A Grain of Truth: The Gluten Summit
Presenter: Dr. Umberto Volta, MD

The Reality of Non-Celiac Gluten Sensitivity and Its Many Manifestations

Dr. O'Bryan: Hello, everyone! Welcome to another edition of A Grain of Truth: The Gluten eSummit. And, it is my distinct privilege to be interviewing today a world leader in the field of celiac disease--and especially in this newer field of non-celiac gluten sensitivity--Dr. Umberto Volta. Dr. Volta holds degrees in cardiology and in internal medicine, as well as specialist diplomas in cardiology and vascular disease, and in internal medicine from the University of Bologna in Italy.

From 1986 to 2010 he served as Adjunct Professor of Diagnostic Immunopathology in the Postgraduate School of Internal Medicine at the University of Bologna, at which he is currently Adjunct Professor of Internal Medicine. He is a member of the Ethics Committee of the University Hospital of Bologna. It is the Ethics Committees that will review applications for research.

From 2009 until 2011 he was Project Coordinator for the European Commission's Celiac Disease MEDICS Project, which stands for Celiac Disease Management, Monitoring, and Diagnosis. In 2012 he was chairman of the International Conference on Celiac Disease, entitled Mastering the Celiac Condition: From Medicine to Social Sciences and Food Technology, which was held in Florence, Italy. Today, Dr. Volta is the director of the Celiac Disease and Malabsorption Syndrome Center at Saint Orsola-Malpighi Hospital in Bologna. He is president of the National Scientific Committee of the Italian Celiac Association. And, there's more. But, the last important thing is that he has authored over 450 scientific publications. And, he is a peer reviewer for the journal *Internal Medicine,* and *Gastroenterology.*

Dr. Volta, thank you very much for joining us today! It is a real honor to speak with you, sir.

So, to begin with, can you tell us what got your interest in celiac disease and gluten sensitivity?

Dr. Volta: Yes. My interest started many, many years ago in the seventies, I can say. When I was a student in medicine at the University of Bologna, in my immunological laboratory **[2:30]** at the University of Bologna I started to study the immunology of celiac disease. This happened because my director at the time was an immunologist. And, he

transmitted me this important feeling for research. So, I started to study celiac disease in the lab, in the immunological laboratories. And, at times, we identified immunological markers. The first marker we described in our lab was, properly, the anti-gliadin antibody many, many years ago.

Dr. O'Bryan: And you were one of the first to ever identify this marker.

Dr. Volta: Yes, because until 1973 or 1974, we had only glutenin antibodies, but not anti-gliadin antibodies. And we set up an ELISA method, a homemade method--it was the first homemade method in ELISA--for identifying antibodies to gliadin of the IgG and IgA class.

Dr. O'Bryan: So, for our listening audience, this is the man who helped to form the test that still is used as the primary test looking for an immune reaction to the peptides of gluten. So, we're still using that test today. Now, it's only a component today of a full program. But, we're still using it forty years later.

Dr. Volta: Yes. And, later my interest in celiac disease developed from a clinical point of view in our outpatient clinic in Sant'Orsola-Malpighi Hospital. We tried to follow a lot of patients with celiac disease. We diagnosed a lot of patients with celiac disease. And, currently in our outpatient clinic, we are following about 2,000 patients with celiac disease.

In the last five years, our interest in a new condition named non-celiac gluten sensitivity developed. And, this interest started [because of] the occurrence of **[5:00]** a lot of patients complaining of symptoms after gluten ingestions without being celiacs or allergic to wheat.

Dr. O'Bryan: So, these were patients who had been checked for celiac disease. And, they had been checked for a wheat allergy, which our listeners, remember, that is when you use a pin prick test on the skin. That's what an allergy is, an IgE test. And, they did not have an allergy. They did not have celiac disease. But, they were feeling better when they would stop eating gluten.

Dr. Volta: Perfect. Perfect definition. We need to exclude celiac disease and wheat allergies in these patients.

Dr. O'Bryan: Yes, of course.

Dr. Volta: And, the exclusion of celiac disease implies perform[ing] serological tests for celiac disease, actually are tissue transglutaminase antibodies and anti-endomysial antibodies. The negativity for these tests, in our opinion, must be completed by including a biopsy, because we know that celiac disease can onset also without the

positivity of serological tests, in rare cases, really. But two or three percent of patients with celiac disease are serologically negative for these antibodies.

