The Conundrum of Gluten Sensitivity 101: Why the Tests are Often Wrong

purring vs. rumbling

Tom O'Bryan DC, CCN, DACBN

In this 4-part Series, we're going to look at the World of Gluten Sensitivity, what the current science tells us, the frustrations Gluten Sensitive and Celiac patients often experience, and how to use the science in getting healthier.

Part 1: Why the Tests are Often Wrong
Part 2: Why Don't I Feel Great on a gluten-free diet: Cross-Reactive foods
Part 3: Why Don't I Feel Great on a gluten-free diet: the Intestinal Milieu
Part 4: Why Don't I Feel Great on a gluten-free diet: Invaders in the House

Many of us believe that the toxic peptides of gluten found in wheat, rye and barley may detrimentally affect any tissue in the body and are not restricted to the intestines. As a matter-of-fact, one of the 'mantras' of the Gluten Sensitivity network comes from an 8-yr old article: "That gluten sensitivity is regarded as principally a disease of the small bowel is a historical misconception.[1]" There is a key word in this statement which I suspect was an emphasis of the Author's message and sets the tone for this article (and this Network Movement). That key word is 'principally'. Is Gluten Sensitivity 'principally' a disease of the small intestine? Point-blank answer-no, it is not. For every Gluten Sensitive patient with the symptoms of an enteropathy (Classic Celiac Disease), there are 8 with no GI symptoms[2 3].

And the importance of recognizing this? Unfortunately, too many doctors will tell their patients that if the intestinal symptoms are not severe, or if there is no advanced intestinal damage (total villous atrophy), then the patient does not need to be vigilant in avoiding gluten exposure at all costs[4]. Many patients are advised to follow the World Health Organization or Food and Agricultural Organization Codex Alimentarius gluten-free diet, which allow up to 0.3% of gluten per 100 g of protein in foods, whereas others follow a strict GFD with no detectable gluten. However, trace amounts of gluten may be responsible for persistent symptoms in some patients with Celiac Disease. Up to 75% of patients with persistent symptoms despite a World Health Organization or Food and Agricultural Organization Codex Alimentarius gluten-free diet will improve when put on a ''no detectable gluten'' diet[5].

We know that for Gluten-Sensitive patients, eating gluten will cause an inflammation response in the intestines, and often in other parts of the body[6 7 8 9]. And the importance of 'quieting down' the inflammatory cascade from gluten exposure? Mortality in Celiac patients is highest (6-fold higher) in those not adherent to a gluten-free diet. Non-adherence to a gluten-free diet was defined as eating gluten once-per-month[10]. Vigilance is paramount. You can't be a little pregnant. There is no convincing evidence that you can have a little gluten if you have Gluten Sensitivity.

The 'Conundrum of Gluten Sensitivity' is when patients know they have a problem with wheat, their Doctors run the standard blood profile, and one of two things happens:
-IgA anti-transglutaminase or anti-endomysial antibodies come back negative[11], or IgA anti-transglutaminase or anti-endomysial antibodies come back negative and anti-gliadin, or anti-deamidated gliadin antibodies come back positive and the Doctor tells the patient "it's OK to eat wheat because the tissue antibodies are negative". The patient is left in a state of confusion. They don't WANT to give up wheat, after all, they believe it's a staple of life. And their Doctor says it's OK to eat it. Yet they know they don't feel as well when they eat it. So many will rationalize "Oh well, it must be the stress of my life making me feel bad", and they order their bagel. That's the conundrum. Where's the problem? The problem is the test.

Gluten Sensitivity is a systemic autoimmune disease with diverse manifestations[12]. Celiac disease, or gluten-sensitive enteropathy, is only one aspect of a range of possible manifestations of gluten sensitivity. And yet, this enteropathy, *'one of the most common lifelong disorders in both the U.S. and Europe*[13]*'*, receives the lion-share of focus to the point of ignoring other manifestations. Auto-immune disease, the 3rd leading cause of Morbidity and Mortality in the industrialized world[14], is ten times more common in a gluten sensitive enteropathy than in the general population[15]. The correlation is undeniable. The exact mechanisms of how this correlation manifests is being heavily investigated. But we can say with a good deal of research behind us is that the toxic peptides of gluten may act as a trigger in the development of the auto-immune mechanism (the immune system attacking our own tissues). But traditionally Drs. do not recognize this connection and wait for the accumulated damage from the immune system attacking our tissue (our thyroid, or our brains, or our skin, or…), they wait until the damage is extensive enough that there are obvious symptoms, and then we receive a diagnosis of an auto-immune disease (Celiac Disease, Hashimoto's Thyroiditis, Type 1 Diabetes,

