

What Does Your Doctor Really Think – Is it Gluten, Wheat Starch, Allergies, the Microbiome or Something Else?

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My Disclosures

- Co-author of “Celiac Disease for Dummies” - royalties
- Glutenostics – Advisory Board - ?
- Ferring, Inc. - Advisory Board - honorarium
- Celimmune - Site PI for a Clinical Trial with anti-IL-15 for Refractory Celiac Disease – research support for the trial

Issues for Consideration

- Update on celiac disease
- What is non-celiac gluten or wheat sensitivity?
- How about wheat allergies?
- Update on GI problems from wheat starch
- How to evaluate someone already on a GFD
- Differentiating and managing wheat-related disorders

Case 1 - A Food Intolerant Patient

- A 58 yr old woman with abdominal bloating and discomfort after eating various foods, abdominal cramping and loose stools ranging from 2 to 3 per day without blood for the past few years. Symptoms are relieved by passage of stool.
- She attended a San Diego Celiac Support Association meeting and comes to my clinic concerned that she has celiac disease.
- No family or personal history of allergic/atopic disorders or autoimmune disease.
- She went on a gluten free diet two months ago. She feels better but reports that she is allergic to onions and peppers since these cause bloating, pain and loose stools. She wants to know what she should eat and what not to eat.

What are my questions for this patient?

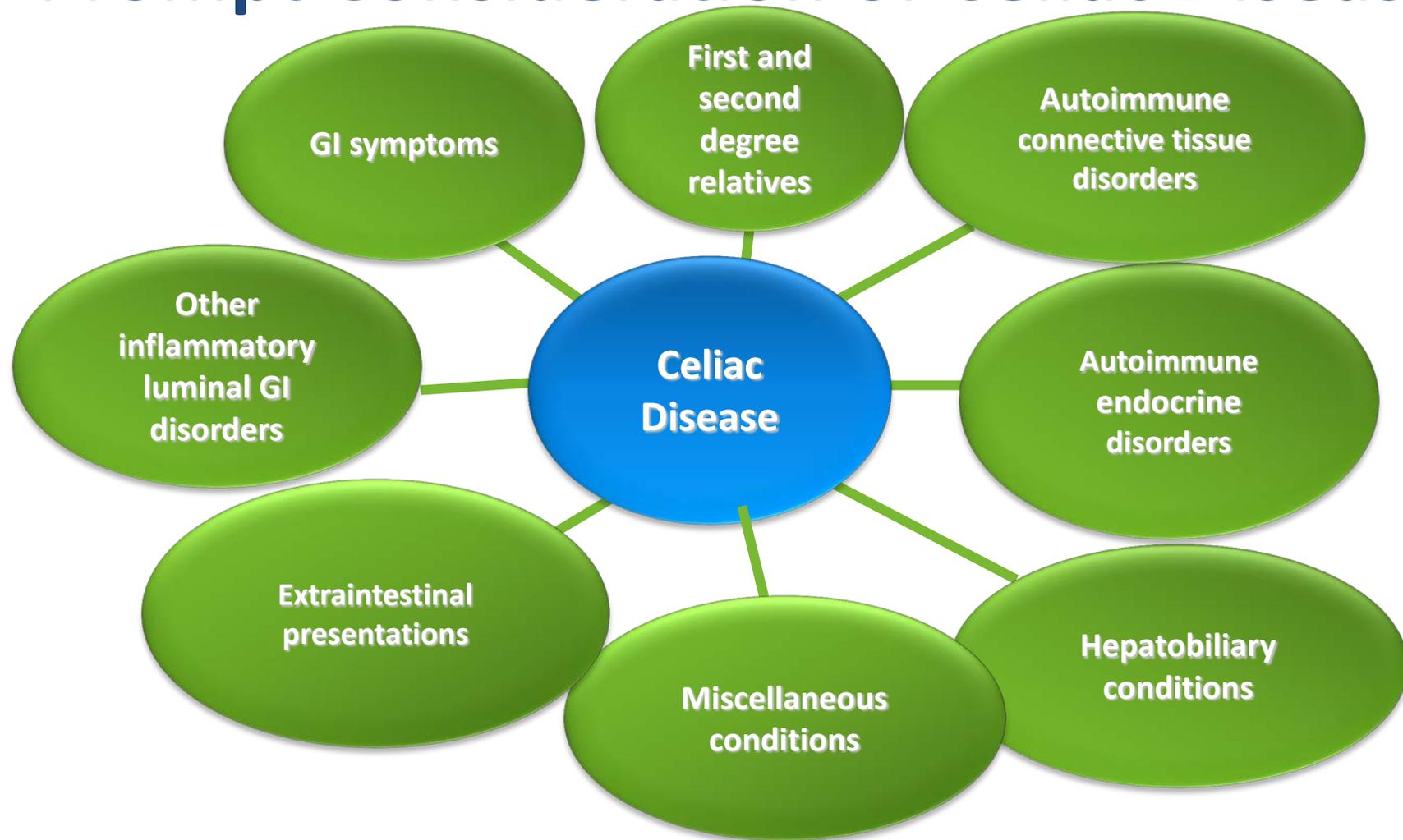
Forms of Adverse Reactions (ARF) to Wheat or Gluten: Clinical Features

Type of ARF	Wheat Allergy	Celiac Disease	Non-Celiac Gluten Sensitivity	Wheat Starch Intolerance
Immediacy of symptoms or dose	Immediate Varying dose	Delayed Varying dose effect	Varies Exquisite dose sensitivity	Varies, generally builds post-prandially
Neurological-psychological	No	Yes, varies	Yes, frequent	Not typically
Anemia Immune tests	No Yes – Wheat specific IgE	Yes Yes – TTG IgA, DGP IgA/G	No ? AGA IgG ? Wheat IgG	No No

Immunological Reactions to Wheat

- Food hypersensitivity (IgE-mediated)
 - GI food allergy – wheat allergy in childhood, rare in adults
- Celiac disease (T-cell mediated) - gluten
- Eosinophilic GI disorders (eosinophils)
 - EoE – wheat is a major factor

Symptoms and Conditions That Should Prompt Consideration of Celiac Disease



Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight, even super-obese
- **Seroprevalence M=F, diagnosis M<F (1: 2 - 3)**
- Other presentations are being increasingly recognized:
 - Reproductive problems
 - Neuropsychiatric manifestations
 - Related autoimmune conditions
 - Many others – true associations or chance?

