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Towards Healing The Planet, One Person At A Time

DIFFERENTIATING GLUTEN RELATED DISORDERS

by DR. THOMAS O'BRYAN, DC, CCN, DACBN

What a paradigm shifting moment in history when the world accepted that the earth was not flat! Opened up new lines of thought, new visions of what was possible and new adventures to dream.

A similar paradigm shift has occurred within the health care field with the recognition that Non-Celiac Gluten Sensitivity is at least six-fold[i], and (so-far) as high as 20-fold[ii] more frequent than Celiac Disease.

How do we differentiate the world of Gluten Related Disorders? A critical discussion. Would you treat an IgE reaction the same as an IgA reaction? Similarities in protocols perhaps but different emphasis. The four most recognized categories of response to gluten as an offensive agent are:

- Allergy (IgE)
- Celiac Disease
- Non-Celiac Gluten Sensitivity
- Non-immune malabsorption syndrome

Below is a segment of a recent interview with the Director of Clinical Services at theDr.com, Michelle Ross, MS, CN and Dr. Tom O'Bryan targeted to Dr. O'Bryan's Certified Gluten Practitioners (CGP) on the topic of differential tests for Gluten Related Disorders

Gluten-Related Disorders

Presenters: Michelle Ross, MS, CN and Dr. Tom O'Bryan

Dr. O'Bryan: Hello everyone! It's Dr. Tom O'Bryan. Welcome to our CGP Webinar! We're going to talk about testing today for gluten-related disorders. And with me is Michelle Ross, Clinical Nutritionist and our Director of Clinical Services.

Hello, Michelle!

Michelle Ross: Hello! And hello to each one of you!
Let's begin by discussing the spectrum of gluten-related disorders.

Dr. O'Bryan: Okay. The spectrum of gluten-related disorders. Now, what does that mean? It means there are at least four different conditions that fall under the category of a gluten-related disorder. And we need to differentiate between them?

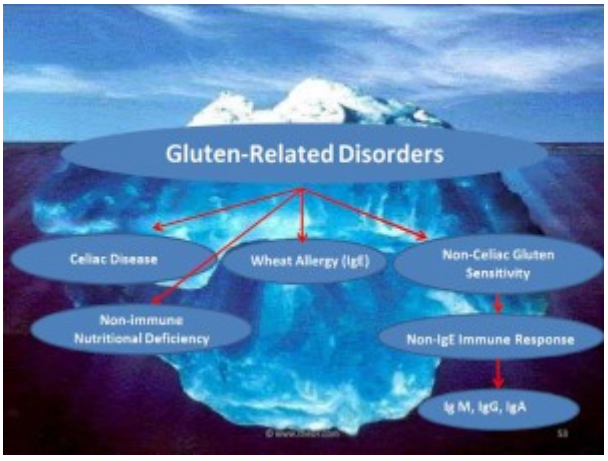
The first one—the oldest of these in terms of being identified in medical literature—is an allergy, a wheat allergy. That's an IgE reaction. And those tests came out in the 1950s. Remember the skin prick test? Still being done today. It can be done by skin pricking or by a blood test. But it's the first one—the oldest of these in terms of being identified in medical literature—as an allergy, a wheat allergy. Any other immunoglobulin response cannot be called an allergy because the first immune response that was identified was coined as an 'allergy'-an IgE response.

Thus, to get your language right so that you are referring to the proper conditions when you're talking with your peers, do not refer to a gluten allergy unless it's an IgE response. Refer to a gluten-related disorder. That's the big kahuna category[iii] [iv] [v][vi] .

So the first one was IgE. The second one is a non-IgE immune response. And that would be IgM, IgG, or IgA. Remember, there are different branches of the armed forces. And this is how we explain it to our patients. "Your immune system is like the armed forces. It's there to protect you. You have an Army, an Air Force, Marines, Coast Guard. IgA, IgG, IgE, IgM." So the second category is non-IGE immune response. There is a tremendous amount of discussion in the literature about this category. This includes the world of Non-Celiac Gluten Sensitivity[vii] .

The third category is celiac disease, unique and separate in its own way. We'll address the confusion in the testing for Celiac Disease and why we have a conundrum with testing here.
And the fourth category is a non-immune malabsorption syndrome.

So, there are four different categories of gluten related disorders that we need to differentiate once we suspect, or the patient reports a gluten-related disorder.