Dr. O'Bryan: So, what you're saying is that even if a patient has negative transglutaminase or negative endomysium blood tests, and if they have symptoms where the clinician suspects this may be celiac disease, in your clinic, your concern is, and you consider, doing an endoscopy to rule out celiac disease.

Dr. Volta: Yes. And now we are a university center, so we need to exclude with certainty the diagnosis of celiac disease. So in the majority of cases--not in all cases, really--but, in the majority of cases, our flow chart is to exclude celiac disease also by doing a biopsy.

As for wheat allergy, we used to perform the Ig-specific test to gluten or to wheat. And, sometimes a skin prick test to exclude by this method the presence of wheat allergy. **[7:30]** And, coming back to tissue transglutaminase antibodies, I forgot to mention that I was the first, together with Professor Schuppan to set up this testing in 1997. This test is very important because tissue transglutaminase is the antigen present in the human body against which the immune system reacts, promotes a reaction.

Dr. O'Bryan: So, for our listening audience, what professor just said is that tissue transglutaminase is the tissue, the part of the human body, that we make antibodies to in celiac disease. And, this is the man who co-created the test back in 1997. This is also the man who co-created the anti-gliadin antibody test back in the seventies. So, I'll say once again, it's an honor to be sitting here talking to you...

Dr. Volta: Thank you very much.

Dr. O'Bryan: ...which means, ladies and gentlemen, we're talking to a visionary, someone who is not afraid to be in the front of the pack leading the way, with over 400 publications, which means all of the research--he's done so much research--so that what he says, we can count on as having good validation behind it.

Dr. Volta: Yes. And this research was published in *Nature*, a very important American medical newspaper. And so talking about non-celiac gluten sensitivity, our interest increased in 2007 and 2008 because we started to meet in our outpatient clinic a lot of patients with the symptoms without having celiac disease and wheat allergy. So the definition of non-celiac gluten sensitivity is currently that of a new gluten-related syndrome characterized by gastrointestinal and extraintestinal symptoms occurring in a few hours or days after gluten ingestion with disappearance very **[10:00]** quickly after gluten exclusion and recurring after a gluten challenge.

Dr. O'Bryan: So very quickly, might that be within a few days?

Dr. Volta: Yes, maybe. Sometimes in a few hours, in six hours, not minutes. Not in minutes, ten minutes, five minutes, like can happen for a wheat allergy. In a wheat allergy, we have a very quick reaction. The symptoms usually appear when the people ingest the gluten in six hours or in one day, two days, usually. And they disappear in a few hours or days after gluten exclusion.

Dr. O'Bryan: In our clinical experience, what we see here is that many people who do not have celiac disease, when they have gluten, it affects their brain. And they have brain fog. They can't think clearly. That seems very common.
Would that be one of the symptoms that someone might have with non-celiac gluten sensitivity?

Dr. Volta: It's a symptom of non-celiac gluten sensitivity, the symptom, in my opinion, more important in non-celiac gluten sensitivity than in celiac disease. Some people with celiac disease complain of this symptom, really, of this loss of concentration, difficulty in thoughts, to [concentrate], yes. But in any case, in non-celiac gluten sensitivity, this presentation is very, very common.

Dr. O'Bryan: Excuse me. May I just ask--because you said, "more important in non-celiac"--might you mean more prevalent in non-celiac gluten sensitivity than in celiac disease?

Dr. Volta: Yes.

Dr. O'Bryan: So if someone is having the brain fog symptoms or difficulty in thinking, it more likely may suggest NCGS as opposed to celiac disease?

Dr. Volta: Yes, in my opinion, yes. In my opinion, yes.

Dr. O'Bryan: Mine, also.

Dr. Volta: We used to find this symptom in about 35% of patients with non-celiac gluten sensitivity. Probably in celiac disease, this presentation occurs in about 5% or 10% of cases.

Dr. O'Bryan: And, you've published on that.

Dr. Volta: We published this data in the *Journal of Clinical Gastroenterology* in 2010.