2- Another Gluten Sensitive Case

- 25 year old male
- Healthy with some symptoms
- 2nd opinion consult for **gluten sensitivity**
- **Bloating & foggy mind** w/gluten for 3 years
- No family or personal history of atopy or autoimmune conditions
- Saw a naturopath purchased supplements and vitamins
- Started GFD after the following testing (paid out of pocket)



TEST

RESULT

Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity

	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
→ Wheat IgG		1.33		0.3-1.5
Wheat IgA	0.43			0.1-1.2
Wheat Germ Agglutinin IgG	0.64			0.4-1.3
Wheat Germ Agglutinin IgA	0.39			0.2-1.1
Native & Deamidated Gliadin 33 IgG	0.68			0.2-1.2
Native & Deamidated Gliadin 33 IgA	0.28			0.1-1.1
→ Alpha Gliadin 17-mer IgG		1.14		0.1-1.5
Alpha Gliadin 17-mer IgA	0.43			0.1-1.1
→ Gamma Gliadin 15-mer IgG			1.84	0.5-1.5
Gamma Gliadin 15-mer IgA	0.28			0.1-1.0
→ Omega Gliadin 17-mer IgG			1.43	0.3-1.2
Omega Gliadin 17-mer IgA	0.40			0.1-1.2
Glutenin 21-mer IgG	0.57			0.1-1.5
Glutenin 21-mer IgA	0.33			0.1-1.3
Gluteomorphin + Prodynorphin IgG	0.98			0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.26			0.1-1.2
Gliadin-Transglutaminase Complex IgG	0.59			0.3-1.4
Gliadin-Transglutaminase Complex IgA	0.48			0.2-1.5
→ Transglutaminase-2 IgG			1.61	0.3-1.6
Transglutaminase-2 IgA	0.58			0.1-1.6
Transglutaminase-3 IgG	0.59			0.2-1.6
Transglutaminase-3 IgA	0.26			0.1-1.5
Transglutaminase-6 IgG	0.78			0.2-1.5
Transglutaminase-6 IgA	0.62			0.1-1.5

Array 2 – Intestinal Antigenic Permeability Screen

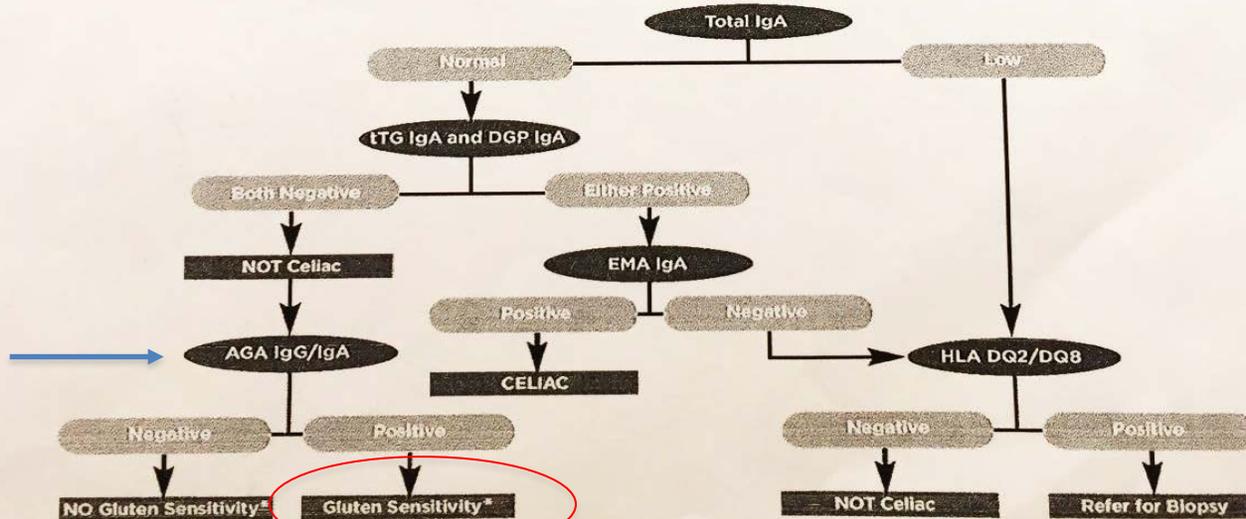
	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Actomyosin IgA **	7.43			0.0-20
Occludin/Zonulin IgG	0.33			0.2-1.5
Occludin/Zonulin IgA	0.22			0.1-1.8
Occludin/Zonulin IgM	1.11			0.1-2.1
Lipopolysaccharides (LPS) IgG	0.69			0.1-1.6
Lipopolysaccharides (LPS) IgA	0.13			0.1-1.8
Lipopolysaccharides (LPS) IgM	1.13			0.1-2.0



Celiac & Gluten Sensitivity (Serum)

Immunologic Markers			
Biomarker	Result		Reference Range
Total IgA	319	{ Sufficient }	69-446 mg/dL
Anti-Tissue Transglutaminase IgA (tTG IgA)	<1.2	{ Negative }	<4.0 U/mL
Anti-Deamidated Gliadin IgA (DGP IgA)	6	{ Negative }	<20 U/mL
Anti-Gliadin IgA (AGA IgA)	20	{ Weak Positive }	<20 U/mL
Anti-Gliadin IgG (AGA IgG)	11	{ Negative }	<20 U/mL

Interpretation
Patient results are consistent with Possible Gluten Sensitivity. Clinical correlation advised.



What are the Best Serological Tests for Screening?

