Gluten-free lactase enzyme supplements,* lactose-reduced or lactose-free products such as Lactaid® milk, aged cheese, and gluten-free yogurt with live, active cultures are usually well tolerated. Alternatives to common dairy products include enriched dairy-free/gluten-free beverages such as soy, almond, or rice milk.

Constipation and Diarrhea

Constipation can best be managed by gradually increasing fluids and dietary fiber (vegetables, fruits with edible seeds such as berries or kiwi, bean flours, and whole, gluten-free grains and seeds[94]). Patients presenting with diarrhea may benefit from a temporary lactose-free or lactose-reduced diet with adequate fluid intake.[94] Gluten-free fiber supplements may be helpful for both diarrhea and constipation.

Nutritional Follow-up

After the educational sessions have been completed, follow-up should be scheduled on an individual basis and should include monitoring the patient's nutritional status based on laboratory tests, diet and activity history, and weight changes. Newly presenting issues, such as increased weight gain and elevated lipid levels from improved absorption, may need to be addressed.[87] Ongoing support, education, and attention to changing nutritional needs are critical factors in the patient's successful adaptation to this new diet and lifestyle.

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* According to the manufacturer, Lactaid® Original Strength caplets, Lactaid® Ultra caplets, and Lactaid® Ultra chewables are considered to have no detectable levels of gluten at the writing of this article.

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The epidemiology, pathogenesis, and clinical manifestations of celiac disease will be reviewed here. Its management and the use of antibodies for diagnosis are presented separately (see "Management of celiac disease in adults" and "Diagnosis of celiac disease in adults"). This topic is also discussed in an official position statement issued by the American Gastroenterological Association [8]. To continue reading this article, you must log in with your personal, hospital, or group practice subscription. Disease: Epidemiology, Pathogenesis, Diagnosis, and Nutritional Management Nutrition. Clinical Care 2005; 8 (2): 54-69. has been cited by the following articleÂ Diagnosis is confirmed by histopathological examination, which shows characteristic changes in the form of chronic inflammation with increased number of intraepithelial lymphocytes, more than 20/100 epithelial cells. The aim of this study was a retrospective analysis of the clinical course of lymphocytic colitis and coexisting diseases, including celiac disease, in children and adolescents. The retrospective analysis included 52 children with lymphocytic colitis, hospitalized in the Gastroenterology Department, Department of Pediatrics Medical University of Silesia Katowice. The epidemiology, pathogenesis, and clinical manifestations of celiac disease will be reviewed here. Its management and the use of antibodies for diagnosis are presented separately (see "Management of celiac disease in adults" and "Diagnosis of celiac disease in adults").Â Establishing the diagnosis of subclinical celiac disease is of potential importance for four reasons: the danger of malignancy, the presence of unsuspected nutritional deficiencies, the association with low-birth weight infants in affected mothers, and the occurrence of autoimmune disorders.Â Oligosymptomatic patients with celiac disease may have significant nutritional deficiencies.