Michelle Ross: This is a great reminder for us to use the proper nomenclature when we're speaking about gluten-related disorders and food sensitivities or food allergies.

Dr. O'Bryan: That is correct! Why? Why is nomenclature important? Because it allows you to follow the path to clinical response and which therapeutic protocols you might consider. You do not treat an IgA reaction as you would an IgE reaction.

Michelle Ross: It's really helpful for me when you use the analogy of the different branches of the military. So let's just do a quick review. IgE stimulates a histamine response that can be life-threatening-like peanut allergies. IgA is a response of the epithelial surfaces, mainly of the intestines and the lungs. IgG is a systemic response. And IgM is a first responder.

And this is important to know because many of the tests available are only testing for one branch of the immune system. Many are looking at the IgG response. So could someone be negative for an IgG reaction, and be having, say, an IgA or an IgM reaction?

Dr. O'Bryan: That's a really good question, Michelle. And the answer is absolutely yes. It's actually very common. We find it clinically very often that someone will not be having an IgG reaction, or it's a very mild response, and they have a substantially elevated IgA reaction. So if you're only looking at the Navy, you may miss that the Air Force is out in full force. That's a very good question.

And that's why we don't ever want to get caught interpreting a single immunoglobulin test—IgG or IgA—as conclusive. If it comes back positive, it's likely positive. But if it comes back negative and you're only looking at one branch, the patient's immune system may be non-responsive. Or they may be having a full-blown reaction with another type of immunoglobulin.

Michelle Ross: So, ideally, we want to find a test that's testing as many branches as possible?
Dr. O'Bryan: Exactly right!

Michelle Ross: Okay. So now that we're discussing testing, let's start with genetic testing and merge away from the immune response for a second. Is it true that you can use genetics to diagnose celiac disease?

Dr. O'Bryan: Absolutely not! No question. Absolutely not! And the old school of thought was a couple of papers suggested that genetic testing may be enough of an indicator to assume someone has celiac disease because many papers have shown us that up to ninety-five percent of celiac patients will have the HLA-DQ2 gene. And the other five percent will have the HLA-DQ8. So that's almost a hundred percent of the people will have one of the two. Papers came out, presented in Chicago at the International Celiac Symposium in June of 2013, showing that up to seven percent of celiacs—card carrying celiacs with total villous atrophy—do not have either gene. And we now know that there are other genes involved besides DQ2 and DQ8. So you can't assume DQ2 and DQ8 are the only ones.

Now, here's the bullet point. The *International Archives of Allergy and Immunology* in 2010[1] showed us—and there have been, I've got three papers since then that have confirmed this—that up to fifty percent of patients with non-celiac gluten sensitivity carry the HLA-DQ2 or the DQ8 gene. 50%! Up to fifty percent of those that don't have celiac disease still carry the gene that we thought was the celiac gene.

So in the years to come, as more of these papers come out on this topic, I think that we're going to find we don't call it "the celiac gene" anymore. I don't know what we'll call it—maybe "the gluten gene"—but there are families of genes associated with gluten related disorders, not just celiac disease, but with the spectrum of gluten related disorders.

But on your question, "Does the DQ2 or DQ8 diagnose celiac disease", now we know conclusively it does not. It suggests a gluten-related disorder very, very strongly. But we don't know what type of disorder—if celiac is a non-IgE immune response—what type of gluten-related disorder they're having if they're positive for DQ2 or DQ8. We don't know. You have to look further.

Michelle Ross: So if they have DQ2 or DQ8 and they have non-celiac gluten sensitivity, could that be the early stage of celiac disease?

Dr. O'Bryan: That's a really good question. And I've had that thought myself. And at this point, the literature has not delineated whether that happens or not. Non-celiac gluten sensitivity are those that had

biopsy in these studies. They don't have villous atrophy. They don't have partial villous atrophy. They don't have crypt hyperplasia. They don't have any of the indicators of celiac disease. They may have increased IELs—some inflammation—but they're not on the celiac spectrum. So will they develop celiac disease? That's a really good question. At this point, we don't know.

So I personally am very comfortable—and I think it's a slam dunk—if they have DQ2 or DQ8, they do have strong vulnerability to a gluten related disorder. That's a slam dunk. But it is nowhere near conclusive that they can be diagnosed with Celiac Disease or even on the celiac spectrum.