- For all screening tests, it depends on prevalence and age of population being examined
- Overall, tTG IgA is the recommended test to screen for celiac disease
- EMA IgA is helpful when positive
- tTG, EMA less sensitive for milder histologic stages
- AGA antibodies are no longer used
- Antibodies to DGP are more specific than old testing (native gliadin) but less sensitive than tTG which is 90% sensitive and 98% specific*

AGA Technical Review, Gastroenterology, 131:1981, 2006

** Lewis, NR, Aliment Pharmacol Ther, 31: 73, 2010*

How Helpful are Endoscopic Findings in Diagnosing Celiac Disease?



- Flattened or absence of folds
- Notching or scalloping of folds
- Fissuring of mucosa

Endoscopic findings are not very sensitive but they are quite specific

If you suspect celiac disease, take biopsies!

Biopsies are the Gold Standard but Have Some Limitations

- False positives
 - Other causes of epithelial changes and/or increased inflammation (peptic duodenitis, bacterial overgrowth, enteric infections, tropical sprue)
- False negatives
 - Subtle findings, insufficient sample, patchy disease, distal disease

Taking ≥ 4 -6 biopsies including at least one from the duodenal bulb and using an experienced pathologist minimizes these pitfalls

Hopper, AD, et al, Endoscopy 39:219, 2007

Bonamico, M et al, JGN, 47, 618, 2008

Weir, DC, et al Am J Gastroenterol 2009

Patients Already on Gluten Free Diet: How to Test for Celiac Disease?

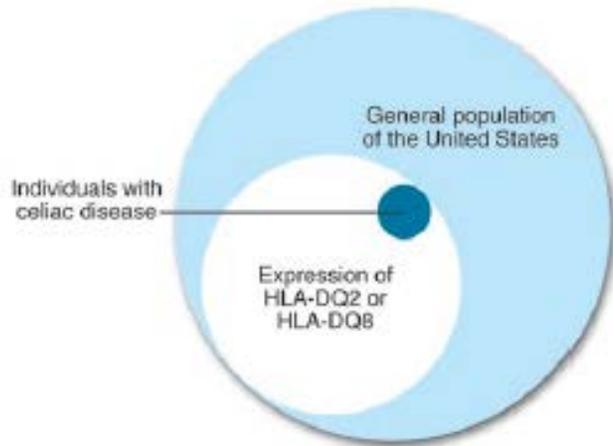
- Depends on duration and stringency of the GFD
 - if truly on a GFD for many years it is difficult to prove CD
 - many patients on a self-taught GFD are not truly or continually gluten-free
- Serology can take over a year to normalize
 - Check TTG IgA +/- DGP IgA, IgG
- Histology can take several years plus to become normal
- If an undiagnosed patient wants an assessment for possible CD assess with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD
- Absence of HLA DQ2.2, 2.5 or 8 effectively excludes CD now or in the future

Sugal, E, et al, Digestive & Liver Disease, 42:352, 2010

Crowe, SE. In The Clinic : Celiac Disease, Ann Int Med, 2011 154:ITC5-14,

Who Develops Celiac Disease?

Genetic and Other Factors



- 70% concordance in twins
- 10-15% prevalence in first degree relatives
- **Other genetic factors** - genes on chromosomes 5, 16, ?6
- GWAS have identified at least 26 celiac genetic risk variants
 - many contain immune-related genes controlling adaptive immune response
- **Environmental factors** - ? Infectious agents
 - Cytokines released during infection - Affecting APCs (e.g., dendritic cells)
 - Cross-reactive amino acid sequences - Adenovirus, *H. pylori*
- Increased frequency of **HLA haplotypes** - DR3-DQ2, DR5/7-DQ2, DR4-DQ8
- Other factors involved since most with these haplotypes do not get celiac disease (confer ~40% of risk)

Alternate Tests for Food Allergy or Food Intolerance

- **Many labs** – specific food IgE (helpful), IgG to food antigens*
- **Cyrex, ALCAT** – as per next slide*
- **MRT/LEAP** – Measures release of immune mediators (histamine, cytokines, etc) via changes to the liquid/solids ratio of a blood sample after incubation with specific food, additive, or chemical*
- **Applied kinesiology** – patient holds putative allergenic food while muscle strength is tested by the practitioner*
- **Electrodermal skin testing** - machine measures electrical resistance at acupuncture points when allergen is placed in the electrical circuit*

* = Expert NIH panel “recommends not using” this test for routine diagnosis of food allergy
Boyce JA et al. JACI.2010;126(6):1105

