

# Celiac Disease and Gluten-Associated Diseases

Posted by Geoff Bond  
Nutritional Anthropologist  
[www.naturaleater.com](http://www.naturaleater.com)

Steve Helms, ND

## Abstract

**Celiac disease develops from an autoimmune response to specific dietary grains that contain gluten. Diagnosis can be made based on the classical presentation of diarrhea, fatty stools, and abdominal bloating and cramping, as well as the presence of specific serum antibodies. In addition, gluten ingestion has increasingly been found to be associated with other conditions not usually correlated with gluten intolerance. The subsequent diversity of the clinical presentation in these cases can complicate decision-making and delay treatment initiation in conditions such as ataxia, headaches, arthritis, neuropathy, type 1 diabetes mellitus, and others. This review explores the etiology and pathology of celiac disease, presents support for the relationship between gluten and other diseases, and provides effective screening and treatment protocols. (*Altern Med Rev* 2005;10(3):172-192)**

## Introduction

Celiac disease (CD), also known as celiac sprue and gluten-sensitive enteropathy, is a type of gluten intolerance that affects nearly one percent of the U.S. population.<sup>1</sup> Destruction of the intestinal villi caused by CD promotes malabsorption, with signs and symptoms including diarrhea and fatty stools as well as abdominal pain and distention. Although this classic presentation makes CD diagnosis easy in pronounced cases during early childhood, when there is mild disruption to the absorptive surface diagnosis can be more difficult, sometimes resulting in diagnosis being delayed until late adulthood. CD is definitively diagnosed by serum antibody tests, intestinal biopsy, and/or mitigation of symptoms upon removal of the implicated dietary glutes. These methods of assessment, developed since the clarification of gluten's

role in CD during the 1950s, have led to evidence of gluten's role in other disorders.

The role of gluten in other disease processes appears to be more widespread than previously thought (Table 1). Numerous endocrine and nervous system conditions are now associated with gluten intolerance, including many common autoimmune disorders, such as type 1 diabetes, thyroiditis, and Sjogren's syndrome. The skeletal, nervous, and integumentary systems may also be affected by gluten intolerance, contributing to such conditions as arthritis, ataxia, depression, neuropathy, and dermatitis herpetiformis. The unifying factor is that withdrawal of specific glutes mitigates symptoms in a significant number of individuals with these gluten-associated diseases (GAD).

The reason for this common thread is unknown at this time, although it seems immune system dysregulation due in part to genetic polymorphisms is central to the pathophysiology. The primary underlying pathology is associated with the escalation of inflammatory and immune system markers. The extent of this pathology is related to a host of factors, including the amount of exposure to glutes, the degree of inflammatory cytokine response, the number and type of antibodies produced, and the respective genotype and phenotype of the individual.

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Steve Helms, ND – Technical Advisor, Thorne Research, Inc; Associate Editor, *Alternative Medicine Review*; Private practice, Sandpoint, ID.  
Correspondence address: 102 S. First Avenue, Ste. 201 Sandpoint, ID 83864  
E-mail: [steveh@thorne.com](mailto:steveh@thorne.com)

**Table 1. Gluten-associated Diseases**

Addison's Disease  
 Alopecia  
 Anemia  
 Anxiety and Depression  
 Arthritis  
 Ataxia  
 Attention Deficit Disorder (ADHD)  
 Autism  
 Autoimmune Hepatitis/Chronic Active Hepatitis  
 Brain White-Matter Lesions  
 Celiac Disease  
 Cerebellar Atrophy  
 Chronic Fatigue Syndrome  
 Crohn's Disease  
 Congenital Heart Disease  
 Cystic Fibrosis  
 Dental-Enamel Hypoplasia  
 Dermatitis Herpetiformis  
 Dyspepsia  
 Epilepsy  
 Farmer's Lung  
 Fetal Growth Retardation  
 Fibromyalgia  
 Fibrosing Alveolitis  
 Follicular Keratosis  
 Gastroparesis  
 Headaches/Migraines  
 Irritable Bowel Syndrome (IBS)  
 Impotency  
 Infertility/Miscarriage  
 Type I Diabetes Mellitus  
 Multiple Sclerosis  
 Myasthenia Gravis  
 Osteoporosis  
 Pancreatic Disorders/Exocrine Pancreatic Insufficiency  
 Peripheral Neuropathy  
 Polymyositis  
 Pulmonary Hemosiderosis  
 Primary Biliary Cirrhosis  
 Recurrent Pericarditis  
 Sarcoidosis  
 Schizophrenia  
 Scleroderma  
 Short Stature/Delayed Puberty  
 Small Intestine Adenocarcinomas  
 Systemic Lupus Erythematosus  
 Thrombocytosis  
 Thrombocytopenia Purpura (ITP)  
 Thyroiditis  
 Vitamin K Deficiency  
 Vasculitis

Adapted from: [www.gsdl.com/home/assessments/ceeliac/CeliacSupportGuide.pdf](http://www.gsdl.com/home/assessments/ceeliac/CeliacSupportGuide.pdf)