Michelle Ross: And we just saw two test results from a person that had the genetic testing and they didn't have either DQ2 or DQ8. And yet, on Cyrex Array 3, they had the gliadin-transglutaminase antibody which is the slam dunk-only seen in the mechanism of development of celiac disease. I'm getting ahead of this because we haven't gotten into the Cyrex testing yet, but that's just an example that they could be in that seven percent…..

Michelle Ross: Of having celiac disease and not carrying the gene.

Dr. Tom O'Bryan: Exactly right.

Michelle Ross: So when would it be beneficial to do genetic testing?

Dr. Tom O'Bryan: That's a good question. There are a couple of situations where it's really useful. For infants and children you don't want to do a blood draw to look for antibodies. For someone who's on steroids where the immune system is likely to be suppressed, and you wouldn't get an accurate test result looking for antibodies, IgG, IgA, IgM. Because if they carry the gene, they are strongly susceptible to a gluten related disorder. Whether it's manifesting yet or not, they do have a gluten related disorder vulnerability. And it's just a question of, "how bad is it?" And we'll talk about the loss of oral tolerance in a few minutes. So the main group, we think, is children. That's a great place to do the gene test if you don't want to do a blood draw or you cannot do a blood draw for some reason.

Michelle Ross: I'd like to say that someone carrying one of those genes is just one baguette away from full-blown celiac disease.

Dr. Tom O'Bryan: [Laughter] That's cute. That's really cute.

And there is one other situation where the gene test is of value. And that is for family members of celiacs, or family members of those with non-celiac gluten sensitivity. They don't want to do a blood draw – all right. Would you mind a scrape of the inside of your gum with a Q-tip to see if you carry the gene? Because if you carry the gene, you're much more at risk of developing the same syndrome as what your family member has. So someone who's defiant and resistant or doesn't want to spend the money, or for whatever other reason they don't want to do the blood test, if you can get them to do a swab on the inside of the mouth then you can check for DQ2 and DQ8, you'll know that they're somewhere on the spectrum of a gluten related disorder.

Michelle Ross: That brings up an important question. Let's ask this now, "Who should be tested for a gluten related disorder?"

Dr. Tom O'Bryan: Yes, that's a really good question. I'm reminded of my good friend Dr. Rodney Ford, pediatric gastroenterologist in New Zealand, that when he's asked that question his answer is just so accurate and that is, "Anyone who is sick should be tested for a gluten related disorder." Whatever type of sickness they have–that if the therapy and protocols you're currently doing or recommending are not getting the results you want, consider that gluten may be like an emergency brake. You're driving your car. You put it in drive to go forward. You put your foot on the gas pedal and it's moving forward, but not very well. You think, "What's wrong with the car, it's not going very well." Well, if the emergency brake is on, it's holding you back. So if you have a gluten sensitivity and you're treating recurrent sinusitis with

antibiotics or whatever other protocols. Or you're treating muscle spasms in the calf. Or you're treating hepatitis. Or you're treating migraines. Or you're treating attention deficit. Whatever condition you may be treating, if you aren't getting the results that you should be getting, perhaps a food that's in the diet every day for most of us, is contributing to inflammation that is the emergency brake holding you back in getting the results.

So the answer is, "Who should be tested for a gluten sensitivity?" Anyone that you're not satisfied with the results you're currently getting, irrespective of their presenting complaints.

Michelle Ross: Okay. As Certified Gluten Practitioners, I think for many of us it's the first thing we think of when they walk into our office.

Dr. O'Bryan: Yes. Yes, it can be. Now, the danger in that for me, as a Speaker is that I can't say that because then I would sound fanatical. "Always consider gluten free first." But clinically in practice, it will come up as a contributor to whatever presenting complaints the patient has so frequently that as doctors just consider this, they're going to find that it becomes a primary approach in their treatment protocols because it is so frequent. If you have proper testing to identify it, you're going to find it time, and time, and time again.

Michelle Ross: Exactly! And what is the statistic for how long it takes on average in the US for someone to be diagnosed with celiac disease – not even the spectrum?