Alternate Tests for Food Sensitivity and Non-Celiac Gluten Sensitivity

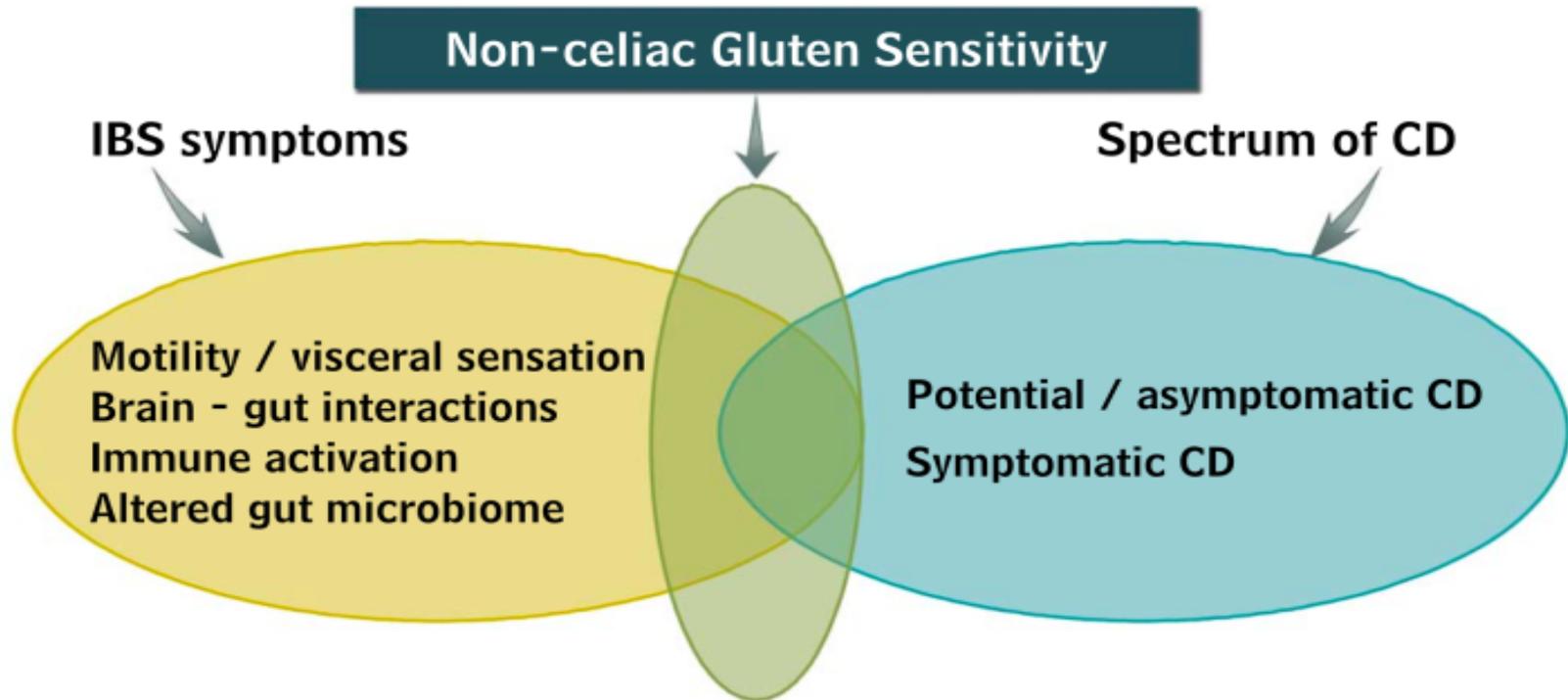
- **LabCorp** – NCGS screen = IgG to native gliadin (not very helpful)
- **ALCAT** – Gut Health Profile (tests specific genetic predisposition to celiac disease as well as antibody testing and immune system activation to food sensitivities), also leukocyte assays for food sensitivities*
- **Cyrex** – Intestinal antigen permeability screen, Wheat/Gluten proteome reactivity/autoimmunity, Cross-reacting foods & food sensitivities (IgG & IgA)*
- **Enterolab** – various stool panels (food Abs, gene tests, celiac Abs) but celiac colleagues have found these tests less accurate than blood
- **Genova Diagnostics** (Great Smokies Diagnostic Lab) – Blood for IgG4 to food*, for celiac & gluten sensitivity, saliva for gliadin sensitivity*

Improvement on a Gluten Free Diet: What Does That Mean?

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten free diet often eliminates other dietary factors – wheat starch
- Potentially other mechanisms explain benefit
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study

Between Celiac Disease & IBS: The “No Man’s Land” of Gluten Sensitivity

Is it IBS, Celiac Disease or Something in Between?



Adapted from Verdu EF, et al. Am J Gastroenterol 2009; 1587:94

What is Non-Celiac Gluten Sensitivity (NCGS)?

- Gluten or wheat sensitivity are terms that encompass individuals who report symptoms or alterations in health related to perceived gluten or wheat ingestion without celiac disease or wheat allergy
- Wheat starch (fructose, fructans) is a FODMAP that may lead to symptoms similar to IBS or other FGIDs as well as celiac disease

Testing for Non-Celiac Gluten/Wheat Sensitivity

Mechanisms are not known, prevalence cannot be established

Activation of innate immune system (IL-8, IFN- γ , etc), increased permeability, mucosal inflammation, basophil activation but these findings are not consistently found¹

- Elevated AGA IgA, IgG (up to 50% +AGA IgG)² but not reproduced
- Other proposed mechanisms include immune complex, autoimmune, microbiota, wheat amylase trypsin inhibitors³, toxicity, false neurotransmitters, leaky gut....
- No compelling biomarkers or reproducible data to explain NCGS
-

1. Sabatino, AD & Corazzo, GR, *Ann Intern Med*, 156, 309: 2012,

2. Volta, U et al, *J Clin Gastroenterol*, 46: 680, 2012

3. Junker, Y et al, *J Exp Med*, 209: 2395, 2013

Diagnosing Non-Celiac Gluten Sensitivity

After excluding celiac disease and wheat allergy, the double-blind gluten placebo controlled trial to assess gluten-induced symptoms was considered the best test to detect NCGS

However, a recent study reveals the limitations of this test

- 10 trials including 1312 adults
- Duration of the challenge varied from 1d to 6 wk
- Gluten dose varied from 2 to 52 g/day; 3 studies < 8 g/day
- Most studies reported symptoms gluten>placebo
- Only 38 of 231 NCGS (16%) showed gluten specific symptoms, 40% nocebo response¹

