CPE: The Gluten Connection
The Relationship between Celiac Disease and Type 1 Diabetes Mellitus

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It is well-established that a strict gluten-free diet can reverse the symptoms associated with celiac disease (CD), an autoimmune condition typically defined as a disease of the digestive system that damages the small intestine and interferes with the absorption of nutrients from food. Furthermore, for many years, it has been documented that the classical presentation of CD is diarrhea with or without a malabsorption syndrome demonstrated by wasting, edema secondary to hypoalbuminemia, hypocalcemia, vitamin deficiency states and osteomalacia. The diagnosis of CD requires the presence of small intestinal mucosal villous atrophy and crypt hyperplasia (Marsh III). The diagnosis of CD requires the presence of small intestinal mucosal villous atrophy and crypt hyperplasia (Marsh III). Marsh type III lesions contain villous atrophy and are associated with typical CD pathology.

Figure 1 demonstrates normal duodenal mucosa with healthy villi (on left) versus atrophied villi of the duodenal mucosa in CD (on right).

Celiac Disease – A Clinical Chameleon
CD is not a condition that occurs overnight. Evidence suggests that small bowel mucosal damage in CD progresses gradually from mucosal inflammation to crypt hyperplasia, and finally to partial and subtotal villous atrophy. However, as our understanding of CD continues to grow, it is becoming increasingly evident that CD may not always manifest as previously thought. It is now accepted that CD may be characterized by more subtle histological changes; in some subjects only epithelial infiltration may be present. In a 2005 paper by Sanders and colleagues in the British Medical Journal, the authors state, “CD used to be perceived as involving gastrointestinal symptoms suggestive of malabsorption, but this manner of presentation is now described as the classic (typical) form.” Furthermore, the authors suggest that patients with CD may have the “silent” or atypical form – that is, without gastrointestinal symptoms — where the condition affects organs other than the small intestine, with manifestations such as altered thyroid function, skin abnormalities, bone disease, iron-deficiency anemia, and even neurological disorders, including depression, mood changes, migraines and inability to focus. As a result, one could potentially have CD but be free of the classic GI symptoms for years. More recently, the term “potential” or “latent” CD has been used to describe patients with sub-clinical pathology and other subtle immunological

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abnormalities, such as celiac-like mucosal immunoglobulin pattern and increased density of intra-epithelial T cells, suggesting a significant risk of developing CD later in life. The "iceberg" is a common model used to explain the epidemiology of CD (see figure 2). Accordingly, only a minority of individuals has clinically overt CD, while the majority of people with CD have the silent form, which may go undiagnosed because they remain asymptomatic. This may explain earlier inaccurately low prevalence figures – 21.8 in 100,000, according to a 1994 study. By contrast, Fasano and colleagues found the overall prevalence rate of CD in the United States in not-at-risk groups to be closer to 1 in 133. Furthermore, "that gluten sensitivity is regarded as principally a disease of the small bowel is a historical misconception," according to Hadjivassiliou and colleagues. As a result, many practitioners who are not familiar with the countless ways in which CD presents may miss the diagnosis and encourage the patient to continue eating wheat-based foods, per USDA government guidelines, thus making matters worse.

Rubio-Tapia and colleagues investigated the long-term outcome of undiagnosed CD and whether the prevalence of undiagnosed CD changed during the past 50 years. Their results indicate that undiagnosed CD was associated with a nearly four-fold increased risk of death, and the prevalence of undiagnosed CD increased dramatically in the United States during the past 50 years. More recently, Katz and colleagues reported that undiagnosed celiac disease affects 1 in 126 individuals and that most were asymptomatic or had atypical presentations.

To demonstrate just how much of a "clinical chameleon" CD can be, the author of an editorial published in the New England Journal of Medicine stated "Celiac disease is one of the most common lifelong disorders in both Europe and the United States. The clinical presentation of this condition can range from the typical syndrome of malabsorption (chronic diarrhea, weight loss and abdominal distention) to symptoms and conditions that can affect any organ system." Furthermore, for every symptomatic patient with CD, there are eight patients with CD who do not experience gastrointestinal symptoms, thus suggesting that CD "out of the intestine" is even more frequent than CD "within the intestine." Autoimmune – The Instigator

Gluten, a complex mixture of glutenin and gliadin protein molecules and the major storage protein of wheat, is the primary immune system instigator in CD. This includes the gluten present in all forms of wheat, including durum, semolina, spelt, kamut, malt, couscous, bulgur, triticale, einkorn and faro, as well as related grains, rye and barley. Although gliadin, the alcohol-soluble fraction of gluten, has been most studied, other proteins, such as glutenin, are probably also toxic to people who have CD. Furthermore, while certain complex carbohydrate-rich foods such as rice, buckwheat, corn, and millet do not contain gluten and are not specific to CD etiology, they may contribute to escalating symptomatology in sensitive individuals by creating and sustaining an inflammatory response.