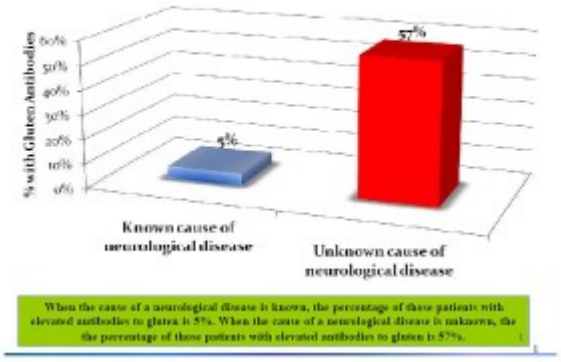
Dr. O'Bryan: Oh my gosh, that's so embarrassing that the average is eleven years[viii] [ix]after the symptoms first presented and they went to a doctor. So you had some symptoms, perhaps migraines and you went to a doctor. He recommended some therapy, some medications or something. It didn't work. You went back three months, six months later, it's not working. He sends you to a neurologist. You have to wait a month or two to see the neurologist, and then you get in. He recommends a different medication, does an MRI, can't find anything wrong. But he recommends a different medication that doesn't work. It works a little bit, but not very well. And you go back to see him again four months later, six months later. You have to wait months to see him. And so, you're now six months out again. And then, he recommends a different medication. And then, if you go back because you really want to be well and you believe it's a good doctor, perhaps he sends you to a tertiary center. A tertiary center is where it's a research center for neurology, in this example.

Now, listen to this, "For those patients in a neurology center," this is from Columbia University in New York, their neurology research center, "Those patients, where the cause of their neurological disorder was known, the number of patients that had elevated antibodies to the peptide of gluten gliadin [anti-gliadin antibodies] was five percent. For those patients where the cause of their neurological presenting complaints was unknown, the number of patients with elevated anti-gliadin antibodies was fifty-seven percent."

Fifty-seven percent of what presented….

Michelle Ross: Wow!

Dr. O'Bryan: …that no one could find the cause of their problems was anti-gliadin antibodies. There are many case studies of unresponsive neurological conditions being arrested or reversed on a GFD.



Michelle Ross: And I think I can speak for everybody listening right now, "That we do not want to be one of those practitioners that fall into an eleven year window of failing a patient."

Let's talk about how we test for gluten related disorder, and maybe it would be helpful to start with the standard test.

Dr. O'Bryan: Good! The standard test that's done looking for a gluten sensitivity is anti-gliadin antibodies. Gliadin is one of the peptides of poorly digested wheat. So it really is not correct to say it's a gluten test. That's just a common term we use, but it's really a test for one of the peptides of wheat. If we use the accurate nomenclature, the accurate terms for it, it helps us understand why it is a good test, but a limited test. So we're not checking for a gluten sensitivity, we're checking for a gliadin sensitivity — one of the peptides of wheat.

And then, the question automatically comes up, certainly for this listening audience, "Well, there are many peptides to the gluten proteins of wheat; not just gliadin. Why are we only checking one?" And the answer is, "Really good question. No answer. Nobody knows." That as far back as 1999[x], we started seeing papers that were saying, "There are many peptides of gluten that the immune system reacts to in wheat." And as Dr. Vojdani said in the Gluten Summit, "Similar to the premise that we all have a unique fingerprint, we all have a unique immune print. Our immune response is different. And when you look at multiple peptides of gluten proteins in wheat, you see that some people react to a bunch of them. Some people react to one. Some people react to a different one. Some people react to most of them. They're all different. So if we're only checking one of the peptides of the poorly-digested gluten proteins of wheat – gliadin, we're not checking gluten; we're checking gliadin, which is just one component of the family of peptides that make up the term, 'the gluten proteins in wheat'." Does that make sense?

Michelle Ross: Yes, and you have a great slide in your presentations that talks about that. It really gives a wonderful visual of how easy it would be to miss a large number of people when you're only testing for one peptide.

Dr. O'Bryan: Yes, and that slide is in the general public education PowerPoint presentation that we give to all of our CGPs.

Michelle Ross: Excellent! Okay, so we do anti-gliadin antibodies typically in western medicine. What would be another test that is one of the standard tests for celiac disease?

Dr. O'Bryan: Well, the standard test for celiac disease, the accepted norm in celiac disease, is looking at transglutaminase antibodies [IgA transglutaminase antibodies], and that's Transglutaminase 2. There are nine different transglutaminases and it's Transglutaminase 2, that's in the intestines. It also covers the

organs, the livers, the kidneys, the heart, the spleen. But it's the one that covers the microvilli in the intestines.