Dr. O'Bryan: I read that **[12:30]** paper. And, I said, "I like that man!" [Laughs]

Dr. Volta: [Laughs] But the clinical epidemiology, the prevalence, of non-celiac gluten sensitivity is still undefined. In the United States, this prevalence is a large variable. In primary care, there is a study published by Professor Peter Green working at Columbia University in New York. And, the paper was published the *Scandinavian Journal of Gastroenterology* this year.

And, in this paper, the prevalence of non-celiac gluten sensitivity was assessed as 0.6% in the general population. But, in tertiary care in the United States at Maryland University, the prevalence of non-celiac gluten sensitivity resulted to be 6% in the general population. So, probably there is a bias. In medical terms, bias means there is a different interest of patients that come in consulting or in contacting the tertiary care instead of primary care, as you can see.

Dr. O'Bryan: And, we have some papers now that have shown that with particular conditions, such as with irritable bowel syndrome, the prevalence of non-celiac gluten sensitivity may be much higher.

Dr. Volta: Yes. In irritable bowel syndrome, the prevalence of non-celiac gluten sensitivity ranges from 28% to 30%. There are two studies, two double-blind placebo-controlled studies. I mean, two studies in people who were treated by gluten or by a placebo without knowing the kind of substance.

Dr. O'Bryan: Which one they were taking they didn't know.

Dr. Volta: Yes. So, the prevalence of non-celiac gluten sensitivity and irritable bowel syndrome ranges from 28% to 30%. So, taken together, this data seems to suggest the prevalence of irritable bowel syndrome in the general population ranges from 16% to 25%. If we took together this data, we can hypothesize that the prevalence of non-celiac gluten sensitivity is very high, **[15:00]** closer to 6% or more than to 0.6% in primary care.

In our Celiac Disease Center at the University of Bologna, in the last two years, the number of new diagnoses of non-celiac gluten sensitivity was exactly the double of the diagnoses of celiac disease.

Dr. O'Bryan: And, these are people who were sent to you after seeing their doctor and sent to the specialty clinics?

Dr. Volta: This was in the specialist clinic, yes. And, another interesting characteristic of this syndrome is that the median age of this patient is higher than the mean age observed in celiac disease. And so the mean age of patients with non-celiac gluten

sensitivity is about 45 years, in comparison with 35 years in the group of celiac disease patients in our institute.

Dr. O'Bryan: Why do you think that may be?

Dr. Volta: It is a very interesting question because the onset of non-celiac gluten sensitivity is sometimes at a certain moment of the life. This patient did not complain in the past of these symptoms. And, they start to suffer, to complain, of these symptoms at a certain point of their life. This condition is very rare in infancy, in children, and is much more common in young adults or in older adults. And, probably, it's more common after the age of 40, 45, or 50.

Dr. O'Bryan: Do we think that in non-celiac gluten sensitivity that the adults have crossed a threshold somehow, and that their bodies no longer can comfortably deal with the consumption of gluten?

Dr. Volta: It's difficult to say because sometimes my impression **[17:30]** is there is a loss of tolerance to gluten in some way.

Dr. O'Bryan: We've spoken about that with some of other guests, about the loss of oral tolerance. So, when you lose tolerance, that means that it's the straw that broke the camel's back. And, for some reason we've crossed over, and we no longer can handle what our bodies were able to suppress in the past.

Dr. Volta: Yes. And, the other interesting point is there is a higher prevalence of female gender versus male gender in non-celiac gluten sensitivity versus celiac disease. In non-celiac gluten sensitivity, the ratio between females and males is 4:1 or 5:1. In celiac disease usually the ratio of females to males is 2:1 or 2.5:1. So, it's another interesting point.

Dr. O'Bryan: So, it's almost double in non-celiac gluten sensitivity, whereas females more often will suffer from this than males.

Dr. Volta: I prefer to talk about the pathogenesis, the causes, of this condition. The pathogenesis is this is an immune disorder, but only with the involvement of innate immunity. Innate immunity is the first phase of the immune response in our body. So, when gluten arrives at the small intestinal level there is a first reaction, probably involving the immune system in the first phase, without the reaction against the autoantigen of celiac disease.

Dr. O'Bryan: So, what that means, for our listening audience, is that it's not an autoimmune condition where the immune system is attacking itself, but rather the earlier form of the immune system where it causes inflammation. It's kind of like firing chemical

bullets. They're called cytokines. And, we're trying to address whatever this toxin is that's coming in.