## Etiopathogenesis

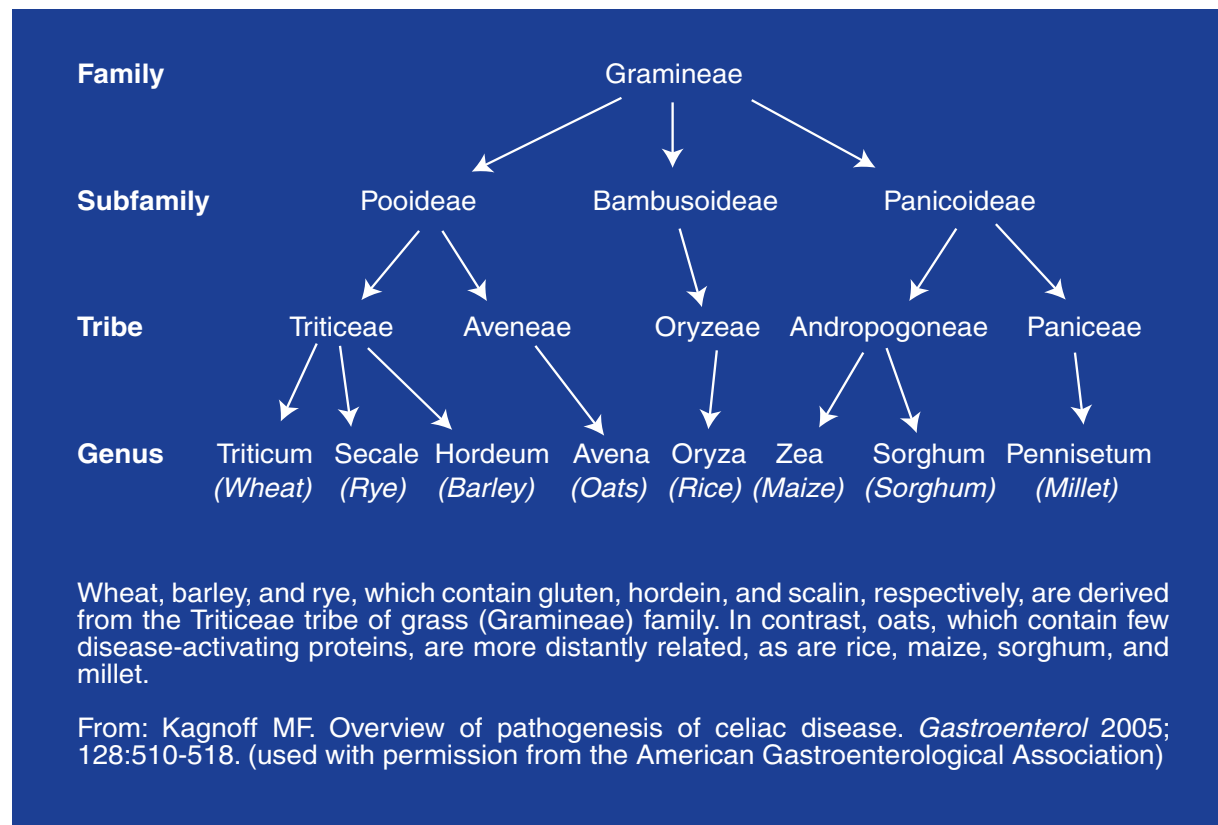
### *Gluten Ingestion*

Specific gluten-containing foods are the primary immune system instigators in CD and GAD. These include the glutes present in all forms of wheat, including durum, semolina, spelt, kamut, malt, couscous, bulgar, triticale, einkorn, and faro, as well as in related grains – rye and barley (Figure 1). The gluten content of different grains is classified by gliadins (alpha, beta, gamma, omega) or glutenin (high and low molecular weight), with varying concentrations among plant species (Table 2). The immunogenicity of some gliadins is related to their creation of glutamic acid metabolites from an abundance of proline and glutamine residues. Gliadins seem to generate the strongest immune response in susceptible individuals, and therefore, have comprised the majority of current research. Although rice, buckwheat, corn, oat, and other grains contain glutes, they are not specific to CD/GAD etiology, but rather, may contribute to escalating symptomatology in sensitive individuals by creating and sustaining an inflammatory response. Unfortunately, numerous confounding variables have complicated attempts to modify gluten's immune reactivity, including genetic transcription via multiple linked gene clusters on different chromosomes, the large degree of allelic variation among different cultivars, and the elastic nature of these molecules.<sup>2,3</sup>

### *Tissue Transglutaminase*

Tissue transglutaminase (TG2) is an enterocyte enzyme pivotal to gluten digestion because the high proline content of gluten resists proteolysis by gastric, pancreatic, and brush border enzymes. TG2 facilitates the breakdown of gluten through one of two pathways, depending on the intraluminal pH and gluten concentration (Figure 2). When antibodies to this enzyme are generated, enterocytes are destroyed and the

**Figure 1. Taxonomy of Common Dietary Grains**



**Table 2. Gluten Content of Various Grains**

Food	Total protein	Gliadins (% of total protein)	Glutenins (% of total protein)
Wheat	10-15	40-50	30-40
Rye	9-14	30-50	30-50
Oats	8-14	10-15	~5
Corn	7-13	50-55	30-45
Rice	8-10	1-5	85-90
Sorghum	9-13	>60	
Millet	7-16	57	30
Buckwheat			High

Adapted from: Pizzorno JE, Murray MT, eds. *Textbook of Natural Medicine*. 2nd ed. New York: Churchill Livingstone; 1999:1601.

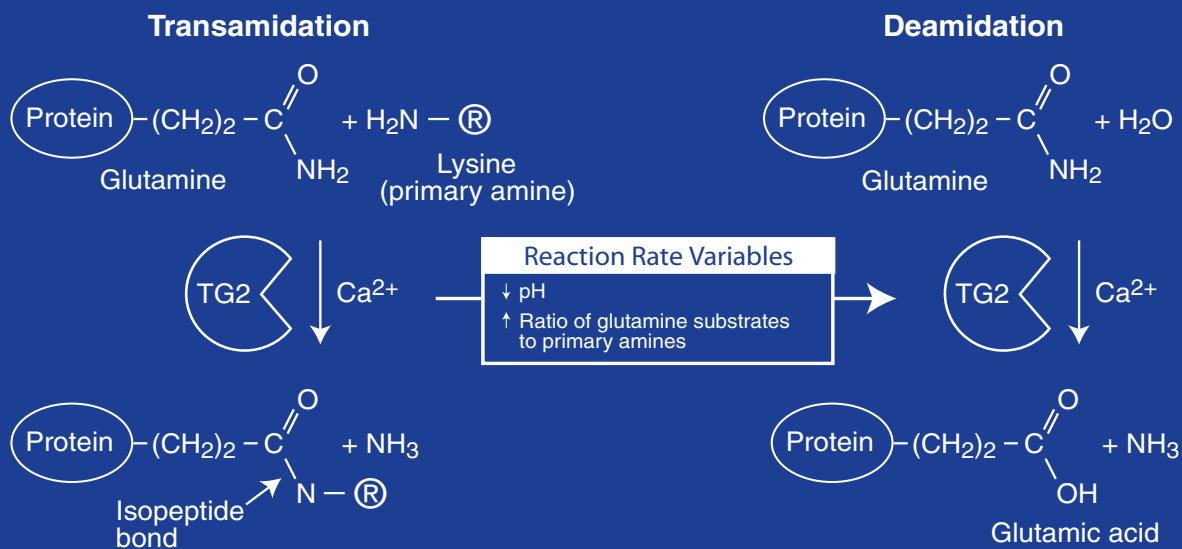
common signs and symptoms of CD present – bloating (as bacteria thrive on undigested food), cramping (due to the autonomic reaction to dysbiosis and cellular destruction), fatty stools (due to disturbed lipid digestion), and the flattened villous architecture noted on biopsy.

### Genetic Component

The creation of autoantibodies to TG2 hinges in part on genetics. The genetic variable is the shape of the transcribed HLA class II molecule (a type of cell surface marker), which allows immune cells to recognize one another, present possible antigen fragments for interrogation, and ramp-up defenses to viral,

**Figure 2. Tissue Transglutaminase Activity**

TG2 catalyzes the transamidation (crosslinking) or deamidation of specific glutamine residues in proteins or polypeptides. The propensity for deamidation compared with transamidation is increased by lowering the pH and by increasing the concentration of glutamine substrates to polyamines.



#### Specificity of TG2

Sequences preferred by TG2

- **Gln**-Xaa-Pro
- **Gln**-Xaa-Pro-(Ile,Leu,Val,Phe,Tyr,Trp,Thr,Ser)

Sequences not preferred by TG2

- **Gln**-Pro
- **Gln**-Gly
- **Gln**-Xaa-Xaa-Pro
- **Gln**-Xaa-Xaa-Gly

Xaa denotes any amino acid. The targeted glutamine (Gln) is indicated in bold.

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

fungal, and bacterial populations. Individuals susceptible to CD and GAD predominantly construct HLA-DQ2 and -DQ8 genotypes that are conformationally unique and present several pockets that favor binding to negatively charged residues like glutamic acid.<sup>4</sup> The combined shape of the HLA-DQ plus the TG2-gluten peptide complex is interpreted by T-cells as non-self, thereby prompting amplified immune system activity.

The phenotypic expression of the HLA-DQ molecule and the probability of inciting an immune reaction is not, in itself, a necessary condition for CD or GAD. Although 90-95 percent of CD patients transcribe HLA-DQ2 molecules and 5-10 percent transcribe HLA-DQ8,<sup>4</sup> 20-50 percent of humans express the DQ2 genotype.<sup>5</sup> Therefore, since only one percent of the population develops CD, there is low concordance between a positive HLA-DQ2 and development of CD.