This test is considered the diagnostic marker for celiac disease. And many, many papers have shown it to be sensitive and specific if there is total villous atrophy. And here's the reason for that, why there's a problem with that test. That, when doctors read the papers from the laboratories that the sales representatives bring out to show you, it shows transglutaminase ninety-seven percent sensitive to identify celiac disease; ninety-nine percent sensitive, ninety-eight percent sensitive, one-hundred percent sensitive.

The problem is that the researchers use celiac patients in these studies, and to qualify as a celiac patient, you have total villous atrophy. That's when a person receives the diagnosis of celiac disease-total villous atrophy. There are no patients' blood in these studies that have partial villous atrophy[xi]. Or crypt hyperplasia. To receive a diagnosis of celiac disease, traditionally total villous atrophy is required. You've had an endoscopy and your microvilli are worn down completely, and you have total villous atrophy. So when you have total villous atrophy, the transglutaminase blood test is going to be accurate 9.5 to 9.9 out of 10 times. It's going to be accurate right on the money.

Other papers have shown that when you have partial villous atrophy or just Marsh II, which is crypt hyperplasia, and not much villous atrophy yet; that the transglutaminase test can be accurate twenty-seven to thirty-three percent of the time meaning that it's wrong with false negatives, almost seven out of ten times. So once again, if you have total villous atrophy, it's right on the money. It's very accurate, very sensitive. The test comes back positive, you've got a problem. But if you have partial villous atrophy, the test may come back negative, and you have a problem. But you won't see it in that blood test because it's only sensitive at total villous atrophy.

Michelle Ross: And not all of us want to wait until our patient or client is in the late stage of an auto immune disease.

Dr. O'Bryan: Oh, that's really a good point. Very good point!

Michelle Ross: Okay, so we have anti-gliadin and transglutaminase 2. What else is on a standard test?

Dr. O'Bryan: Good. Well, let's see. Anti-gliadin antibodies will not differentiate between a celiac disease patient and a non-celiac gluten sensitivity patient. For example, in the *Journal of Clinical Gastroenterology* in 2012[xii], they showed that celiac patients will be positive for IgG anti-gliadin antibodies 81.2 percent of the time. So eight out of ten times a celiac will be positive for this peptide of the gluten protein of wheat, anti-gliadin.

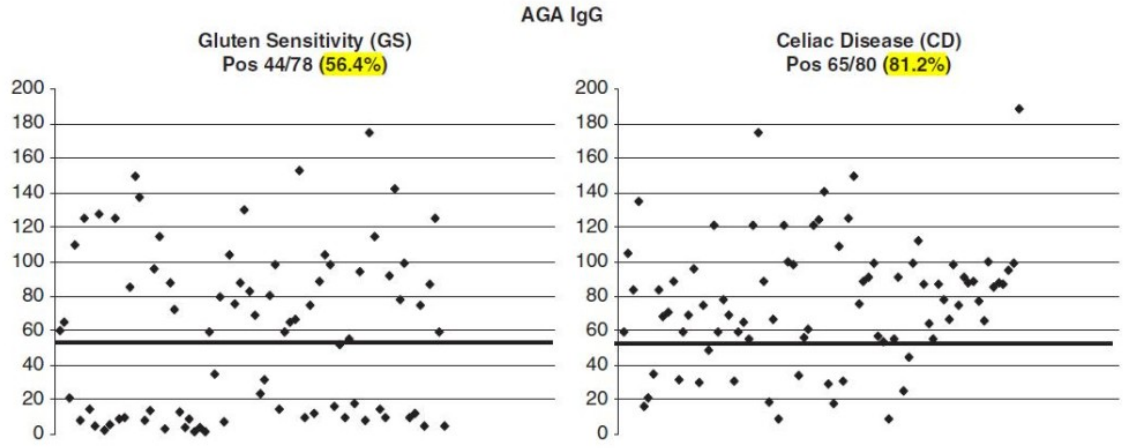


FIGURE 1. ELISA activities of AGA IgG in gluten sensitivity and CD patients. Cut-off level ≤ 50 AU. AGA indicates antigliadin antibodies; AU, arbitrary units; CD, celiac disease; ELISA, enzyme-linked immunosorbent assay; GS, gluten sensitivity; IgG, immunoglobulin G.