Dr. Volta: Yes. This inflammation is very important because in the small intestinal mucosa of patients with non-celiac gluten sensitivity, **[20:00]** we have an increase of intraepithelial lymphocytes, a mild increase in comparison with celiac disease. The normal number of intraepithelial lymphocytes in the small intestinal mucosa usually is under 25%. And, in this condition, the number, in non-celiac gluten sensitivity, of lymphocytes usually ranges from 25 to 40. And, in celiac disease, it's higher to 40%.

Dr. O'Bryan: For our listening audience, the intraepithelial lymphocytes are the soldiers that are standing guard just inside the lining of the intestines. So, any food that's coming through, if it's trying to get into the body, get in through the walls into the bloodstream, these are the soldiers that are first there to try to protect you. They're called IELs or intraepithelial lymphocytes. So, when you have more soldiers, the body is trying to protect you. There's a reason it's trying to protect you.

Dr. Volta: Another typical feature of this condition is the abnormality of the permeability. The first study on this condition demonstrated a reduced permeability of small intestinal mucosa in non-celiac gluten sensitivity. But, more recently, a recent study has shown that intestinal permeability is probably increased in non-celiac gluten sensitivity like in celiac disease, in the same way. And, this increased permeability favors the passage across the intestinal mucosa by antigens. So, in some way, it causes inflammation in the small intestinal mucosa.

Another interesting point is related to the synthesis of anti-glidain antibodies. Anti-gliadin antibodies probably suggest that adaptive immunity can be involved in this condition because anti-gliadin antibodies are autoantibodies--so, are antibodies produced by the immune system against a food antigen--but imply a **[22:30]** reaction of our immune system.

The clinical presentation of non-celiac gluten sensitivity is variable because in some patients there is a prevalence of gastrointestinal symptoms, and in others of extraintestinal symptoms. Gastrointestinal symptoms can vary from symptoms of the upper part of the stomach or esophagus. I mean, with gastroesophageal reflux, pyrosis, or another condition may be pain in the stomach. But, in the majority of cases, these are most frequent symptoms. We have bloating, abdominal pain. And, the bowel habits are a variable tool because in about 50% of patients, we have diarrhea. But, in 25% of patients, we have constipation. And, 25% of patients have sometimes alternate bowel habits. So, this group of patients probably can have IBS, irritable bowel syndrome.

Dr. O'Bryan: Yes. So, these patients who are having abdominal symptoms, 25% of them may have constipation. 50% of them may have diarrhea. And, the other 25% may alternate back and forth. And, that's for those that have abdominal symptoms, which is only one component as we are about to talk about how it can manifest outside the intestines. But in the intestines it could be loose bowels, limited bowel movements, or a combination of both.

Dr. Volta: Yes. And, as for extraintestinal symptoms there are several really because the most frequent extraintestinal symptoms are general symptoms: fatigue, present in about 75% of our patients, and headache in 55% of cases. **[25:00]** We have also arthralgia or myalgia in about 40% of cases. And foggy mind. Foggy mind is the symptom we spoke of before. And it's characterized by a loss of concentration, difficulty thinking, and so on. And other symptoms are skin rashes, dermatitis. And, this is very particularly interesting because some symptoms are very similar to those present in celiac disease. And, I mean, iron deficiency anemia, for example, or folate anemia--folic acid deficiency anemia--or, also, aphthous stomatitis, aphthous stomatitis is a typical sign of celiac disease.

Dr. O'Bryan: Those are mouth ulcers.

Dr. Volta: Yes, ulcers. And, this symptom is present in about 20% to 25% of our patients. It's much more frequent in celiac disease than in non-celiac gluten sensitivity.

Dr. O'Bryan: So, the 20% to 25% with aphthous stomatitis, is that celiacs or NCGS?

Dr. Volta: NCGS. And, in celiac disease, in our experience, it's about 40%.

Dr. O'Bryan: What about osteopenia and osteoporosis?

Dr. Volta: Osteopenia is a problem. Not all of these patients usually perform a bone densitometry. I suggest to perform it. In our center, we have started with this program, with the complete program. And, in people performing bone densitometry, people who we suspect or people with the diagnosis of non-celiac gluten sensitivity, used to find this bone disorder in about 40% of cases.