The Italian National Twin Registry study (6,048 cases), while citing genetic evidence for the HLA region, strongly suggests the HLA region is not the only genetic component in CD and GAD.<sup>6</sup> Interestingly, DQ2 is nearly absent from populations that have traditionally consumed gluten-free diets – Japanese, Native Americans, and Polynesians.<sup>5</sup>

To further complicate the picture, HLA-DQ transcription may not be complete in some individuals, which might help to explain the delay in symptomatology in these patients. While a homozygous cis genotype confers 100-percent transcription of the HLA-DQ molecule, the heterozygous (one cis and one trans) avails 50-percent expression, and partial transmission (only one cis or trans) allows only about 25-percent expression.<sup>4</sup>

The enhanced expression of DQ2/DQ8 molecules is further dependent on interferon-gamma (IFN- $\gamma$ ) secreted by activated DQ2/DQ8-restricted T-cells in response to inflammation, and is perpetuated by TG2 up-regulation due to tissue injury.<sup>4</sup> Therefore, development of CD and GAD is not entirely dependent on genetics, although DQ2/DQ8 individuals are statistically predisposed.

### *Immunity, Cytokines, and Inflammation*

The mucosal inflammation caused by gluten is not only generated by gliadin and TG2 antibodies, but is also established and maintained by the interaction of cytokines, including interleukin-15 (IL-15), IFN- $\gamma$  (Figure 3), and those developed from nuclear factor kappaB (NF- $\kappa$ B) induction (Figure 4). The induction of cytokines occurs as gluten peptides are continually absorbed by endocytosis and by the transport of proteins through damaged zonulin (a regulator of tight junctions between intestinal epithelial cells).<sup>7</sup> Once activated by gliadin, DQ2- and DQ8-restricted T-cells also secrete IFN- $\gamma$ , which promotes other T-cells to be activated, while releasing enzymes such as matrix metalloproteinases that can damage the intestinal mucosa.<sup>4</sup> Continued gluten ingestion perpetuates this feed-forward cycle, promoting a concert of inflammatory mediators that overwhelm the body's ability to repair this mucosal barrier to infection and foreign proteins.

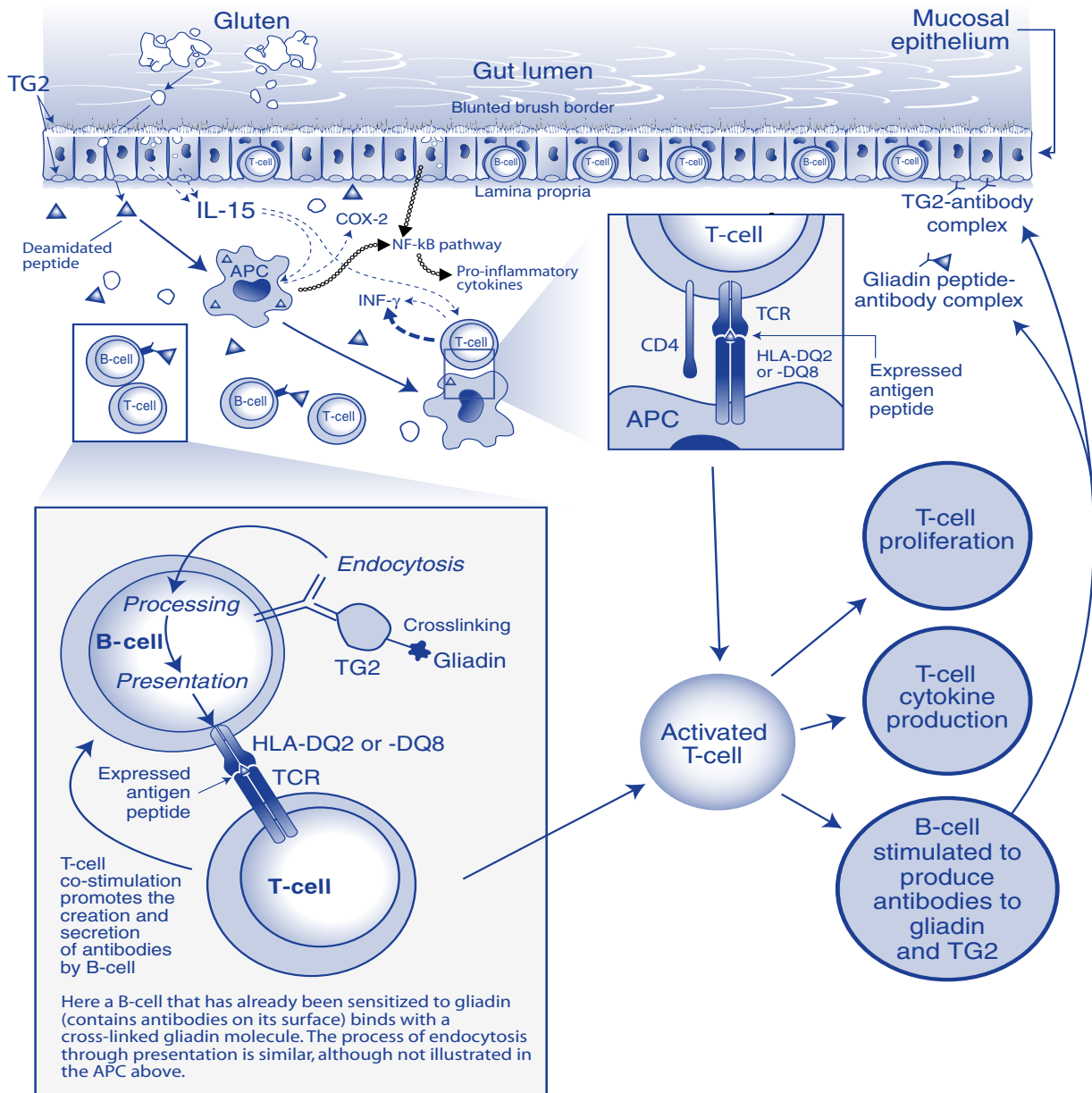
### **IL-15**

IL-15 is the initial inflammatory cytokine expressed in sensitive individuals after gluten ingestion. Gluten up-regulates IL-15 production by epithelial and lamina propria cells,<sup>8,9</sup> and promotes cyclooxygenase-2 (COX-2) induction (Figure 3).<sup>10</sup> IL-15 has also been shown to alter the properties of the intraepithelial lymphocyte population in two ways: (1) by inducing IFN- $\gamma$  in lymphocytes, thereby promoting macrophage and T-cell activation,<sup>11</sup> and (2) by promoting antigen-specific T-cell transition to a phenotype of natural killer-like cells capable of epithelial cell damage (suggested to occur without antigen-specific T-cell recognition).<sup>4</sup> Furthermore, synthesized gliadin-alpha peptides induce HLA-DQ mRNA production and increase the release of IL-15.<sup>10</sup> Such studies suggest IL-15 directly promotes localized inflammation after gluten exposure in sensitive individuals.