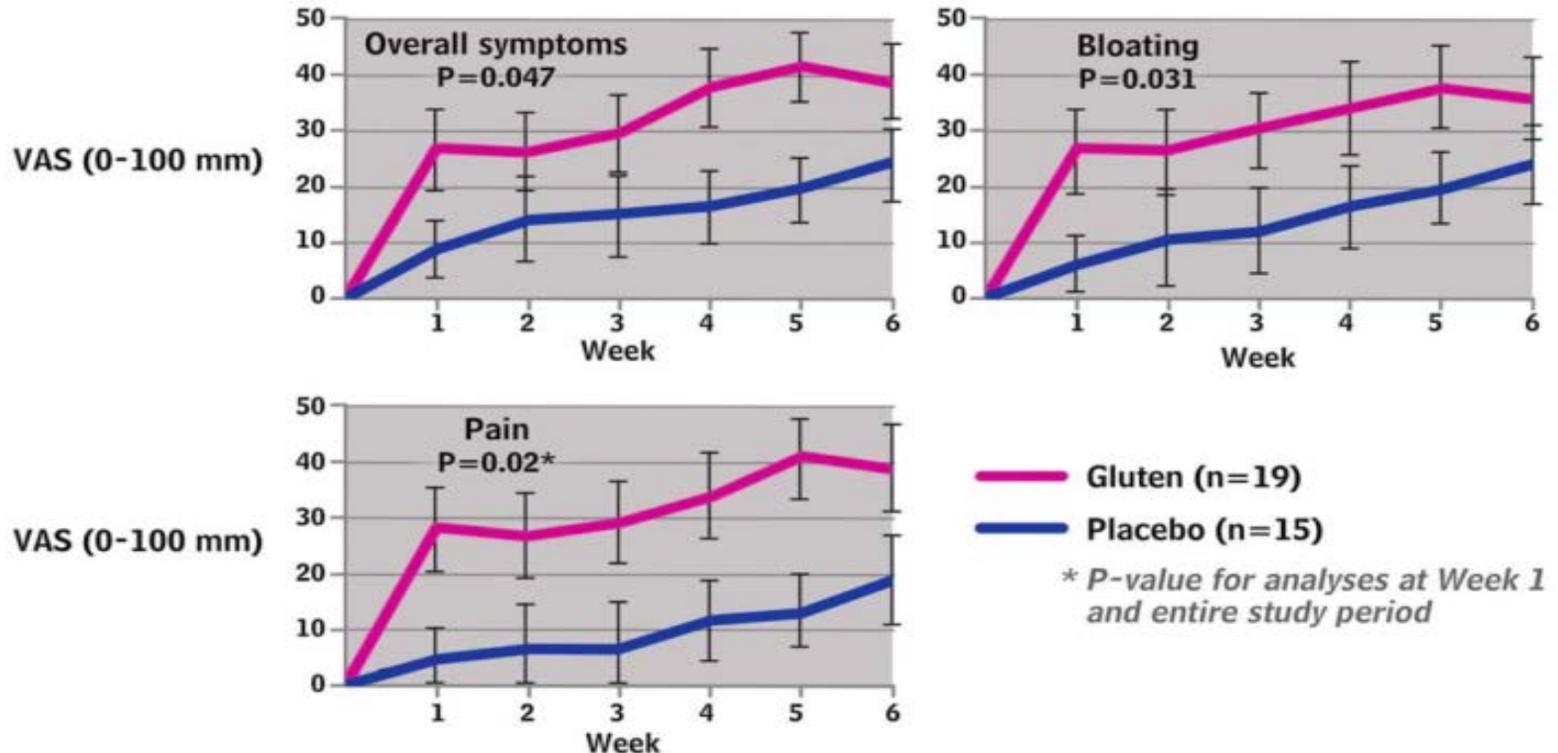
1- a detrimental effect on health produced by psychological or psychosomatic factors such as negative expectations of treatment or prognosis.

J. Molina-Infante, A. Carroccio, CGH: 15; 339, 2017

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

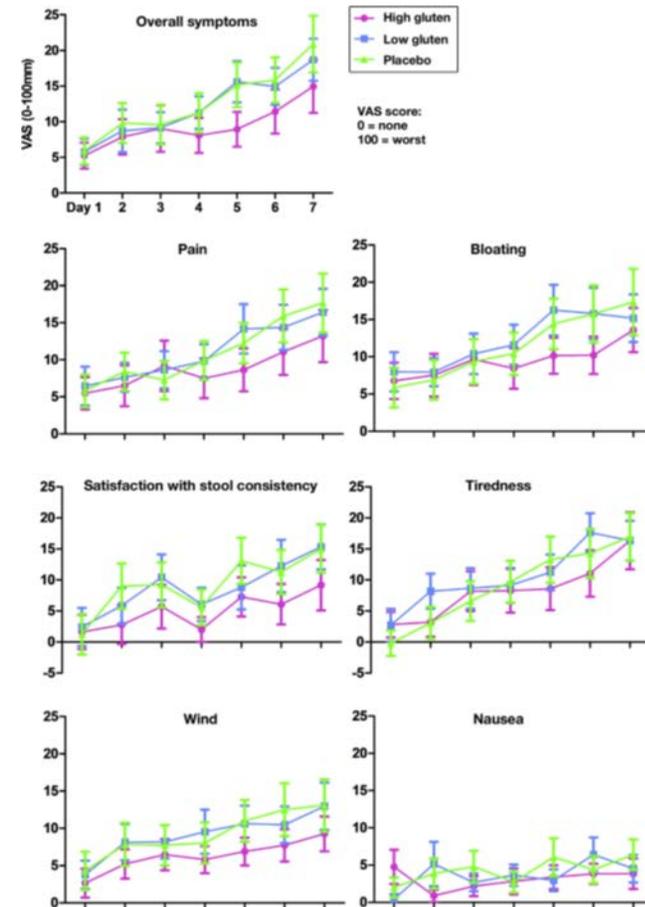
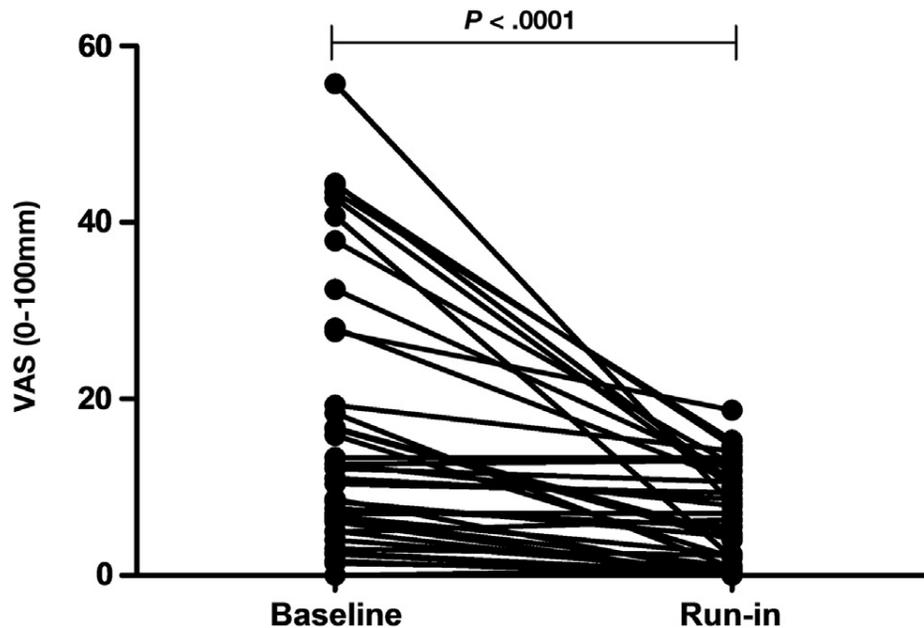
Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean change in symptoms over 6 weeks