Dr. O'Bryan: My goodness. So, we're looking at a malabsorption syndrome with NCGS that may be just as significant as in celiac disease.

Dr. Volta: Yes. And, also, the laboratory abnormalities. If we test this patient, we perform in this patient the determination of ferritin, folic acid, vitamin D, vitamin B12, **[27:30]** we can find abnormalities. The most frequent probably is represented by low levels of vitamin D. It usually is associated with osteopenia in these patients. So we

used to treat these patients with supplements of vitamin D, usually very frequently. For the levels of calcium, usually they are normal. But, another problem when there is osteopenia, these patients usually do not tolerate treatment with calcium.

Dr. O'Bryan: They will have some reaction when they take calcium tablets?

Dr. Volta: Yes. Some reaction in the small intestines, so it's difficult to treat them with calcium. And the other symptoms present in these patients are related to associated disorders. The most frequent associated disorder is presented by IBS. Irritable bowel syndrome is present in about 50% of non-celiac gluten sensitive patients. But, it's very interesting because we can find in these patients other food intolerances. And, the most frequent is lactose intolerance, in about 40% of cases. And with a lower prevalence also, a nickel allergy or sometimes fructose allergy. And we can have the confirmation of this diagnosis by a fructose breath test or a lactose breath test.

Dr. O'Bryan: And, do you check for antibodies to nickel? Or, do you look for total levels of nickel?

Dr. Volta: Patch test. The patch test is the best test to confirm the diagnosis. And, this is an important point because when we talk about treatment of these patients, as you know, the consumption of large amounts of corn can increase the sensitivity to nickel. It can give problems for these patients.

Dr. O'Bryan: What is the mechanism behind that?

Dr. Volta: It is unknown, really. But, in some way there is a close association **[30:00]** between non-celiac gluten sensitivity and allergy to nickel.

Dr. O'Bryan: So, if someone has an allergy to nickel--and, this is new information for me, I'm very excited to hear this, thank you for sharing it--if someone has an allergy to nickel, how might that manifest? What might be the clinical picture?

Dr. Volta: First with dermatitis, a skin rash, but also with abdominal pain. Abdominal pain in some of these patients who were already on a gluten-free diet, can have the recurrence of abdominal symptoms, not only skin symptoms, due to a nickel allergy confirmed by the examination. It's very interesting.

And, for the other associated disorders, different from the past, from two or three years ago, we now realize that these patients can have an association with autoimmune disorders such as autoimmune thyroiditis. And, also, in some cases, autoimmune gastritis. And, among other presentations, alopecia.

Dr. O'Bryan: So, with the autoimmune gastritis, would that be parietal cell antibodies?

Dr. Volta: Yes, parietal cell antibodies, and, also, sometimes atrophy of the gastric mucosa detected by endoscopy and biopsy.

Dr. O'Bryan: Yes. And then we're looking at, perhaps, an ulcer that forms. So, we are looking at non-celiac gluten sensitivity, which may be contributing to autoimmune conditions.

Dr. Volta: This is very important. Another characteristic of this condition from a clinical point of view is that this condition is very frequent in first-degree relatives of celiac patents. When we diagnose, usually, a patient with non-celiac gluten sensitivity, we suggest to perform the screen for celiac disease in all the first-degree relatives of these patients. **[32:30]** And, sometimes we can find a new celiac disease. It happens very frequently now in our experience in our center in Bologna.

Dr. O'Bryan: That's very important for those that are diagnosed as celiac, that the family has to be checked. If it's a child that's diagnosed, the parents have to be checked. If it's the parent that's diagnosed, the child has to be checked. It's very important.

Dr. Volta: I used to say that non-celiac gluten sensitivity and celiac disease are like two sisters. The oldest is celiac disease, and the youngest is, obviously, non-celiac gluten sensitivity.

Dr. O'Bryan: [Laughs] That's very good.

Dr. Volta: And, for the biomarkers of this condition, unfortunately, we have no specific biomarkers currently different from celiac disease. In celiac disease, we have tissue transglutaminase antibodies, endomysial antibodies, the very sensitive biomarkers, specific biomarkers. And, with this condition we try to identify cytokines secreted by peripheral blood mononuclear cells, put in contact with gluten or other cereals or old cereals like kamut. And, in these patients with non-celiac gluten sensitivity, we were unable to identify a specific cytokine produced by peripheral blood mononuclear cells.

