Rocky Mountain Analytical®
Changing lives, one test at a time

Celiac Profile

Clinical Information for Professionals

Celiac disease (CD) 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, CD can manifest symptoms in virtually any organ. Given the magnitude of missed diagnoses, an easy to adminster, minimally invasive test is highly desirable. Our 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

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

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 CD.[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 CD is almost certainly present. When either EMA or tTg are positive, the intestinal biopsy is usually positive.

Seronegative CD, 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 CD, while elevated antibodies to tissue transglutaminase almost always indicate CD.

Note: The anti-deamidated gliadin IgG antibody test appears to be more useful for *excluding* CD (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 CD. Duodenal biopsy may find evidence of CD 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 CD. 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

IgA 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 (CD). For CD, 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.

Equivocal or High

Equivocal or high results can have two possible meanings:

- recent exposure to gluten in patients with known sensitivity or CD.
- 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 CD 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 CD.

IgA-EMA

A 1992 study found that anti-EMA strongly correlated with presence of CD: 21/21 patients with undiagnosed CD (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. 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 the jejunum, and 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 CD, 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 CD.[9]

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

Insulin Dependent Diabetes: CD is 10 to 30 times more prevalent in Type I diabetes patients than in a normal population. CD 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 cardiomyopathy is associated with an increased prevalence of CD. In a 2001 study, all patients positive for tTg antibodies with symptoms of autoimmune myocarditis were positive for cardiac antibodies.[11]

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

Other autoimmune diseases associated with CD 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 spontaneous abortions, infertility, decreased age of menopause onset, low birth-weight infants, and intrauterine growth restriction. The mechanism appears to be immunological, with decreased placental angiogenesis secondary to elevated tTg antibodies as the hypothesized cause.[8]

Neurological and Psychiatric Disease

Over the past 50 years, it has become increasingly understood that CD is significantly associated with neurological and psychiatric comorbidities including, but not limited to: neuropathies, ataxia, dementia, epilepsy, depression, migraines, anxiety and schizophrenia.[20] In some patients, the neurological and/or psychiatric symptoms may in fact be the initial manifestation of CD leading to its recognition. Data suggests that up to 22% of patients with CD develop neurologic or psychiatric dysfunction, and as many as 57% of people with neurological dysfunction of unknown origin test positive for anti-gliadin antibodies.[21]

Depression and Anxiety: Although the mechanisms are not well understood, depression and mood disorders have been reported to be associated with both gluten sensitivity and Celiac Disease. A 2002 study from Carta et al. showed a significantly higher lifetime risk of Major Depressive Disorder and Panic Disorder in 36 adult celiac patients.[26] A follow-up 2015 case control-study from Carta confirmed these results, demonstrating that 30% of 60 CD patients had a lifetime diagnosis of Major Depressive Disorder (5x higher than the healthy subjects) and an 18% prevalence of Panic Disorder (nearly 4-fold higher risk than healthy subjects).[27] Conversely, patients with prior bipolar disease or depression have been shown to have had an increased risk of subsequent celiac disease diagnosis.[14]

Various types of depression-independent anxiety have been associated with gluten intolerance. One study found that CD patients were significantly more likely to experience states of anxiety than controls, and that adopting a gluten-free diet for a period of one year showed significant improvement in their anxiety symptoms.[28]

Schizophrenia: Perhaps the most robust evidence for a link between CD and psychiatric illness comes in the case of schizophrenia, with clinical studies dating back to the 1950s.[13,25] A series of seminal studies by Dohan in the 60's and 70's found significant benefits for a gluten-free diet in schizophrenia. The first of these demonstrated that the prevalence of schizophrenia was lower in areas of lower grain consumption. Following this, he showed in several studies that a milk- and cereal-free diet would improve symptomology of clinically admitted schizophrenic patients, and that patients on this diet were moved to a non-locked ward up to twice as quickly as those with gluten added to their diet.[22,23] More recently, a large epidemiological study assessing nearly 8000 schizophrenic patients, found a 3.2 increased relative risk of developing schizophrenia for those individuals with a medical history of CD.[24]

Mood Disorders: Patients with prior bipolar disease or depression had increased risk of subsequent CD diagnosis. Patients with CD were at increased risk of subsequent depression.[14]

Other

Celiac disease (CD) is more common in Down Syndrome, Turner Syndrome, Williams Syndrome and selective IgA deficiency.[2] There may be some association between autism and CD.[12] Frequently, CD is accompanied by malabsorption and vitamin deficiencies.[29]

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]

Osteoporosis: Active CD 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.

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 sensitivitity is estimated to occur at 6-times greater frequency than CD, and is best defined as a state of heightened immunological responsiveness in genetically susceptible people, exhibiting an altogether different type of immune-mediated reaction than CD.[15] Patients with GS do not have villous atrophy or antibodies to tTG or EMA, but rather they can test positive for antibodies to gliadin.[20]

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."[16]

Candida: In rare cases, an immunodeficiency state called chronic mucocutaneous candidiasis (CMC) may cause elevated gliadin antibodies. A 4-year-old boy admitted to hospital with typical symptoms of celiac disease: severe dystrophy, anemia 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.[17]

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.[15]

Systemic lupus erythematosis: 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.[18]

Celiac disease: IgG antibodies to gliadin may also be useful for monitoring compliance to a gluten-free diet.[19]

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