### **NF- $\kappa$ B**

Activation of NF- $\kappa$ B is a crucial step in the amplification of proinflammatory gene expression.<sup>12</sup> As macrophages react with gliadin, the NF- $\kappa$ B pathway directly signals DNA to transcribe inflammatory mediators at a pre-translational level (Figure 4).<sup>13</sup> A mucosal biopsy study from untreated CD patients confirmed NF- $\kappa$ B activity when initially cultured and after administration of gliadin.<sup>14</sup> Gliadin promotes the phosphorylation of inhibitor-kappaB (I- $\kappa$ B) with or without IFN- $\gamma$  co-stimulation, thereby enabling NF- $\kappa$ B to activate proinflammatory gene segments.<sup>13</sup> With IFN- $\gamma$  co-stimulation, gliadins accelerate the production of IL-8 and tumor necrosis factor-alpha (TNF- $\alpha$ ), but will deliver small amounts of these proinflammatory cytokines in the absence of IFN- $\gamma$ .<sup>13</sup> In the presence of IFN- $\gamma$ , gluten and gliadin fragments also promote inducible nitric oxide synthase (iNOS) through the NF- $\kappa$ B pathway.<sup>14,15</sup> iNOS is also up-regulated in a concentration-dependent manner,<sup>15</sup> as would seem appropriate in a cell designed to use this pro-oxidant to thwart microbial attack. Therefore, the NF- $\kappa$ B pathway helps to explain the generalized inflammatory response noted in some individuals on gluten exposure.

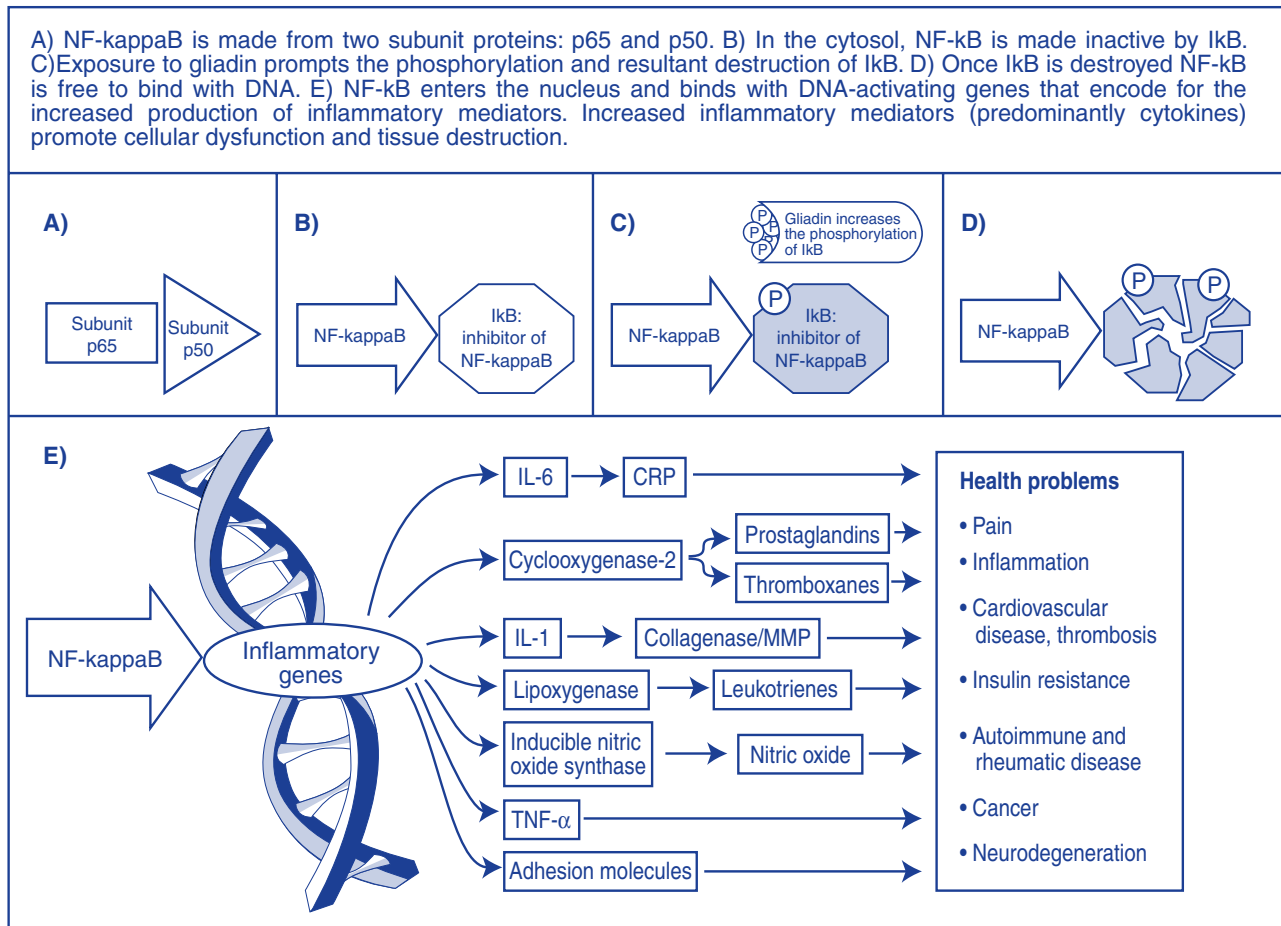
**Figure 3. Immune Reactivity to Gluten**



Gluten prompts a sequence of activity whose degree of resultant damage is dependent on immunity, genetics, cytokines, and environmental triggers. T-cells are activated by presented antigen and in turn these activated T-cells stimulate other immune cells, promoting their respective activity – B-cells to create antibodies to said antigen and APCs to destroy said antigen. Once antigen and antibody bind to create a complex they are destroyed/neutralized by the complement system and/or phagocytosis. All cells create diverse cytokines that act as immunoenocrine communicators to proximal and distal tissues. INF- $\gamma$ , the main cytokine produced from activated T-cells, subsequently activates other T-cells and enhances the killing power of macrophages.

Abbreviations: APC (Antigen Presenting Cell); HLA (Human Leukocyte Antigen); INF- $\gamma$  (Interferon-gamma); TCR (T-cell Antigen Receptor); TG2 (Tissue Transglutaminase).

**Figure 4. NF-κB Proinflammatory Pathway Induction**



Key: MMP = matrix metalloproteinase; TNF-α = Tumor Necrosis Factor Alpha; CRP = C-reactive Protein; NF-kappaB = Nuclear Factor kappaB; IκB = Inhibitor kappaB; IL = Interleukin.

Adapted from: Vascuez A. *Integrative Orthopedics: The Art of Creating Wellness While Managing Acute and Chronic Musculoskeletal Disorders*. Houston, TX: Natural Health Consulting Corporation; 2004. [www.OptimalHealthResearch.com](http://www.OptimalHealthResearch.com) (used with permission)

**External Triggers**

Matzinger recommends that immunological theory be expanded to include “danger signals” released by tissues that not only designate whether tissues respond to a potential threat, but also signal the type of immune response to be given.<sup>16</sup> It has been shown that treatment with IFN-γ, normally released endogenously from cells to communicate danger (usually viral), has induced CD during exogenous interferon treatment of hepatitis C.<sup>17,18</sup> The reason that perpetuating a normal physiological response

would cause autoantibodies to TG2 in this situation is unknown.<sup>19</sup>

Viral<sup>20,21</sup> and fungal<sup>22,23</sup> triggers have also been explored. The viral and fungal models share a common theme – similar amino acid sequences between gliadin and a microbe incite cross-reactivity. The initial antibody production is due to a normal immune reaction to the invading pathogen. Future gluten ingestion generates a peptide sequence bound to HLA-DQ that is misinterpreted as being the virus/fungus, with resultant antibody production to gluten.