As for genetic markers, there is no correlation between non-celiac gluten sensitivity and the genetic markers of celiac disease, HLA-DQ2 or DQ8. HLA-DQ2 or DQ8 are positive in about 45% or 50% of non-celiac gluten sensitive patients, versus 30% in the general population. So, it's not a significant statistic.

Dr. O'Bryan: So, what we have always referred to as "the celiac genes" are not necessarily just the celiac genes. If people with NCGS, 45% to 50% of them have the

gene, **[35:00]** but about 30% of the general population has the gene, it's not that strong a correlation. But, with celiac disease, it's 93%--depending on the study--95%. We saw studies this week here at our conference.

Dr. Volta: It's a very, very different situation. For antibodies, no antibody resulted to be closely related to non-celiac gluten sensitivity, but with a variable prevalence. Many groups have reported a fairly high prevalence of anti-gliadin antibodies of first generation in non-celiac gluten sensitivity. There are three groups who published data with an immune prevalence around 50% for anti-gliadin antibodies of the IgG class in non-celiac gluten sensitivity. My group published the study "Serological Screening" in the *Journal of Clinical Gastroenterology*, reporting a positivity of 56% of these antibodies in non-celiac gluten sensitivity in comparison with the positivity of 81% for anti-gliadin antibodies of IgG class in celiac disease.

Dr. O'Bryan: For our doctors who are listening in, why is it that the IgG anti-gliadin antibodies are more prevalent in non-celiac gluten sensitivity than the IgA?

Dr. Volta: Yes. This is a very good question because IgA anti-gliadin antibodies, although not highly sensitive for gluten-related disorders, are more specific for celiac disease than for non-celiac gluten sensitivity. When we started to study gluten-related disorders in the 1970s, we realized immediately that anti-gliadin antibodies of an IgA class were more specific for small intestinal damage than IgG antibodies. And, this opinion is confirmed by the present data because, usually, the prevalence **[37:30]** yolkmgy8jof anti-gliadin antibodies of IgA class in non-celiac gluten sensitivity is around five, six, or seven percent, no more.

Dr. O'Bryan: That's not that much.

Dr. Volta: Yes. And, in celiac disease patients, it's around 70% or 60%. So, it's high. Not so high as the tissue transglutaminase antibodies that are positive in 95% and 98% of cases, but not so low prevalence.

And another interesting feature from a serological point of view is a negativity of anti-gliadin antibodies of second generation deamidated anti-gliadin antibodies in non-celiac gluten sensitivity. In our experience, these antibodies are usually negative in these patients or can be found with the prevalence of two percent or three percent, no more, with a very low titer. And, why is this feature important? Because these antibodies--the anti-gliadin antibodies--explore a process that in vivo represents the reaction between gliadin and tissue transglutaminase. Tissue transglutaminase modifies the gliadin molecule, so creating a new antigen--an autoantigen--for celiac disease.

Dr. O'Bryan: So, for our listening audience, what that means is that the fragment protein of wheat, when we eat wheat, is gliadin. If we produce antibodies to gliadin, if it's

IgG, it's more likely a non-celiac gluten sensitivity. What is more accurate in using the gliadin antibodies to look for celiac disease if inside the body, the gliadin molecule, it gets transformed because it interacts with transglutaminase, and it becomes deamidated. At that point, it's much more specific to the development of celiac disease.

So, if you have an elevation of deamidated gliadin antibodies, the mechanism is much more likely to be the mechanism of celiac disease than it is for non-celiac gluten sensitivity. **[40:00]** And, if you have elevated antibodies to native gliadin, it could be celiac. But, a higher percentage of those IgG antibodies are to non-celiac gluten sensitivity.

That's important for our clinicians to know, and for our mothers of children who are really confused by the blood tests that are out there. Hopefully, if you rewind this and listen to it a couple of times, you'll write down some notes so that you've got it. And, you'll be able to look at your child's test result and understand what you're looking at.