Adapted from Biesiekierski JR, et al. Am J Gastroenterol, Jan. 11, 2011 [Epub ahead of print]

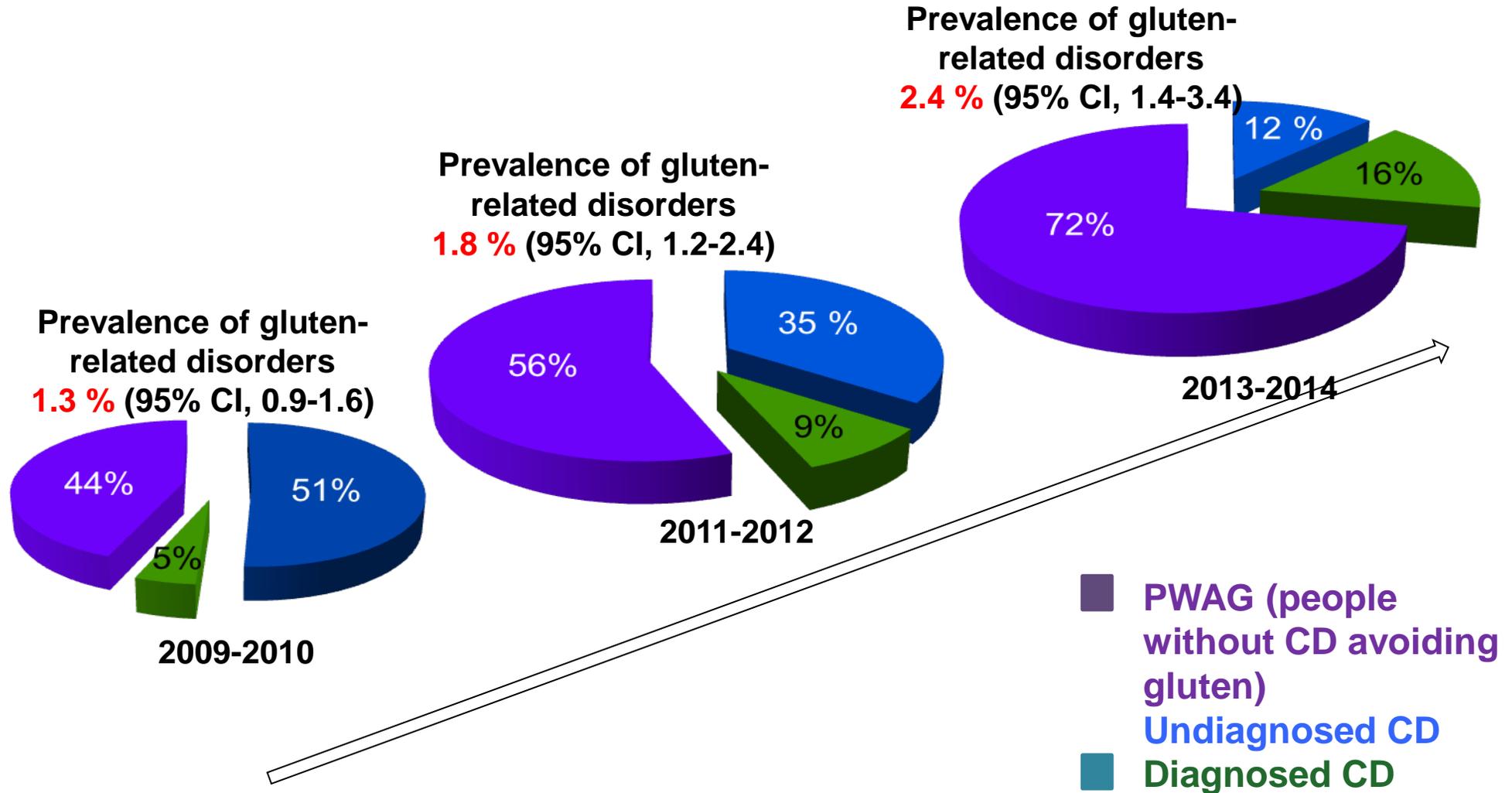
No Effect of Gluten after Reduced FODMAP Diet in IBS Patients



Fructan rather than Gluten Induces Symptoms in NCGS

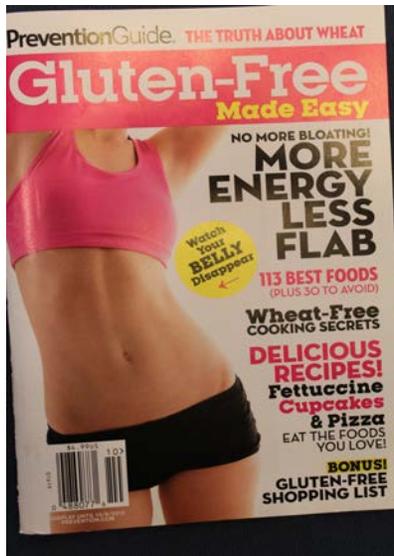
- Double-blind crossover challenge of 59 individuals on a self-instituted GF diet for whom celiac disease was excluded
- Oslo University Hospital Oct 2014-May 2016
- Randomized on diets gluten (5.7 g), fructans (2.1g) or placebo (muesli bars)
- Overall GSRS-IBS and GSRS-bloating scores were significantly higher on fructan vs gluten or placebo

Changes in prevalence and proportions of gluten-related disorders between 2009 and 2014



“Gluten-free the Most Popular Diet Ever”¹

- Compared to gluten-containing foods
 - Expensive
 - Not always available
 - Higher fat & levels of trace metals



- The drawbacks of the GF diet
 - Expensive, not always available
 - Lower fiber, higher fat and sugar content in processed GF foods
 - Recent study suggests that avoiding gluten is associated with increased CAD²

Confounded due to retrospective designed, dietary details, other risk factors

- Increased levels of trace metals³
- NHANES self-reporting 7471 subjects including 73 eating gluten-free
- Measured levels of arsenic, cadmium, lead and mercury in urine and blood
- Greatest differences were with arsenic and mercury

¹ Medscape May 7, 2017, ²Lebwohl, B, et al, BMJ, 2017, 357; ³Argos, M, et al, Epidemiology: 28; 2017

Common Symptoms in Celiac Disease: Overlap with Irritable Bowel Syndrome

- Altered bowel habits
 - **Diarrhea, constipation and mixed pattern**
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
 - **However patients with CD can be overweight and even obese**
- Abdominal distention or bloating
- Note that there are many other presentations of celiac disease including an asymptomatic state

Niewinski MM. J Am Diet Assoc. 2008;108:661-672.