Concurrently, TG2-gluten complexes develop cross-reactivity to TG2, establishing TG2 autoantibodies. The viral suspect is human adenovirus<sup>13</sup> that demonstrates a region of amino acid sequence homology with alpha-gliadin and HLA association. However, due to low concordance with developing CD, researchers have proposed that additional environmental factors may be important in the pathogenesis of celiac disease.<sup>20,21</sup>

The fungal hypothesis involves *Candida albicans*. As well as stimulating IFN- $\gamma$ , the amino acid sequences of *C. albicans* are very similar to gliadin sequences and have been shown to stimulate T-cell epitope receptors.<sup>22</sup> Hyphal cell-wall component protein 1 (HWP1) of *Candida* and gamma-gliadin both simulate T-cell epitope receptors and repeat similar sequences in a similar cadence, while alpha-gliadin has one of its sequences selectively deamidated by TG2, generating a metabolite with a similar sequence to HWP1.<sup>22</sup>

Nieuwenhuizen theorizes the HWP1 sequence of *C. albicans* reacts with TG2 and demonstrates cross-reactivity with identical amino acid sequences in common gliadin subtypes. This process may unfold as TG2, freed from damaged enterocytes, links with HWP1 and is then crosslinked by HWP1 back to the intestinal epithelium.<sup>23</sup> The resultant molecule stimulates antibodies that perpetuate the cross-reactivity to gluten.

### Review of Etiopathogenesis

The pathogenesis of CD probably involves a sequence of interrelated events. Improper digestion probably plays an important role as the deamidation of glutamine to glutamic acid by TG2 is driven by a low pH in the intestine. Genetically, the rate of HLA DQ2/DQ8 expression confers more or less receptors to bind glutamic acid residues. The generation of a larger number of suspect complexes escalates immune system investigation to these conformations.

**Table 3. Diagnostic Clues to CD/GAD**

- Chronic diarrhea
- Chronic fatigue
- Unexplained
  - anemia
  - ataxia
  - elevation of transaminase
  - epilepsy
  - infertility
  - peripheral neuropathy
  - recurrent pericarditis<sup>155</sup>
  - weight loss
- Personal History of type I diabetes or thyroid disease
- Family history of celiac disease
- IgA deficiency
- Osteoporosis (especially those with anemia)
- Pregnancy with hemoglobin less than 11g/dL
- Decreased D-xylose<sup>156</sup>
- Enamel defects (commonly affecting the incisors and the molars)<sup>157</sup>

T-cells may therefore become activated and further be more sensitive to activation based on “inflammatory load.” Cytokines, particularly IFN- $\gamma$ , prime immune cells to overreact to gluten peptides and may be most sensitive during concurrent generation of viral or fungal antibodies with similar peptide sequences to gluten. Unfortunately, the mechanism of CD and the associative link(s) to GAD are not completely understood.

### Diagnosis and Screening

Clinicians should monitor suggestive signs and symptoms to ensure proper diagnosis (Table 3) and appropriately screen for gluten-induced antibodies. Intestinal biopsy is still considered the “gold standard” to confirm CD, although laboratory results can now be considered confirmatory. Mitigation of symptoms by gluten withdrawal provides the most accurate diagnosis.



Specific serum antibodies include anti-gliadin (AGA), anti-transglutaminase (tTG), and anti-endomysial (EMA).<sup>24</sup> AGA should not be used alone in diagnosis. The best predictor in patients with a normal secretory IgA status is both a positive IgA-tTG and a positive AGA. In cases of IgA deficiency, a positive IgG-tTG will corroborate diagnosis. CD patients are 10-15 times more likely to exhibit IgA deficiency, while in the general population the incidence is 1 in 600.<sup>25,26</sup> Conversely, CD can be ruled out by a negative IgG- and IgA-tTG,<sup>27</sup> or by a negative AGA with a positive tTG.<sup>28</sup> The latter scenario necessitates further inquiry to recant a possible false-negative result or to evaluate for complex immunological dysfunction. Note that anti-neuronal antibodies are also commonly elevated in CD patients with neurological dysfunction ( $p < 0.0001$ ).<sup>29</sup>

Notable facts concerning anti-gliadin antibodies include:

- ▼ Elevations have been noted in 5-12 percent of individuals without CD;<sup>30</sup>
- ▼ May be appropriate when screening larger populations, particularly in a research setting;
- ▼ The best marker for CD in children under two years of age who have not begun to produce more diagnostic antibodies;<sup>31</sup>
- ▼ Combined with a positive EMA confers a 99-percent chance of flattened intestinal mucosal villi.<sup>32</sup> In addition, citrulline, an amino acid not incorporated into proteins, can be used to confirm diffuse total villous atrophy and more pervasive absorptive deficiencies. Look for plasma citrulline levels  $< 10$  mcg/L.<sup>33</sup>

Note that a celiac disease diet (CDD) – a diet excluding all forms of wheat, rye, and barley – will provoke a rapid fall in titers with an associated decrease in test accuracy. After 30 days on a CDD, tTG is 94-percent accurate, but after 90 days accuracy drops to 71 percent, while EMA accuracy drops to 88 and 59 percent, respectively.<sup>34</sup> AGA begins to decrease within a month and returns to normal within a year, providing a clear indicator of compliance.<sup>35</sup>

## Gluten-Associated Diseases *Neurovascular/Neurological/ Neuropsychiatric Presentations*

Diverse neurological manifestations are present in 10 percent of CD cases.<sup>36,37</sup> Early brain atrophy and dementia (before age 60) have been noted in previously undiagnosed celiac disease cases.<sup>38</sup> Other neurological findings, including gait disturbances and peripheral neuropathy, have been confirmed.<sup>39</sup>

The mechanism by which anti-gliadin antibodies gain access to the central nervous system remains obscure, although cell-mediated inflammation has been implicated.<sup>29,40</sup> Active CD patients exhibit IgA antibodies that react with human brain vessel structures and have a high affinity for the vasculature of the blood-brain barrier.<sup>41</sup> The resulting vascular inflammation can increase permeability and cause ischemia. White-matter lesions or calcifications of ischemic origin have been suggested as secondary to CD-generated vasculitis.<sup>37</sup>

### Ataxia

Ataxia is an atypical symptom of CD and when accompanying CD diagnosis is referred to as gluten ataxia. Circulating antibodies to cerebellar Purkinje cells have been identified,<sup>42</sup> and cross-reactivity between anti-gliadin antibodies and Purkinje cells as well as enterocytes suggests a common epitope.<sup>42,43</sup> Implementation of a CDD can halt the disease process, although CD is commonly a missed diagnosis<sup>44</sup> as gastrointestinal symptoms are only present in 13 percent of gluten-ataxic patients.<sup>45</sup> The duration of gluten ingestion positively correlates with ataxic severity and, conversely, the longer a person avoids gluten the greater the therapeutic benefit.<sup>46</sup>