Dr. Volta: Yes, yes. Of course. And, another typical immunological feature of this disorder is the complete negativity, as I told before, of anti-endomysial antibodies and anti-tissue transglutaminase antibodies. As for diagnosis, this diagnosis of non-celiac gluten sensitivity is usually suspected in the majority of cases by this same patient as the patient feels that the gluten is something toxic for his body, and in some way intends to avoid gluten. But, in about 40% of cases, the gastroenterologist in Italy suspects usually the existence of non-celiac gluten sensitivity. So, now there is an increasing awareness of this condition in our country.

Dr. O'Bryan: We can only hope that it comes here to the United States, also, where our gastroenterologists become more aware.

Dr. Volta: Yes. For the intestinal biopsy, as I told before, the small intestinal mucosa of this patient cannot be considered in our own mucosa because there are signals of inflammation in the small intestinal mucosa. And, this inflammation is responsible for the malabsorption of vitamin D or the other vitamins or iron deficiency or iron malabsorption.

Dr. O'Bryan: So, these are patients where the microvilli do not wear down. **[42:30]** There's no villous atrophy. But, they have inflammation in the intestines. And, because of that, they get malabsorption. So, for those that have had an endoscopy in the past and it came back negative, but they feel better on a gluten-free diet, you very likely may be non-celiac gluten sensitive.

Dr. Volta: Another clinical feature of this patient--usually, anyway--starts with a gluten-free diet. We'll talk in a minute about the treatment of these patients. But, when they

start with a gluten-free diet, usually, as they lose weight, they tend to lose weight differently from celiac disease patients.

In celiac disease there is small intestinal atrophy. And, small intestinal atrophies disappear after six or twelve months on a gluten-free diet. And, there is an improvement of absorption of nutrients. And so, as a result, there is an increase of weight in this patients. In patients with non-celiac gluten sensitivity, by avoiding gluten and cereals containing gluten, usually, there is a decrease of general weight.

Dr. O'Bryan: Now, that appears to be a dichotomy because if we have malabsorption with non-celiac gluten sensitivity, and malabsorption with celiac disease--

Dr. Volta: But, we have a different clinical response to a gluten-free diet.

Dr. O'Bryan: A different clinical response. So, could it be that with celiac disease with the villous atrophy, not only are they malabsorbing their nutrients, but they're malabsorbing their calories? They can't get the calories in. Whereas with NCGS, perhaps they're able to pull in the calories, but they're not getting the nutrients? Is that reasonable to assume?

Dr. Volta: Yes, maybe. Maybe it is. And, for the treatment of these patients...Before the treatment, perhaps it's better to talk about the only diagnostic test currently recognized as the proof for the existence of this condition is a double-blind placebo-controlled study. We are performing in **[45:00]** our university this study. And, we enrolled about 60 patients with non-celiac gluten sensitivity already on a gluten-free diet. And, we gave them pills containing gluten or rice in a quantity of four grams in a day. The mean quantity of the Mediterranean diet is about 12 or 20 grams of gluten in a day.

Dr. O'Bryan: Yes, so, it's a tiny amount.

Dr. Volta: A tiny amount, but enough to evoke symptoms. It's a cross-sectional study. So, the same patient ingests in a week the pills containing gluten. After another week without pills, there is a third week with the other kind of pills containing gluten or rice. So, it's a cross-sectional study.

And, in this way, we hope to demonstrate the real existence of this condition. Many studies have already confirmed the existence of non-celiac gluten sensitivity, many double-blind placebo-controlled studies. There is a study presented today at the International Celiac Disease Symposium in Chicago showing that gluten is not the only agent probably involved in this syndrome. But, there are other factors including fermentable oligo-, di-, mono-saccharides and polyols - FODMAP. These FODMAPs are substances present in milk and dairy products, legumes, onion and other foods, and

are particularly toxic for people suffering from irritable bowel syndrome. And probably, they can have a role also in non-celiac gluten sensitivity. But, I am sure that gluten has a role in these conditions, **[47:30]** the main role.

Dr. O'Bryan: Yes, yes.

Dr. Volta: In some patients, probably it's not the only agent. But, gluten concurs together with FODMAP to the appearance of symptoms. As for the treatment of this patent, we suggest usually start with a gluten-free diet. But, our suggestion is to follow a gluten-free diet first of all, by ingesting foods naturally free of gluten.

There is a reason. The reason is because commercial gluten-free products or foods that contain a lot of additives, preservatives, in some way can cause bloating, abdominal pain, and also the neurological disturbances, which we used to observe in non-celiac gluten sensitivity. So, if this patient eats many of these commercial gluten-free products, it can worsen their situation.