Autoimmune Inflammatory Disease – The "Epidemic of Epidemics"

Originally considered a rare malabsorption syndrome of childhood, CD is now recognized as a common autoimmune condition that may be diagnosed at any age and may affect multiple organ systems. In fact, while many individual autoimmune diseases appear rare, collectively they are thought to affect approximately eight percent of the United States population. In a 2006 seminar entitled Understanding the Origins and Applying Advanced Nutritional Strategies for Autoimmune Diseases, Jeffrey Bland, Ph.D., explained that "collectively autoimmune diseases have been identified in about 24 million people in the United States, and only one-third are diagnosed. That means about 72 million people have an autoimmune disease. It's not looked for [during routine exams or even hospitalizations]. Our system waits until the signs and symptoms are severe enough, with organ failure and irreversible damage, before we identify it." Autoimmune disorders can be classified as either organ-specific, such as Type 1 diabetes mellitus or Hashimoto's thyroiditis, or systemic, such as CD, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In a paper on celiac disease-associated autoimmune endocrinopathies, Kumar and associates state, "In organ-specific autoimmune diseases, the autoantibodies are specifically directed against antigens localized in a particular organ and are often detected in circulation." The proposed mechanisms of autoimmune endocrine disease involve a sequence of immune, inflammatory events in a genetically susceptible individual. In most cases, the immune response to the target cell progressively destroys the...
endocrine gland, and hypofunction is the main clinical manifestation.21

**The Celiac Disease and Type 1 Diabetes Mellitus Connection**

Indeed, several autoimmune disorders are more prevalent in CD patients and their close relatives. For this population, risk of developing other autoimmune diseases is related to the duration of exposure to gluten.22 The most frequently reported CD-associated conditions are type 1 diabetes mellitus (T1DM) and autoimmune thyroiditis.23 In fact, the association between CD and T1DM was recognized more than 30 years ago.23 After the introduction of serological antibody tests, such as antiendomysial and antigliadin antibodies, a number of studies have been carried out to assess the frequency of CD in patients with T1DM. Virtually all studies have shown an increased frequency of the disorder compared to that of the general population (0.5-1.0%).23 Statistics show that the prevalence of CD in people with T1DM is an astounding 10-30 times that found in the general population.20 Additionally, 3-8% of individuals who have T1DM have CD, while at least 5% of individuals who have CD have T1DM.20 Similar to those with silent CD, about one in 20 people with T1DM have asymptomatic CD but have not developed classic CD symptoms of the gut.20

It is well-established that specific antibodies, glutamic acid decarboxylase (GAD) and islet cell antibodies (ICAs), are considered to be predictive markers of T1DM. Interestingly, in a review of associated autoantibodies in CD, at least one T1DM-related autoantibody was present in 11.1% of 90 CD subjects at diagnosis and resolved within 12 months on a gluten-free diet.22 In fact, in a 2002 article by Nelson published in the American Family of Physicians, T1DM was described as the most prevalent autoimmune disorder associated with CD followed by autoimmune thyroid disease.24 However, the question remains: What is the common denominator between CD and T1DM? While they are both autoimmune diseases, the latter is organ-specific and the former is not. It appears that gluten consumption may be a shared causative factor, as both share a similar genetic basis. That is, both conditions have the same human leukocyte antigen (HLA), which genetically predisposes an individual to both CD and T1DM.25

A recent article by Barker and Liu confirms this connection. They state, "The HLA association with celiac disease is largely accountable for its link to other autoimmune diseases, including type 1 diabetes and autoimmune thyroid disease, and the majority of risk for celiac disease in these populations is related to HLA genotype. Celiac disease also carries an increased risk for type 1 diabetes and autoimmune thyroid disease."26