CD should be included in the differential diagnosis for idiopathic ataxia, especially when there are few features of multiple system atrophy (MSA) – including cerebellar (MSA-C) or Parkinsonian (MSA-P). There is a significant 41-percent positive CD association with sporadic idiopathic ataxia, but only a 15-percent connection between CD and MSA-C.<sup>45,47</sup> Patients with gluten ataxia often present with brisk reflexes and will often show cerebellar atrophy on MRI. Immune-mediated damage to the cerebellum, posterior columns of the spinal cord, and peripheral nerves has been noted.<sup>48,49</sup>

### Neuropathy

Peripheral neuropathy occurs in 49 percent of CD patients.<sup>50,51</sup> The most common peripheral neuropathy in CD is chronic, symmetric, sensory neuropathy, although motor and autonomic forms have been reported. Unfortunately, neither anti-ganglioside antibodies nor positive electrophysiologic diagnosis are consistently found.<sup>52</sup> There are inconsistent reports on the clinical efficacy of a CDD in limiting progression and symptomatology.<sup>53-56</sup>

### Headache

Headache is present in approximately 28 percent of CD patients.<sup>52,57,58</sup> Brain imaging studies, pre- and post-CDD, revealed significant improvements in calcifications and brain tracer uptake, with concomitant reduction in headache frequency and symptomatology after a CDD.<sup>57,59</sup> A recent study found a significant incidence of headache in CD patients versus controls, and in 16 of 31 CD headache sufferers resolution or significant improvement was noted post-CDD.<sup>50</sup> In two case reports of patients (ages 11 and 45 years) with headaches since childhood, the headaches were not only resolved post-CDD, but were the only manifestation of CD in these patients.<sup>60,61</sup>

### Epilepsy

Studies have revealed an association between CD and epilepsy.<sup>62-64</sup> In fact, there is a higher prevalence of CD in epilepsy patients compared to the general population (0.8-2.5% versus 0.4-1.0%)<sup>63-65</sup> although a mechanism involving cerebral calcifications has yet to be confirmed.<sup>65,66</sup> Initiation of a CDD may reduce seizure frequency and antiepileptic medication dosage, but infrequently completely resolves seizures.<sup>63,67,68</sup>

### Depression

Depression and other psychiatric symptoms are common complications in CD patients.<sup>51,69</sup> Untreated CD patients have decreased levels of tryptophan and other monoamine precursors, as well as dopamine and serotonin, in cerebrospinal fluid.<sup>70,71</sup> Rapid improvement in depressive symptoms with a CDD has been noted in case reports<sup>72,73</sup> and progressive improvement is also seen with vitamin B6 supplementation (80 mg/day for six months;  $p < 0.01$ ).<sup>71</sup>

## Endocrine Presentations

### Addison's Disease

Patients with autoimmune Addison's disease have demonstrated a greater risk of developing CD, with a prevalence of 7.9-12.2 percent.<sup>74,75</sup> Mild forms of Addison's disease often go undiagnosed, which can limit the recommended screening for CD in this population.<sup>74,76,77</sup>

### Type 1 Diabetes

Type 1 diabetes, like CD, is thought to be mediated by an autoimmune process.<sup>78,79</sup> A 10-year, age-matched study found a highly significant correlation ( $p < 0.003$ ) between endocrine disorders in CD patients versus controls, and concluded that CD patients have a significantly higher prevalence of type 1 diabetes.<sup>80</sup> More recent studies show a 5.4-7.4 percent incidence of CD in type 1 diabetics.<sup>81,82</sup>

Early identification of CD and subsequent treatment improves growth and diabetic control in children with type 1 diabetes.<sup>83,84</sup> Feeding gluten-containing foods in the first three months of life yields a four-fold greater risk of developing islet cell autoantibodies (and potentially subsequent diabetes) than exclusive breast feeding. Children starting gluten foods after six months of age demonstrated no such association.<sup>85</sup>

### Thyroiditis

Thyroiditis has been repeatedly associated with CD.<sup>78-80,86</sup> A highly significant association exists between CD and autoimmune thyroiditis (Graves' disease and Hashimoto's thyroiditis), as evidenced by elevated EMA antibodies ( $p < 0.01$ ) in these thyroid conditions.<sup>86</sup> In addition, abnormal liver enzymes (transaminases) are common in both thyroid disorders and subclinical celiac disease.<sup>87</sup>

## Malabsorptive Presentations

### Anemia/Chronic Fatigue

Iron and folate deficiency are commonly found in CD, and may occur with or without anemia. A prospective study of adults with iron deficiency anemia (average age of 50), found 2.8 percent to have celiac disease.<sup>88</sup> Although vitamin B12 absorption is thought to be normal in CD patients because

absorption occurs in the unaffected terminal ileum, B12 levels are statistically decreased in celiac patients compared with controls, and 12 percent of CD patients have actual deficiency.<sup>89</sup>

### Osteoporosis

One study found osteoporotic individuals are more likely to suffer from CD – 3.4 percent compared to 0.2 percent among non-osteoporotic controls.<sup>90</sup> In fact, there is a direct relationship between tTG levels and the severity of osteoporosis, demonstrating that the more severe the reactivity to gluten the more severe the resulting osteoporosis.<sup>90</sup> Because of this association, osteoporotic patients (especially those with anemia) should be screened for tTG antibodies.<sup>91</sup>

The use of ultrasound to evaluate mineral density in children has been explored, although it has not been generally accepted.<sup>92</sup> Early diagnosis and treatment of celiac disease during childhood protects against osteoporosis.

## Other Presentations

### Arthritis

TG2 has only been found in limited amounts in the synovium of trauma patients and patients with osteoarthritis.<sup>93</sup> Conversely, TG2 has been found to be increased in the synovium of patients with rheumatoid arthritis (RA),<sup>93</sup> and dietary trials of gluten exclusion have significantly reduced RA symptomatology and immunoreactivity.<sup>94,95</sup> Mitigation of arthritic symptoms with a CDD has been noted<sup>96,97</sup> and may reflect a reduction in the overall “inflammatory load” in some arthritis sufferers as opposed to injury from TG2 autoantibodies. Of 23 arthritic patients who responded to a CDD, abdominal symptoms were present in approximately 60 percent of cases, while 74 percent showed signs of malabsorption evidenced by B12-, folate-, or iron-deficiency anemia.<sup>96</sup>

### Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is one of the most common dermatologic presentations of gluten intolerance. The characteristic IgA granular deposits in the dermal papillae are highly pruritic and form vesicles reminiscent of herpetic eruptions. This inflammatory response is sustained by autoantigens to epidermal transglutaminase and is mitigated by gluten

withdrawal.<sup>98,99</sup> Laboratory studies show consistently elevated intestinal permeability on lactulose/mannitol assay, but there is a high variability of actual enteropathy.<sup>7</sup> In fact, only 10 percent of DH patients have symptoms attributable to malabsorption.<sup>100</sup>

DH presents more frequently in men (16%) than in women (9%).<sup>101</sup> In one case report a male patient’s active DH was curtailed after discontinuing a multivitamin that contained gluten as a filler.<sup>102</sup>

### Sjogren’s Syndrome

The frequency of CD in the Sjogren’s population has been reported to be almost five times that of CD in the general population (4.5:100)<sup>103</sup> Earlier accounts found a similar prevalence of CD in Sjogren’s (3:100;  $p < 0.001$ ).<sup>80</sup> There is a lack of mechanistic association, although in a study of 34 patients with Sjogren’s syndrome, HLA-DQ2 was present in 56 percent of studied Sjogren’s patients and all Sjogren’s patients with CD. Sjogren’s patients also had a high incidence of small bowel mucosal inflammation.<sup>104</sup>

## Treatment

The current undisputed treatment for CD is a CDD. There is an occasional patient who, after an interval of six months to two years on a CDD, will be able to successfully reintroduce gluten.<sup>105</sup> This is indeed the exception, however, and there has been no speculation as to the operative variables for these successes.