Presuttii JR et al. Am Fam Physician. 2007;76:1795-1802.

Green PHR JAMA. 2009;302(11):1225-1226.

Crowe, SE, In The Clinic : Celiac Disease, Ann Int Med, 154:ITC5-14, 2011

So What do We Know about Dietary Treatments for IBS and Other FGID?

Diet	Evidence for use
Low fat	Limited
Gluten-free	Limited
Low FODMAP	Increasing data
Histamine-free diet	Little to none
Paleolithic	Minimal
Candida	None
Elimination	Little to none

**Limited evidence overall but for low FODMAP diet studies there are 6 randomized and 7 observational studies¹ plus a recent US RCT³
Only 3 of 17 elimination diets met eligibility criteria²**

1-Nanayakkara, WS et al. Clin Exp Gastroenterol. 2016; 9:131

2-Moayyedi, P, et al, Clin Trans Gastroenterol, 2015; 6, e107

3-Eswaran, SL, Chey, WD, et al, Am J Gastroenterol, 2016

What are FODMAPs

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

- Fructose and fructans
- Sorbitol
- Sucrose
- Lactose

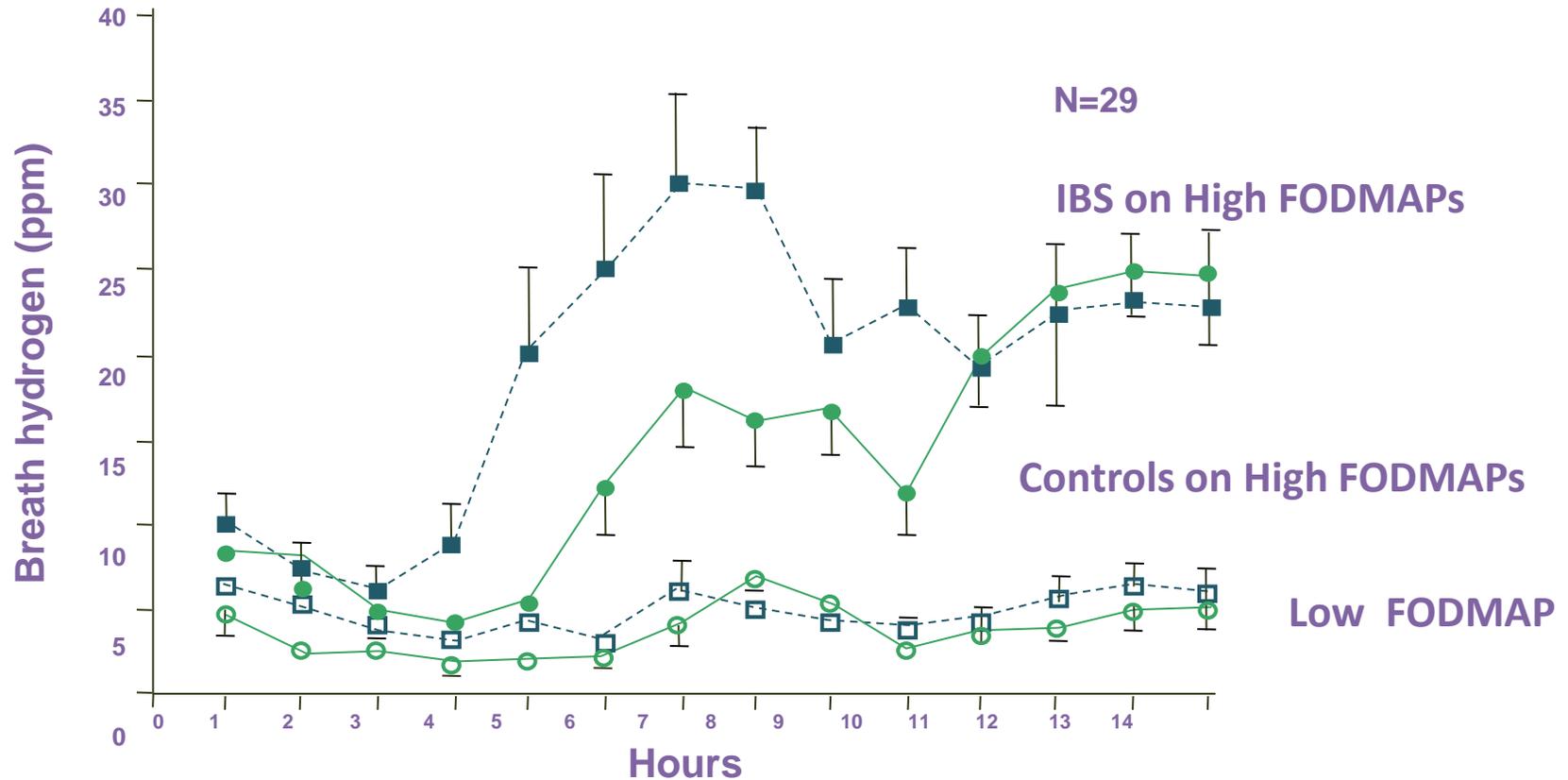


Many foods (grains, starches, fruits, vegetables, lactose, sweeteners) contain FODMAPs