Systemic Lupus, Inflammatory Bowel Disease, Inflammatory Skin Diseases, ….)[16]. Thus, the burden on society from Gluten Sensitivity cannot be overestimated. Earlier identification might result in earlier treatment, better quality of life and an improved prognosis for these patients[17].

The diagnosis of Gluten Sensitivity has been proposed to include not only if the affect is in the intestines (Celiac Disease), but also gluten-reactive patients without intestinal lesions. From the skin (Dermatitis Herpetiformis, Psoriatic arthritis, Alopecia areata, Dermatomyositis, Cutaneous vasculitis,), to the muscles (inflammatory myopathies), to the brain (Gluten Ataxia, altered neurotransmitter production, Schizophrenia, anxiety, depression, ADHD,…) to the nerves (peripheral neuralgias, carpal tunnel syndrome, idiopathic neuropathies,…), and beyond. Pathology to gluten exposure can occur in multiple systems without evidence of intestinal damage[18-27].

Now, what about this Conundrum? The tests are negative, yet the person feels better when they do not eat gluten. Many studies have validated the Sensitivity and Specificity using anti-endomysial and/or anti-transglutaminase antibody testing to identify Celiac Disease[28 29]. This means that the science says these tests are very, very accurate. Then how is it that there is a Conundrum? Here's the problem-the definition of Celiac Disease requires total villous atrophy[30].Not partial villous atrophy; not increased inflammation without any visible atrophy yet, the definition of Celiac Disease requires total villous atrophy. Thus, when researchers look at populations who have Celiac Disease confirmed by biopsy, and look to see how accurate the blood tests are, they come up with percentages above 95%, because they're only including people who have total villous atrophy in their Study Group-because that's the definition of Celiac Disease. If we were to expand the definition of Celiac Disease to include those with partial villous atrophy, or include those whom as of yet just show the mechanism that wears down the villi (increased intraepithelial lymphocytes), then the Sensitivity and Specificity of anti-endomysial or anti-transglutaminase goes down, in some studies dramatically down, to as low as 27-32%[31 32 33 34].

So do we want to base our health guidance and decisions on blood tests that are limited to identifying Celiac Disease at its end stage of intestinal deterioration (Total Villous Atrophy)[35 36]? Or would we want to include testing that has a much bigger picture in mind and looks to identify Gluten Sensitivity inside and outside the intestines at earlier stages?

If we recognize the now well-known fact that Gluten Sensitivity may manifest as Celiac Disease, or it may manifest outside of the intestines[37], one of the ways of expanding our diagnostic range is to focus on whether or not our immune system is saying that gluten is a problem. We may know where the problem is manifesting, or we may not. But if our immune system is saying "We've got a problem here", it likely is worth listening to.

As a comparison, if your car is running fine on the highway at 60 miles per hour, do you listen when the immune system of the car (the dashboard gauges) says "we've got a problem here", and the hot light has lit up, or do we say "the cars running fine-I don't see or feel any problem", and keep driving? I think most would agree that is not a very wise move. The same is true for your body. You may 'feel' a problem, you may not. We'll talk more about that in a future article. For now, the point I want to make is that we will benefit from 'listening' to what our immune system is saying to us. We just have to be able to hear what it's trying to say.