Oral peptidase supplementation, specifically prolyl endopeptidase (PEP), has been shown to directly inhibit one of the two preferred sequences of TG2,<sup>106</sup> but such limited activity is not a satisfactory treatment. Future enzyme therapies may prove beneficial, as has been shown with lactase supplementation in lactose intolerant individuals, although the damage caused by gluten is more pervasive than found in dairy intolerance.

## Celiac Disease Diet

A CDD requires the removal of all forms of wheat, rye, and barley from the diet. These grains contain glutes that incite an immune reaction precipitating CD and GAD. Other grains, however, do indeed contain “glutes,” but do not incite the same immune dysregulation and creation of TG2 autoantibodies

(Table 2). Therefore, the phrases “gluten-free diet,” “gliadin-free diet,” and even “wheat-free diet” are inappropriate terms. Unfortunately, there does not seem to be an appropriate unique identifier that explains the nature of the troublemakers other than to suggest avoidance of wheat, rye, and barley.

Rice, buckwheat, and other grains do not affect a response in CD/GAD patients, and therefore are safe replacements for wheat, rye, and barley. Millet, sorghum, corn, and oats, on the other hand, may incite their own unique reactions in sensitive individuals, especially during the first months post-CDD, and therefore need to be introduced with care.

**The Oats Controversy**

Avenin, the prolamin fraction of oats, has fewer glutamine residues available for deamidation by TG2 and is therefore considered less immunogenic than wheat gluten.<sup>107</sup> Studies have shown induced villous atrophy from oat ingestion in some celiac patients,<sup>107,108</sup> although well-designed studies have shown the majority of CD patients tolerate oats.<sup>105,109,110</sup> Gluten contamination, common to commercial oat products, may help explain such inconsistencies (Table

4).<sup>111</sup> Celiac disease patients will rarely maintain a true sensitivity to oat ingestion.

**Other Grains**

Reactions to more distantly related grains (Figure 1) are commonly related to contamination as well. Grain contamination and a non-compliant diet have together led to the difficulty in freeing many

**Table 4. Contamination of Oat Products**

Product and Lot No. or Best-by date	Gluten (ppm)		
	Extraction A	Extraction B	Mean of A & B
McCann's Steel Cut Irish Oats, 28 oz container			
150134	12	12	12
150934	BLD	BLD	BLD
270934	24	21	23
160634	705	745	725
Country Choice Old Fashioned Organic Oats, 18 oz container			
July 13, 2004	131	130	131
Dec. 13, 2004	200	220	210
Dec. 17, 2004	116	124	120
March 12, 2005	BLD	BLD	BLD
Quaker Old Fashioned Oats, 18 oz container			
L309; Jan. 9, 2005	326	349	338
L309; Jan. 18, 2005	997	944	971
L110; Feb. 12, 2005	1861	1752	1807
L109; March 22, 2005	375	352	364

BLD – denotes below the limit of detection. The limit of gluten detection for the assay used in this analysis was 3 ppm.

From: Thompson T. Gluten contamination of commercial oat products in the United States. *N Engl J Med* 2004;351:2021-2022. (used with permission)

grains from suspicion. Hidden and minute re-exposures frustrate patient and clinician alike, especially during the first six months post-CDD, when the immune system may exhibit a strong secondary immune response to limited exposures (as noted in microbe re-exposure studies).

### *Initiation of CDD and Reintroduction of Grains*

The reintroduction of other grains is dependent on the significant resolution of gastrointestinal (GI) inflammation by CDD. As the inflammatory load diminishes with a diet devoid of CD/GAD troublemakers, GI tissue healing commences with the resolution of gut dysbiosis and permeability, which is further reflected in reduced immune exposure to suspect grains, peptides, and other antigens. This promotes immune system healing and the reduction of alert status to a less inflammatory, surveillance baseline. During this transition the immune system is better able to correctly interpret peptide sequences that may have been flagged as suspect during the inflammatory crisis. Therefore, the propensity of other grains to induce inflammation during this conversion to health is dependent on many variables – the interval of gut dysbiosis and the amount of destructive inflammation generated, genetic susceptibility of the immune system and GI tract, and environmental variables such as “toxic load” and stress-induced autonomic dysfunction.

It is recommended that reintroduction be started 2-3 months post-CDD, one grain at a time each month; for example, reintroducing millet first, and then moving to sorghum (not “durum sorghum” which contains wheat). Corn and oats should be reintroduced last because they appear to have the strongest penetration into immune system memory and induce a greater immune/cytokine reaction than other non-CDD grains.<sup>112</sup> This process promotes immune system stability by allowing immune system recalculation to a continually falling inflammatory state while clinically affording dietary compliance through variety, satiety, and fiber.<sup>113</sup>

### *Reading Product Labels*

The product labeling language “gluten free” has slightly different meanings in different countries, although it always refers to items that lack glutes from all forms of wheat, rye, and barley. CODEX Alimentarius (a United Nations commission appointed to establish international food standards and food trade guidelines) has designated gluten contamination below 200 ppm to be “gluten free.” The United States and Canada have a zero tolerance rule for the designation of “gluten-free,” although it has been found that up to six percent of foods labeled “gluten-free” in North America contain more than 300 mg gliadin/kg of product.<sup>114</sup> Therefore, despite the host country, a degree of routine gluten exposure is probable. Fortunately, because the acceptance of CODEX by most European countries is based on years of research and the follow-up care of thousands of people with celiac disease, it does not appear that such limited exposure greatly affects the majority of CD/GAD sufferers. A notable exception is a case report of symptom recurrence in a Catholic patient who daily ingested a fragment of a communion wafer (containing 1.0 mg gluten with 0.5 mg gliadin).<sup>115</sup>

### *Compliance*

The degree to which patients will ingest grains related to CD/GAD is dependent on their tolerance of the more distressing symptoms. Compliance with a CDD is variable – ranging from 33-50 percent in adults and 16-65 percent in teenagers.<sup>116-118</sup> A reduced gluten diet may alleviate the gross pathological GI distress, but not the immune system dysregulation and associated symptoms. Patients receiving only 2.5-5.0 g of gluten per day for six months showed no significant morphological changes to the intestinal mucosa, but intra-epithelial lymphocytes were significantly increased, confirming a sustained immune response.<sup>119</sup>

### *Nutritional Deficiencies*

Commonly noted nutritional deficiencies should be addressed: vitamin B12,<sup>120,121</sup> vitamin E,<sup>122,123</sup> folate,<sup>124,125</sup> iron,<sup>116,125</sup> carnitine,<sup>126,127</sup> and selenium.<sup>127</sup> Even after maintaining a CDD for 10 years, many patients still exhibit poor vitamin status, including significant deficiencies in folate and

B12.<sup>128</sup> In CD, mineral deficiencies correlate with a higher prevalence of osteoporosis and increased risk of fracture.<sup>90,129</sup> Celiac patients are also sensitive to long-term corticosteroid therapy for other conditions, sometimes precipitating osteonecrosis of the femoral neck.<sup>130</sup>

### Other Therapies

After proper diagnosis and introduction of a CDD, repair of the GI mucosa should be initiated and will help decrease other food sensitivities that may have resulted because of gluten ingestion. Glutamine, the preferred substrate of the endothelial cells of the small intestine, is suggested to restore structural integrity.<sup>131-133</sup> Concern has been raised in internet forums regarding the use of glutamine in CD; however, there is no evidence that glutamine incites CD/GAD or increases their symptomatology. Dosages vary greatly depending on the clinical situation, but are in the range of 2-4 g daily in divided doses. Dietary supplementation with N-acetylglucosamine provides proper mucin production, is a constituent material of GI goblet cells,<sup>134</sup> and, as a molecular cousin to glucosamine sulfate, is presumed to have a similar safety/dosage profile. Herbal medicines should be prescribed individually, as some cases may need more astringent herbs while other presentations will require demulcents. The use of bulking agents helps strengthen peristaltic activity and re-establish autonomic tone.