However, non-celiac gluten sensitivity patients will be positive for the same antibody 56.4 percent of the time. So when it comes back positive, you don't know if it's celiac or non-celiac gluten sensitivity. What you do know is this is a good marker for a gluten related disorder. If you come back positive with antibodies to gliadin [anti-gliadin antibodies], you've got a gluten related disorder. "What type?" "Well, I don't know, yet! Let's look further." But we at least confirmed, you've got a gluten related disorder. That's very important!

Michelle Ross: And if it comes back negative?

Dr. O'Bryan: If it comes back negative, it's not as likely that your immune system is reacting to gliadin. But once again, it's only the Navy. The Air Force might come out and that would be IgA, so it's possible to have a different response. For example, IgA for anti-gliadin antibodies is a good marker for celiac disease because if you have non-celiac gluten sensitivity, the IgA for anti-gliadin antibodies will be positive 7.7 percent of the time; not very often, less than one out of ten times.

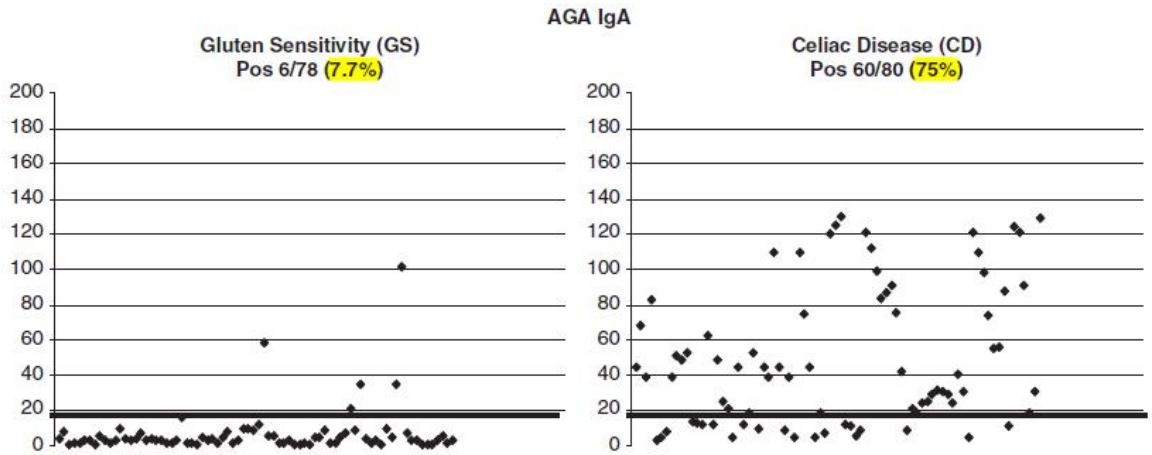


FIGURE 2. ELISA activities of AGA IgA in gluten sensitivity and CD patients. Cut-off level ≤15 AU. AGA indicates antigliadin antibodies; AU, arbitrary units; CD, celiac disease; ELISA, enzyme-linked immunosorbent assay; GS, gluten sensitivity; IgA, immunoglobulin A.

Michelle Ross: Right.

Dr. O'Bryan: But if you have celiac disease, the IgA [anti-gliadin antibodies] comes back positive seventy-five percent of the time. So if you've got IgA [anti-gliadin antibodies], 7.5 out of 10 times, that's celiac. It's not going to be non-celiac gluten sensitivity. If it comes back negative, you don't know if there's something going on or not because that's only one branch. But if it comes back positive, it's a good marker to differentiate between celiac and non-celiac gluten sensitivity.

A better marker to differentiate between the two is deamidated gliadins. Now, deamidated gliadins, [the process of deamidating the gliadin molecule], what has to occur is that molecule has to go from the lumen of the intestines through a permeable intestine, into the submucosa where the immune system deamidates it. It breaks it apart a little bit. Your body makes antibodies to that molecule. If you have antibodies to deamidated gliadin, 1.3 percent of those people are non-celiac gluten sensitive [almost none of them]. But if it comes back positive, 88.7 percent of those people are positive for celiac disease. They've got celiac disease. So it's a really good biomarker. If it comes back positive, not only to differentiate between celiac and non-celiac gluten sensitivity, but it strongly heads over to celiac disease.