Now the problem is accurate communication. The current blood test that every laboratory offers in looking for an immune reaction to the gluten peptide of wheat is elevated antibodies to gliadin or deamidated gliadin. Every laboratory. And there are many studies that have shown looking for elevated antibodies to gliadin is not as accurate in identifying Celiac Disease as looking for elevated antibodies to Transglutaminase or Endomysial antibodies. Why? Because sometimes the antibodies to Gliadin are positive and the biopsy shows there is no Celiac Disease. And sometimes the Gliadin antibodies are negative and the biopsy shows there is Celiac Disease. Thus, the consensus in the scientific community is that looking for antibodies to wheat (gliadin) is not sensitive enough when looking for Celiac Disease. You can't rely on it. Now that doesn't make much sense, does it? If the gluten peptide is the problem, why can't we measure the immune reaction to it when other gauges on the dashboard are hot? Two reasons:

1) Researchers tell us it is "inappropriate" to compare gliadin antibodies against Transglutaminase or Endomysial antibodies because Gluten Sensitivity can exist without villous atrophy. Thus the gliadin antibodies may be elevated (and often are) without recognizable Celiac Disease. It's showing us a bigger problem than just Celiac Disease. They're not 'false positives', it's the immune system saying "we've got a problem here" that is not currently manifesting in the intestines-it likely is manifesting somewhere else, such as in the brain or the nervous system[38].
2) Identifying antibodies just to the peptide of gluten called Gliadin is not thorough enough in looking for an immune reaction to gluten[39].

Amino acids are the building blocks of protein. When we eat protein, any protein, it's the job of the digestive system to break down that protein into 1, 2, or at most 3 amino acid peptides that are easily absorbed into the blood stream through the 'cheesecloth' of the intestines. When someone has Gluten Sensitivity, the gluten molecules in wheat, barley and rye are not digested into small enough molecules to easily fit through the cheesecloth, be absorbed into the blood stream, and they remain in larger peptides, sometimes very large peptides. These large peptides, called Macromolecules trigger the immune system to say "these are not good for me[40 41]". An exposure to a large peptide on a rare occasion would not likely have initially been a problem. But with pancakes for breakfast, a sandwich for lunch, pasta for dinner, toast for breakfast, a sandwich for lunch, croutons on the salad at dinner, day in and day out, eventually you've got a hot light on the dashboard that is reaching the critical stage[42]. Then 'boom' your engine overheats and you begin to notice symptoms-perhaps in the intestines, perhaps in the joints, perhaps in the skin, perhaps in the skull (depression, anxiety, headaches), perhaps fatigue,…..

So let's get back to the large peptides left in the intestines due to an inability to digest the gluten molecule. We know there are many peptides of gluten produced by poor digestion[43]. One study identified over 60 putative peptides of gluten[44]. Yet the current blood tests only test for one-gliadin. Studies have said that gliadin is the primary toxic peptide. But, only about 50% of celiac patients have antibodies to the gliadin peptide of gluten[39]. And the rest of the Celiacs don't. They have antibodies to other peptides of gluten[45]. This is the reason for the Conundrum-you test for it, the test only looks for antibodies to gliadin, the test comes back negative, and yet you 'know' you feel better off of gluten. It's the test! In that example, the person does not react to the gliadin peptide-they are likely to be reacting to a different peptide of gluten.

"Why don't laboratories test for other peptides of gluten"?

Good question. I do not know the answer to that. Some of the studies on this go back to the mid 90's. Probably a supply and demand issue for commercial laboratories.

Well, no longer.

There is a new blood test, looking at 12 different peptides of gluten-not just Gliadin. You can go to www.cyrexlabs.com or to my web site www.theDr.com to read more about this test. Looking at antibodies to 12 different peptides of gluten

(including gliadin) will certainly increase the detection rate of the immune system saying “we’ve got a problem here with gluten”. We know Celiac Disease is due to sensitivity to the peptides of gluten found in wheat, barley and rye.Many of the peptides of gluten-not just to Gliadin. And now, another diagnostic tool has been added to your Doctors repertoire assisting in accurately identifying Gluten Sensitivity with or without the serious end-stage of tissue destruction-Total Villous Atrophy.

And my personal prayer is that as a result of this expanded test looking for a reaction to gluten, we no longer miss those with earlier stages of Celiac Disease and Gluten Sensitivity thus being able to calm down the ‘fire in the belly’, the hot light on the dashboard, before the engine blows up. Before the diagnosis of Attention Deficit Hyperactivity Disorder, before the diagnosis of Autoimmune Thyroid Disease, before the diagnosis of Type 1 Diabetes, before the diagnosis of migraines, before the loss of a pregnancy,…. And Doctors will have the tools to truly guide their patients in increasing one’s health-tuning the engine before it blows up with a diagnosable disease. So our bodies can carry us through life purring instead of rumbling along.

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