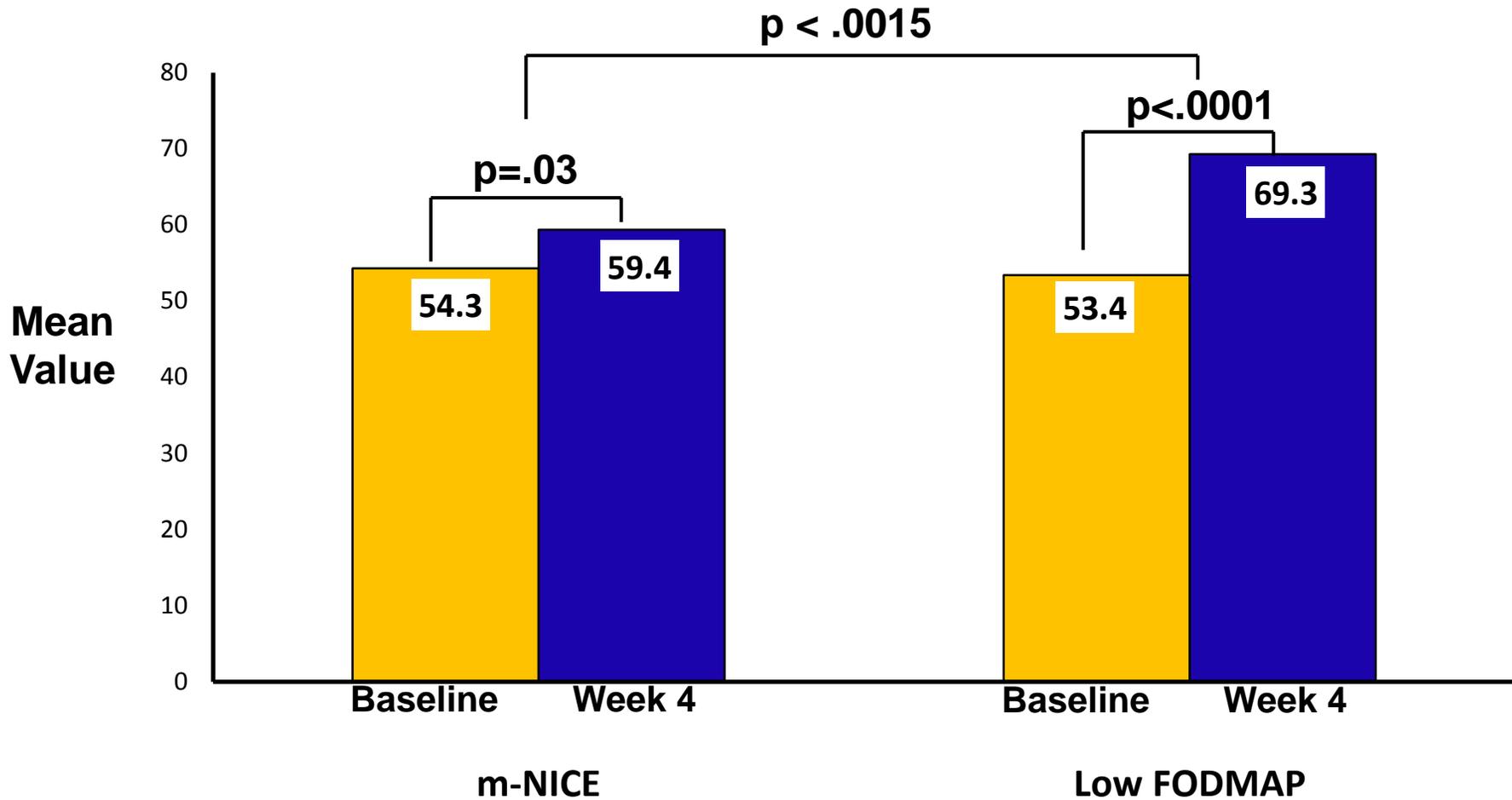
Pathophysiology of FODMAPs

- Poor absorption in the small intestine
- Osmotic effects in the colon, increased water
- Fermentation with gas production
- Luminal distension
- Effects on microbiota
- Immune modulation
- Alteration of intestinal barrier

Effect of FODMAPs on Breath Hydrogen



Overall IBS-QOL Scores



Back to the 1st Food Intolerant Patient

- Reviewed prior records - she had a normal EGD and colonoscopy a few years ago while eating gluten. Duodenal biopsies, no evidence of celiac disease.
- I reassured her history was not consistent with food allergy
- Referred to a RD knowledgeable with GI disorders
- After a year she returned to my clinic to let me know how much I had improved her life after starting a strict low FODMAP diet and re-introducing foods back in to her diet. She had lost weight, greatly improved symptoms and her whole outlook on life.
- She had 6 visits with the RD. She paid out of pocket but felt this payment was very worthwhile.

Back to the 2nd Food Intolerant Patient

- He spent money for “food allergy testing” that NIH deems as “not recommended this test for diagnosis of food allergy”
- I reassured him that his history was not consistent with food allergy but celiac disease was possible
- He received conventional testing that did not detect celiac disease; he wanted genetic testing but no HLA DQ alleles
- We tested for nutrient deficiencies but none detected
- However, he felt better on the GF diet.
- I suggested that his PCP to refer him to a neurologist but no diagnosis was made.
- What did I think he has? – gluten sensitivity without celiac disease

Take Home Messages

- Symptoms of celiac disease, NCGS/NCWS, IBS and other FGID can overlap – testing and treatment can differentiate
- NCGS/NCWS in some but may be due to coexisting dietary wheat starch (fructans) - the low FODMAP diet is helpful
- Bacterial overgrowth and dysbiosis occur but leaky gut is not a disease, and Candida is part of our microbiome
- Culprits are often comfort foods (sweets/starches, fatty foods, lactose, histamine containing foods)
- In the USA 2-4% of adults have food allergy, ~1% have celiac disease and IBS affects 15% of the US population
- Unless one is poorly nourished or not healed from the underlying GI disorder there is no need for supplements (vitamins, other pills, IV infusions), herbs, etc.
- Make sure your health provider is Board certified and will use testing that meets NIH and other national metrics