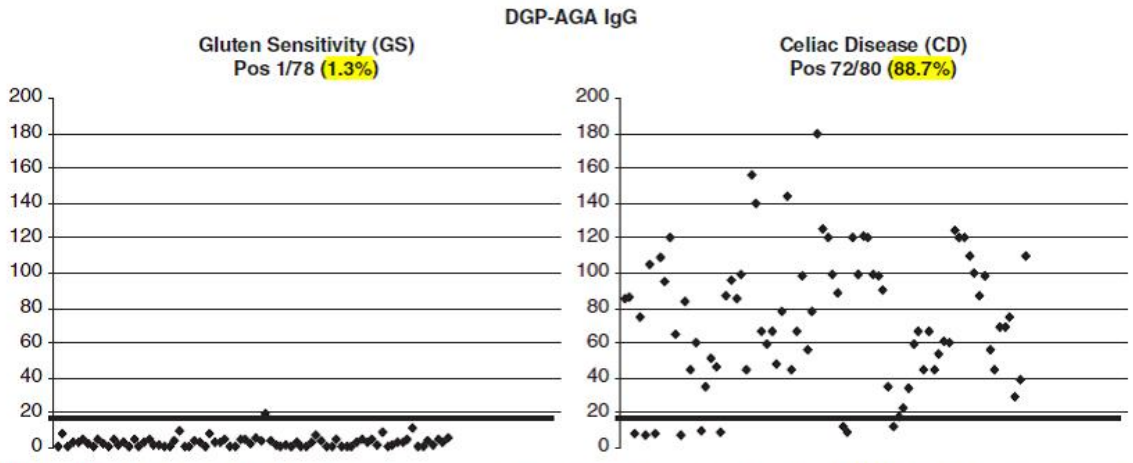


FIGURE 3. ELISA activities of DGP-AGA IgG in gluten sensitivity and CD patients. Cut-off level ≤16 AU. AU indicates arbitrary units; CD, celiac disease; DGP-AGA, deamidated gliadin peptide antibodies; ELISA, enzyme-linked immunosorbent assay; GS, gluten sensitivity; IgG, immunoglobulin G.

Michelle Ross: But are these Marsh III late stage celiac patients?

Dr. O'Bryan: That is correct. In the study that was published in the *Journal of Clinical Gastroenterology*, they were Marsh III. So if you're positive, IgG [deamidated gliadins] that person is on the celiac spectrum – somewhere on the spectrum.

Transglutaminase [IgA for transglutaminase] comes back positive for non-celiac gluten sensitivity zero percent of the time. It comes back positive for celiac disease 98.7 percent of the time. That's why transglutaminase is a really good marker for celiac disease. Once again, but only sensitive with total villous atrophy. So if transglutaminase comes back negative, it doesn't mean you don't have celiac disease because you may have Marsh II or Marsh I, the earlier stages. But in Celiac Disease (Total Villous Atrophy), it will come back positive 98.7 percent of the time. Now, in this most recent study, you've got celiac disease. So with the standard tests that are out there, I know that this is a little confusing, and I'm hoping that you'll go back and listen to this section a couple of times and take some notes.

