Rocky Mountain Analytical
Changing lives, one test at a time

Celiac Profile

Clinical Information for Professionals

Celiac disease affects approximately 1% of the general population, most of whom go undiagnosed. Children are particularly at risk, with a large British study concluding that more than 90% of celiac disease went undetected in asymptomatic children.[1] In adults, it is estimated that there are 53 undiagnosed celiacs for every 1 known celiac. Although usually considered a gastrointestinal condition, celiac disease can manifest symptoms in virtually any organ. Given the magnitude of missed diagnoses, an easy to adminster, minimally invasive test is highly desirable. Our dried blood spot Celiac Profile provides sensitive and specific tests for both gluten sensitivity and celiac disease.

Diagnosing Celiac Disease

Diagnostic tests for celiac disease must be performed while patient is consuming gluten.[2] Long-term adherence to a gluten-free diet means antibodies to gluten are no longer present and cannot be accurately measured. Our Celiac Profile measures three different types of antibodies in a dried blood spot sample: anti-tissue transglutaminase IgA antibodies, anti-gliadin IgA antibodies and anti-gliadin IgG antibodies.

Gliadin IgG and Gliadin IgA

Antibodies to gliadin, the toxic protein fraction of gluten, are considered very sensitive but not very specific, for celiac disease. Consequently, elevated gliadin antibodies often occur in the absence of celiac disease. However, elevated gliadin antibodies have been associated with a variety of autoimmune diseases, not just celiac disease.

Tissue Transglutaminase

According to the National Institutes for Health (NIH), the anti-tissue transglutaminase IgA (tTg-IgA) is the best test currently available to diagnose celiac disease.[2] The anti-tTg is more sensitive than anti-endomysial antibodies (anti-EMA), but is less specific. In other words, a negative result for tTg is more likely to rule out disease than the EMA, but a positive result for the EMA means celiac disease is almost certainly present. When either EMA or tTg are positive, the intestinal biopsy is usually positive.

Seronegative celiac disease, where blood tests are negative but the biopsy is positive, may occur in up to 20% of celiac patients.

Summary: In practical terms, elevated antibodies to gliadin do not necessarily indicate celiac disease, while elevated antibodies to tissue transglutaminase almost always indicate celiac disease.

Note: The anti-deamidated gliadin IgG antibody test appears to be more useful for *excluding* celiac disease (i.e. a negative result rules out celiac disease) than for diagnosing CD. Gliadin IgA antibody tests (both deamidated gliadin IgA and gliadin) are considered less accurate than tTg and anti-EMA) [3]

Sensitivity versus Specificity

To understand what test results mean, it is important to understand the difference between sensitivity and specificity. A highly sensitive test identifies borderline disease, but due to its high sensitivity, could produce false positives. A highly specific test may miss mild forms of disease, but positive results are considered reliable evidence of disease.

Tissue transglutaminase
Gliadin IgA
Gliadin IgG

Celiac Profile screens for gluten sensitivity and celiac disease

Clinical Consideration for

Antibody	Reaction	Interventions

IgA tissue transglutaminase

negative < 15

positive > 15

No Reaction

- IgA deficiency is found in up to 4% of celiacs. Low IgA can potentially lead to a false-negative result for tTg-IgA antibodies.[4]
- Check gliadin IgA and IgG: if either or both are elevated, a trial gluten-free diet (GFD) is indicated.

Equivocal

- Equivocal results indicate presence of antibodies, but are insufficient to confirm celiac disease. Duodenal biopsy may find evidence of celiac disease despite low IgA-tTg levels.
- Decreased stomach acid has been associated with increased incidence of food reactions. In theory, an equivocal result *could* be a sign of low stomach acid.

High

- Elevated IgA antibodies to tissue transglutaminase are highly specific for celiac disease. A result in the high range means a gluten-free diet should be initiated. Confirmation through biopsy or other serum tests is worthwhile.

IgG gliadin

negative < 15

positive > 15

No Reaction

- Because gliadin IgG and IgA are highly sensitive (but not very specific), a negative result generally rules out both gluten sensitivity and celiac disease. The predictive value of a negative result is 99.7% [5]
- Patients who are negative for gliadin antibodies but have difficulty digesting wheat could try restricting their consumption of wheat to products made from spelt or kamut as these grains may be easier to digest.

IgA gliadin

negative < 15

positive > 15

Equivocal or High

Equivocal or high results can have two possible meanings:

- indicate recent exposure to gluten in patients with known sensitivity or celiac disease.
- suggest a sensitivity to gluten.