Dr. O'Bryan: So, if I'm hearing you correctly, what you've seen in your hospital setting and in your research center is that non-celiac gluten sensitive people who go on a gluten-free diet, some of them will be sensitive to the gluten-free commercial products. So, foods that are naturally gluten-free...

Dr. Volta: To the additives present in commercial gluten-free products.

Dr. O'Bryan: Yes, yes, the additives. So, you're recommending that we focus on eating naturally gluten-free food, which would be quality meats--

Dr. Volta: Rice, corn, vegetables, meat.

Dr. O'Bryan: --rice, corn, vegetables, good meats.

Dr. Volta: Eggs. We recommend to buy commercial pasta and bread without gluten because, in these kinds **[50:00]** of food, usually the amount of additives is very low. And, we suggest, also, to buy flours without gluten and to prepare with these flours, snacks, sweet or savory snacks, at home.

Dr. O'Bryan: So, just to be clear, for our audience, the recommendations that come from your center are gluten-free pastas are probably okay. Gluten-free flours to make your own birthday cake or your own breads are probably okay. But, when you're eating a volume, regular consumption of some of the prepared gluten-free products that have so many preservatives in them and stabilizers and other non-food ingredients, that may be a problem for the NCGS patients.

Dr. Volta: Yes, because these products must remain in a good condition for a lot of time. So, they include a lot of additives and other things.

Dr. O'Bryan: Yes, so the additives, the preservatives are because the shelf life has to be maintained.

Dr. Volta: And, as for drugs, usually in this patient, we used to prescribe or treat this patient by supplements of iron or vitamins. And, sometimes they need also minerals because usually they can have also low levels of magnesium, zinc, and other minerals.

Dr. O'Bryan: We recommend to all of our clinicians to do a nutrient evaluation. And, here in the U.S. there are some fairly inexpensive evaluations. They look at 20 or 25 different nutrients.

Dr. Volta: Another suggestion is to check the health or the general condition with well-defined examinations every 12 months, about. And, we prescribe a series of examinations to perform after a period of a gluten-free diet. **[52:30]**
But, usually, in our opinion, non-celiac gluten sensitivity needs a gluten-free diet for all the life, in our opinion. Our patients, recently, we performed a survey to check the status of alimentation of our patients on a gluten-free diet. And, after one year, about 95% were still on a gluten-free diet.

Dr. O'Bryan: Marvelous.

Dr. Volta: So, it's very difficult for these patients to reintroduce gluten. We don't know currently if non-celiac gluten sensitivity is a permanent condition or a transient condition. Celiac disease is a permanent condition. Wheat allergy can be a transient condition because it's typical of first infancy and tends to disappear at the age of 14 or within the age of 14 or 15 in about 60% of cases. And, non-celiac gluten sensitivity, probably, we don't know currently if it's a permanent or transient condition. In my opinion, patients with non-celiac gluten sensitivity cannot tolerate gluten and cannot reintroduce gluten in their alimentation.

Another important point is that of the small amounts of gluten for these patients represented by contamination in consuming food outside the home, probably, the majority of these patients do not tolerate small amounts of gluten presented by contamination. So, the situation is similar to those with celiac disease, probably not for the possibility of complications or major complications. But, because small amounts of gluten are able to cause the reappearance of symptoms.

Another important point is that of the possibility of a **[55:00]** major complication. In celiac disease, we know that in a small percentage of cases--about 1% or probably less

than 1%--a series of studies, also in the United States, a recent study, and also our studies in Italy promoted by the Celiac Disease Foundation, we are publishing this study. And, we demonstrated that only 0.7% of our celiacs can develop a lymphoma or ulcerative jejunitis or refractory celiac disease. And, these complications are quite unusual or they don't exist in non-celiac gluten sensitivity, luckily.

Dr. O'Bryan: Yes, that is very lucky. Very lucky for them.

Well, Dr. Volta, this has been just an education to sit at the feet of the master. And, I'm hoping that our audience will listen to this interview multiple times to pull out the so many pearls that you've given us.

Thank you very much for your time. We wish you much health and success in your future studies.

Dr. Volta: Thank you very much.

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