Traditionally, children with T1DM also have an increased risk of CD, with T1DM coming first, followed by gluten intolerance. Furthermore, the prevalence of T1DM is related to the duration of exposure to gluten,27,28 and the older the patient is when diagnosed with CD, the higher the probability of being diagnosed with other autoimmune diseases. Therefore, it appears that the elimination of dietary gluten is associated with a lower frequency of T1DM. However, this is no longer the case when patients already reveal islet-autoantibodies and beta cell destruction.29 Collin and colleagues examined the influence of a strict gluten-free diet on the metabolic control of individuals with diabetes in a prospective, controlled one-year trial. Even though a definite improvement in adherence to the gluten-free diet was achieved in the celiac group, this had no effect on the metabolic control of diabetes.21 Moreover, the impact of a gluten-free diet on the metabolic control of diabetes may depend on the symptoms of CD in individuals with both conditions. In severely malnourished subjects with T1DM, the treatment of newly detected celiac disease has had an unequivocal positive effect: intestinal symptoms were rapidly alleviated and a significant weight gain was evident. In addition, the metabolic control of T1DM improved in general, and in particular the number of severe hypoglycemic episodes declined.30,31 Importantly, however, James Braly, MD, author of Dangerous Grains, reminds us that "after the complete autoimmune destruction of insulin-producing islet cells, a gluten-free diet does not reverse or stabilize Type 1 diabetes."32

The question remains whether or not untreated celiac disease worsens the rate and progression of diabetic complications. In any case, it appears that neurological complications commonly occur in CD, and it has not been excluded that untreated CD may predispose individuals with diabetes to neuropathy.33 A study by Smyth, et al., published in the New England Journal of Medicine, described a genetic susceptibility to both T1DM and CD, which shares common alleles.34 This suggests that common biologic mechanisms, such as autoimmune-related tissue damage and intolerance to dietary antigens, such as gluten, are etiologic features of both diseases.

**Salivary Testing for Antibodies in Celiac and Type 1 Diabetes**

The problem with conventional blood-analysis testing for CD is that it will not reveal intolerance to gluten unless there is extensive damage to the intestinal villi.35 Animal studies have demonstrated that when a bacterial antigen – from milk or gluten, for example – is consumed, anti-gliadin IgA (AGA) and anti-tissue transglutaminase antibodies (tTG-Abs) are not always detected in the blood. However, these antibodies can be detected in the animal’s stool or saliva.36 As a result, salivary assays have been developed to test for AGA and tTG-Abs. A recent study demonstrated that it is possible to detect salivary tTG-Abs with high sensitivity not only at CD diagnosis, but also during a gluten-free diet.37 This contradicts previous data that
showed conflicting results regarding salivary assays for CD. Essentially, patients who have AGA in their saliva are considered to be gluten intolerant. A positive test for both AGA and tTG-Abs confirms celiac disease. A positive test for only tTG-Abs, which is present in T1DM, demonstrates an autoimmune for only tTG-Abs, which is present in T1DM, demonstrates an autoimmune 

The Unifying Hypothesis

It appears that gluten consumption is a dietary factor in T1DM leading to the alteration of gut immune system function and its effects on the pancreatic immune system. Furthermore, insulin and its precursors are major targets of the T and B lymphocyte autoreactive response in T1DM. Knip and colleagues speculate that "you may need a triggering gastrointestinal infection inducing primary target cell damage and/or a proinflammatory cytokine milieu in the gut epithelium to initiate the disease process subsequently driven by dietary gluten toward clinical celiac disease in genetically predisposed individuals." Additionally, genes that are classified as autoimmunity genes, due to their association with T1DM, may contribute to CD. The latter, according to Knip et al, explain about half of the familial clustering in both diseases, while the former must be due to non-HLA genes and/or a shared environment.

Take Home Message for Integrative and Functional Medicine Practitioners

There is no doubt that many patients with CD primarily contact specialists other than gastroenterologists. The majority of cases thus remain undetected. A close association between T1DM and CD has been shown in numerous studies. The diagnosis of CD requires a small-bowel biopsy. However, sensitive and specific antibody serological assays, including antiendomysial and antitissue transglutaminase tests, and salivary tests, are helpful in preliminary screening for gluten intolerance in cases where symptoms are atypical, appear outside the gastrointestinal tract, or are entirely absent (the latter being of possible interest in those individuals with an immediate family history of CD). Prevention of T1DM advocates the early diagnosis and treatment of even asymptomatic CD. The benefits of screening for CD in T1DM remain to be confirmed by prospective follow-up studies. However, there seems to be a good case for this type of extensive screening.

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References

18. US Dept of Health and Human