A finding of elevated gliadin antibodies may be most clinically relevant when gluten sensitivity manifests in tissues other than gut tissue: e.g. neurologic

Other Tests

Anti-deamidated gliadin peptide IgG antibody (DP-AGA) may help exclude CD, but the IgA DP-AGA showed inferior accuracy. [3]

OTHER LABORATORY TESTS

Total IgA

If gluten sensitivity or celiac disease is strongly suspected despite a negative tTg-IgA, consider testing total IgA.

If Total IgA is low, testing for IgG antibodies to tTg may be useful for diagnosis of celiac disease.

IgA-EMA

A 1992 study found that anti-EMA strongly correlated with presence of celiac disease: 21/21 patients with undiagnosed celiac disease (confirmed by biopsy) had elevated anti-EMA, compared to 0/47 healthy controls.[6] It was later discovered that the specific antigen within the endomysium that appears to react with gluten is tissue transglutaminase.

Intestinal biopsy

Biopsy is still considered the gold standard for celiac diagnosis. However, mucosal changes can be widely scattered, and since villous atrophy is often more severe in the proximal jejunum (an area not usually reached by endoscopic biopsies), false negatives are not uncommon.[7] Up to four biopsies may be needed to ensure an accurate diagnosis.[1]

SUPPLEMENTS

Glutamine: may be useful for restoring structural integrity of intestinal epithelium.[8]

N-acetylglucosamine: assists mucin production and is a component of GI goblet cells.[8]

Probiotics: restore healthy gut microflora and promote production of secretory IgA.[9]

Folic acid: approximately 1/3 of untreated celiacs have folate deficiency. Folic acid is absorbed in jejunum, duodenum and requires an acidic environment. 5-MTHF is preferred form.[9]

Vitamin B_{12}: over 40% of untreated celiacs have a B_{12} deficiency. [9]

Iron: iron deficiency anemia is common in celiac disease, and often remains even after a gluten free diet has been adopted.[9]

Zinc: absorbed primarily in the jejunum, zinc deficiencies are common in patients with active celiac disease.[9]

Pancreatic enzymes: decreased enzymes are common in celiac disease. Celiacs on GFD still experiencing diarrhea may require enzymes.[8]

Conditions linked to Celiac Disease

Gastrointestinal

Recent studies indicate that less than 42% of children and only 43% of adults with celiac disease have GI symptoms, unlike the 1990s, where it was more than 70% . The average delay from time of symptom presentation to time of celiac diagnosis is almost 12 years according to the Canadian Celiac Health survey. The most common alternate diagnoses were anemia (40%), stress (31%), and irritable bowel syndrome (29%). Osteoporosis and low bone density were also common findings (35%). [10]

Auto-immune disease

Celiac disease shares a similar genotype to other auto-immune diseases, which may explain why these patients to react to gliadin. Therefore, patients with autoimmune endocrine disorders (Addison's, thyroiditis, type I diabetes) should be assessed for celiac disease or gluten sensitivity regardless of whether or not gut symptoms are prevalent.

Insulin Dependent Diabetes: Celiac disease is 10 to 30 times more prevalent in Type I diabetes patients than in a normal population. Celiac disease may precede type I diabetes or vice versa.[11] Gliadin appears to bind to GAD (glutamic acid decarboxylase) and insulin, leading to the production of anti-GAD and anti-insulin antibodies.

Cardiomyopathy: Idiopathic dilated cadiomyopathy is associated with an increased prevalence of celiac disease. In a 2001 study, all patients positive for tTg antibodies with symptoms of autoimmune myocarditis were positive for cardiac antibodies.[11]

Thyroiditis: Celiac disease patients have a 3 to 4 fold increase in incidence of thyroid auto-immunity.

Other autoimmune diseases associated with celiac disease include rheumatoid arthritis and Sjogren's Syndrome.[8] Gluten withdrawal has not been shown to prevent development of autoimmune disease, but autoantibodies may decrease or disappear when a gluten-free diet is initiated.

Reproductive health: Subclinical celiac disease has been implicated in recurrent abortions, infertility, decreased age of menopause onset, low birth-weight infants, and intrauterine growth retardation. The mechanism appears to be immunological, with decreased placental angiogenesis secondary to elevated tTg antibodies as the hypothesized cause.[8]

Neurological disease: Gliadin antibodies can cross-react with synapsin I, a protein found in most neurons.[13] GAD is the enzyme used in production of the neurotransmitter GABA and 96% of patients with neurological symptoms along with gluten enteropathy have GAD antibodies.