Digestive enzyme use is often helpful. Theories from the 1960s regarding poor disaccharide digestion in CD patients are still purported by some<sup>135</sup> and pancreatic insufficiency has been noted in 8-30 percent of celiac patients.<sup>112</sup> Hydrochloric acid deficiency has been associated with dermatitis herpetiformis<sup>136</sup> and is commonly employed as adjunct supplementation in CD as well.

Re-establishing a healthy luminal micro-environment often ravaged for many years prior to diagnosis is therapeutically significant. The introduction of *Lactobacillus* species will facilitate this modification while promoting increased sIgA secretion that is often reduced in these patients. *Saccharomyces boulardii* has been found to be a particularly beneficial sIgA promoter<sup>137,138</sup> while inhibiting many infectious microbes, including *Clostridium difficile*.<sup>139</sup> Such

treatments focusing on healing the GI tract should be maintained for 3-6 months through the reintroduction of beneficial dietary grains.

### Prognosis

A CDD will usually initiate CD-symptom abatement in less than one week due to the high turnover rate of luminal endothelial tissues.<sup>140</sup> Other GAD manifestations often require more time to restore aberrant immune inflammatory processes and resultant damage. Often reduction in neurological symptoms is not noted until 6-12 weeks on a CDD, with continued improvement often noted past the first year on a CDD. Anti-gliadin antibodies and organ specific antibodies, such as anti-thyroperoxidase, anti-islet cell antibodies, and anti-Purkinje cell antibodies, disappear after 3-6 months on a CDD.<sup>141</sup>

The resolution of nutritional deficiencies is dependent on diet and condition. In osteoporosis a CDD provides significant improvement in clinical and laboratory parameters within 6-12 weeks<sup>91</sup> and improves bone mineralization within one year.<sup>142</sup> Symptoms of anemia will abate over the course of weeks as the percentage of new, fully-functioning red blood cells compensate for the suboptimal stores. Other mineral deficiencies will be restored as absorption is improved via reduced inflammation post-CDD.

The results of poor dietary compliance include increased risk for anemia, infertility, osteoporosis, intestinal lymphoma, and jejunal adenocarcinoma.<sup>143,144</sup> Unfortunately, many of the pathological changes in CD are known to increase malignancy and mortality.<sup>145</sup> Non-Hodgkins lymphoma and small bowel adenocarcinoma are associated with increased CD incidence compared to the general population. Fortunately, a CDD started early in life appears to protect against these malignancies.<sup>146</sup>

### Other Considerations

#### Pregnancy

Special nutritional concerns apply in pregnant celiac patients and can help identify undiagnosed CD. For instance, low iron levels, with hemoglobin of less than 11 g/dL, should raise suspicion of CD.<sup>147</sup> Regarding the increased need for folate, one study has shown that women with CD tend to have babies

with a greater incidence of neural tube defects (1 in 60) relative to the general population (1 in 1000).<sup>148</sup> Female CD patients, therefore, need to be compliant with gluten restriction as well as be properly supplemented with folate during childbearing years.<sup>124</sup>

Women with CD who maintain a CDD appear to have fewer incidents of miscarriage, higher birth weight babies, and maintain longer breast-feeding periods than untreated controls.<sup>149-151</sup> A more recent multi-centered study, however, did not substantiate these trials. Interestingly however, the inclusion criteria established a sample of 5,055 women who did not have diagnosed CD, and concluded that those mothers later found to have CD (51 women) did not appear to have significant unfavorable outcomes of pregnancy when compared to the non-CD mothers – including miscarriage and low birth weights.<sup>152</sup> Therefore, regarding unfavorable outcomes in pregnancy, those severely afflicted to the point of warranting diagnosis (increased immune dysregulation and inflammatory involvement) will greatly benefit from a CDD, while those with undiagnosed CD (having a relatively lower immune dysfunction index) maintain a similar rate of unfavorable outcomes to the general population.

### Breast-feeding

Continuing breast-feeding for one month after introduction of wheat flour was found to protect against CD.<sup>153</sup> Family history of HLA-related diseases (especially type 1 diabetes) and immune-related conditions suggest a need for prudent introduction of grains and the promotion of breast-feeding to reduce CD probability.<sup>85</sup>

### Implications of Wheat Over-indulgence

Since the 1980s, almost 20 percent of the total caloric intake of U.S. adults has been bleached, refined wheat flour cultivated almost exclusively from two species – *Triticum aestivum* and *Triticum turgidum*.<sup>154</sup> Depending on processing, numerous vitamins and minerals are removed, then the flour is “enriched” by adding back vitamins B1, B2, B3, folic acid, and iron.<sup>154</sup> Over the last 100 years, the increased ingestion of gluten-containing products, and wheat in particular, has undoubtedly brought many individuals’ genetic sensitivities to gluten to the foreground.

### Conclusion

Celiac disease is more prevalent than has been commonly believed, affecting nearly 1 of 100 people, with the majority of patients awaiting diagnosis. Gastrointestinal symptoms are common in celiac disease; however, neurological, endocrinological, and other organ system presentations can deflect clinicians from diagnosing celiac disease. Undiagnosed patients often spend years seeking help for complaints such as ataxia, arthritis, epilepsy, depression, neuropathy, and a host of other conditions seemingly unrelated to digestion. Until recently, gluten intolerance was not considered as a possible etiological factor in such a long list of diseases. Fortunately, after proper diagnosis the treatment is straightforward – avoidance of specific gluten-containing grains.

The pathophysiology of celiac disease is incompletely understood, although researchers continue to uncover new information regarding the connection of CD to generalized inflammation, autoantibodies, genetics, and microbial triggers. Further understanding of these processes may one day allow restrictive dietary protocols to be removed as the primary therapy for CD. One therapeutic challenge is the diversity of host cells modulated by gluteins to direct the cytokine network. A second hurdle is the cross-reactivity of gluten and the subsequent autoantibody production to various tissues, which appears to have a significant genetic component. Understanding these variables will dictate the timetable for changes in CD/GAD therapy.

Although the ingestion of specific gluteins in susceptible individuals can result in damage to many organ systems, treatment has been shown to restore lost function and prevent further tissue injury. Routine screening for celiac disease is often of clinical benefit to patients with known autoimmune diseases, as well as in patients with symptoms suggestive of gluten intolerance. Thorough assessment can facilitate a life-changing diagnosis, allowing for treatment initiation that will ensure a more healthful future for CD/GAD patients.

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