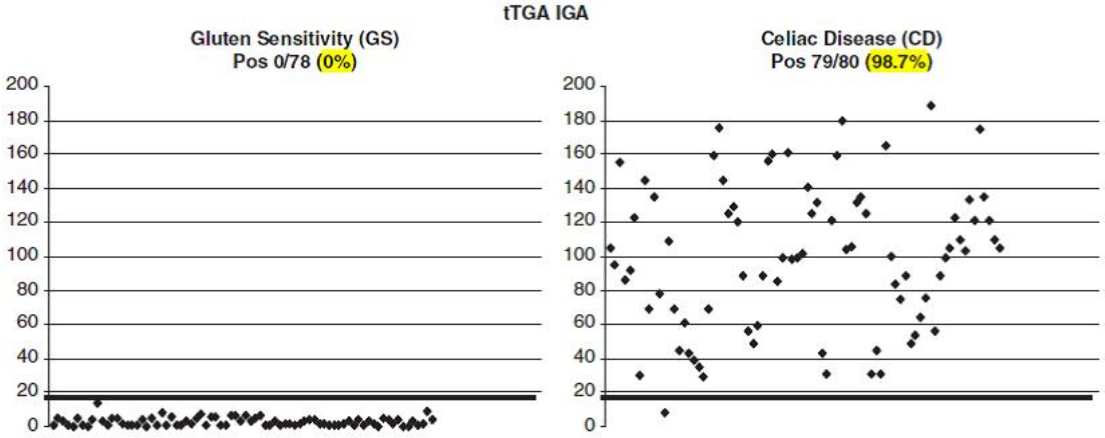


FIGURE 4. ELISA activities of tTGA IgA in gluten sensitivity and CD patients. Cut-off level ≤16 AU. AU indicates arbitrary units; CD, celiac disease; ELISA, enzyme-linked immunosorbent assay; GS, gluten sensitivity; IgA, immunoglobulin A; tTGA, tissue transglutaminase antibodies.

The summary is gluten related disorders — anti-gliadin antibodies. It doesn't matter if it's IgA or IgG. It's a gluten related disorder. You can differentiate between celiac and non-celiac gluten sensitivity with

deamidated anti-gliadin antibodies. With anti-gliadin antibodies think about what is IgA? It's produced to protect epithelial surfaces, right, epithelial surfaces? And that's what causes villous atrophy is that the epithelium becomes inflamed and being attacked and starting to wear down. So if anti-gliadin antibodies come back positive IgA, it suggests somewhere on the celiac spectrum. If it comes back positive IgG, it's a gluten related disorder. You don't know what type. It might be celiac, it might not be.

Transglutaminase. Transglutaminase comes back positive – celiac. But remember from the Training, there are at least six causes of elevated transglutaminase 2 antibodies. Celiac is the most prevalent, but there are at least 6.

Deaminated gliadin? Deaminated gliadin comes back positive – celiac. Deamidation of gliadin has only been identified in the mechanism of development of celiac disease.

There are three tests that are directly associated with celiac. These are in the classic tests that can be done anywhere in the world. There are three. Transglutaminase, deaminated gliadins and IgA anti-gliadin antibodies. Those three are suggestive for celiac. IgG anti-gliadin antibodies – celiac or gluten related disorders. That's the best that we could do right now with the standard tests that can be done most anywhere in the world.

References

[i] Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Cartenì M, Casolaro V, A.Fasano Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol. 2010;152(1):75-80. doi: 10.1159/000260087. Epub 2009 Nov 24.*

[ii] Volta, Umberto Personal interview available at www.theglutensummit.com

[iii] Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C., The Oslo definitions for coeliac disease and related terms. *Gut. 2013 Jan;62(1):43-52.*

[iv] Vojdani A, Tarash I. Cross-reaction between gliadin and different food and tissue antigens. *Food Nutr Sci. 2013;4(1):20-32.*

[v] PerlmutterD, MD, FACN, ABIHM; Vojdani A, PhD, MSc, CLS, Differentiation between Celiac Disease, Nonceliac Gluten Sensitivity, and Their Overlapping with Crohn's Disease: A Case Series, *Case Reports in Immunology Volume 213, Article ID 248482, 9 pages*

[vi] Vojdani A, O'Bryan T, Green JA, et al. Immune response to dietary proteins, gliadin and cerebellar peptides in children with autism. *Nutr Neurosci. 2004;7(3):151-161.*

[vii] PerlmutterD, MD, FACN, ABIHM; Vojdani A, PhD, MSc, CLS, Association Between Headache and Sensitivities to Gluten and Dairy, *Integrative Medicine • Vol. 12, No. 2 • April 2013*

[viii] Van Heel DA, West J., Recent advances in coeliac disease. *Gut. 2006 Jul;55(7):1037-46*

[ix] Goddard CJ, Gillett HR., Complications of coeliac disease: are all patients at risk? *Postgrad Med J. 2006 Nov;82(973):705-12.*

[x] Van de Wal Y, Kooy YM, van Veelen P, Vader W, August SA, Drijfhout JW, Peña SA, Koning F., Glutenin is involved in the gluten-driven mucosal T cell response. *Eur J Immunol. 1999 Oct;29(10):3133-9.*

[xi] Tursi, A., Can histological damage influence the severity of coeliac disease?: An unanswered question *Digestive and Liver Disease*, *Volume 39, Issue 1*, *January 2007*, *Pages 30-32*

[xii] Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, Fiorini E, Caio G., Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol. 2012 Sep;46(8):680-5*