Dermatitis herpetiformis is a dermatological manifestation of gluten intolerance. IgA antibodies to epidermal transglutaminase result in highly pruritic IgA granular deposits in dermal papillae, which form herpes-like vesicles.[8]

Psychiatric

Autism: A 5-year old boy diagnosed with severe autism at a clinic for autistic spectrum disorders was suspected of having celiac disease and/or nutritional deficiencies as contributing factors. A gluten-free diet was instituted and GI symptoms rapidly resolved as signs and symptoms of autism gradually abated.[14]

Schizophrenia: Studies by Dohan in the 60's and 70's found significant benefits for a gluten-free diet in schizophrenia. 102 male schizophrenics were randomly assigned to either a cereal-free (CF) or a high-cereal diet. 62% of patients on CF diet were released to a non-locked ward after 7 days versus only 36% of those on the high-cereal diet. These results were later replicated in another trial. Although neither study was blinded, gluten was added in a blinded fashion and was shown to obliterate the observed effect. [15]

Mood Disorders: Patients with prior bipolar disease or depression had increased risk of subsequent celiac disease diagnosis. Patients with celiac disease were at increased risk of subsequent depression.[16]

Osteoporosis: Active celiac disease is associated with decreased bone density or osteomalacia due to decreased calcium absorption, elevations in parathyroid hormone, and loss of cortical bone.[9] Autoantibodies to bone may also play a role in bone disease seen in celiac patients.

Other: Celiac disease is more common in Down Syndrome, Turner Syndrome, Williams Syndrome and selective IgA deficiency.[2]

Grains to Avoid

The following grains are to be avoided in celiac disease or gluten sensitivity:

- wheat
- barley
- rye
- triticale
- kamut
- spelt

The following grains are more distantly related to wheat, and are generally considered safe.*

- oats
- millet
- sorghum
- maize
- rice

***It is important to keep in mind that grains are often transported together, so 'safe' grains could potentially be contaminated by reaction-provoking grains.[8]**

Conditions linked to Gluten Sensitivity

Gluten sensitivity is best defined as a state of heightened immunological responsiveness in genetically susceptible people. [17]

Gluten Sensitivity

Subjects with high levels of gliadin antibodies were compared with a negative control group in a double-blind study. Significantly more of the gliadin antibody positive subjects experienced unexplained diarrhea and increased prevalence of chronic fatigue. The high gliadin antibody group also showed signs of anemia including decreased transferrin saturation, MCV and MCH and folic acid levels. Recurrent headaches were the only other complaint more prevalent in the gliadin antibody positive group. However, of the 48 subjects in both groups, 15 had clinical and laboratory features consistent with celiac disease: 14 of those 15 were in the gliadin positive group. The authors concluded that "these findings raise the possibility that a sub-clinical form of gluten intolerance may be relatively common." [18]

Candida: In rare cases, an immunodeficiency state called chronic mucocutaneous candidasis (CMC) may cause elevated gliadin antibodies. A 4-year-old boy admitted to hospital with typical symptoms of celiac disease: severe dystrophy, anaemia and elevated gliadin IgG antibodies, was found on upper endoscopy to have *Candida* esophagitis, but no evidence of celiac disease. Presence of impaired T-cell function along with recurrent Candida infections of the skin led to a diagnosis of CMC. Treatment with systemic antifungals produced excellent results and a steady decline in gliadin antibody levels.[19]

Neurological disease: 57% of patients with neurological disease of unknown etiology were found to have a higher prevalence of circulating antigliadin antibodies compared to healthy controls (12%) or those with neurological disorders of known cause. (5%) Ataxia, peripheral neuropathy and epilepsy were the most common neurological conditions implicated. A gluten-free diet is helpful in some cases, but has not been consistently useful.[17]

Systemic lupus erythmatosus: A 2004 paper discusses 3 case reports of patients diagnosed with SLE, later resolved with a gluten free diet. One was diagnosed with SLE at 20 months, and was treated with steroids and azothioprine. At the age of 17, she was tested for gliadin antibodies, started on a GFD, and six months later was symptom-free, drug free and had normal lab values. [20]

Celiac disease: IgG antibodies to gliadin may also be useful for monitoring compliance to a gluten-free diet.[21]

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