MCGILL 70TH ANNUAL REFRESHER COURSE FOR FAMILY PHYSICIANS 2019

Is it Celiac disease or Gluten hypersensitivity?

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Disclosures

- None

Learning Objectives

1. Review what foods contain gluten
2. Learn the various signs and symptoms of celiac disease
3. Work through the diagnostic algorithm of celiac disease vs. gluten hypersensitivity
4. Understand the treatment and follow up of a patient with celiac disease

Typical case

- 24 year old woman describes a 1 year history of generalized post-prandial bloating and mild cramping.
- She has loose stools 3 times per day
- She recalls that it began after a trip to South America
- She finds that her symptoms are worse with dairy, bread and sweets

Thoughts: Is this ?

- Celiac disease
- Gluten hypersensitivity
- Lactose or fructose intolerance
- IBS
- Infectious diarrhea
- IBD

Severity of the Problem

- **Quality of life**
  - Missed work or classes
  - Missed social occasions
  - Skipping meals
  - Poor sleep

If quality of life is unaffected then it buys time to work through the diagnosis and treatment

Alarm features

- The main alarm features we consider in this type of case is anemia and weight loss
  - But these are not always true alarm features in celiac disease or gluten sensitivity

Weight loss

- The problem is that most patients that begin to avoid gluten containing foods tend to lose 5-10% of body weight fairly quickly

Anemia in Celiac disease

Caused by malabsorption:

- Iron deficiency anemia
- Folate deficiency
- Vitamin B12 deficiency

- But would it be surprising that our young woman has a mild iron deficiency?

Vitamin D deficiency

- Common in celiac disease
- Osteoporosis is common due to both the Vitamin D and calcium malabsorption

- Again, would it be surprising that this young Canadian woman would have mild Vitamin D deficiency?

Case continued

- She has an maternal aunt who has celiac disease and a maternal cousin that has Crohn's disease

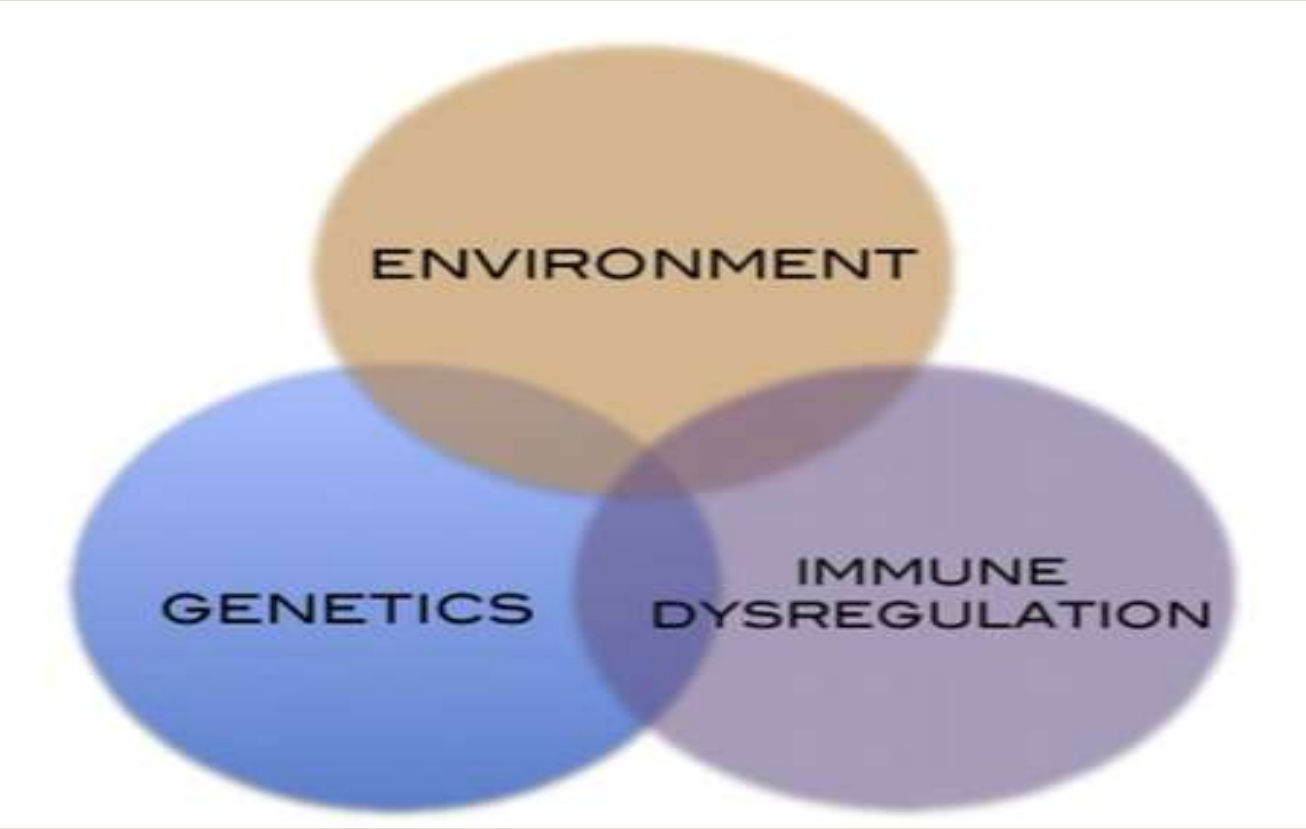
Does this change anything?

Family history

- The prevalence rate among 1st degree relatives is 1/22 and second degree 1/39[1]
- The AHRQ report (2004) included studies that considered the prevalence of celiac disease in first-degree relatives of people who had had a diagnosis of celiac disease.
  - These studies showed a prevalence of 2.8 to 17.2% with serology (five studies) and 5.6 to 44.1% with biopsy (12 studies)[2]

1. *Fasano A et al. Arch Intern Med 2003:163:286*
2. Agency for Healthcare Research and Quality (2004) Evidence Report/Technology Assessment No. 104 Celiac Disease. AHRQ Publication No. 04-E029-2

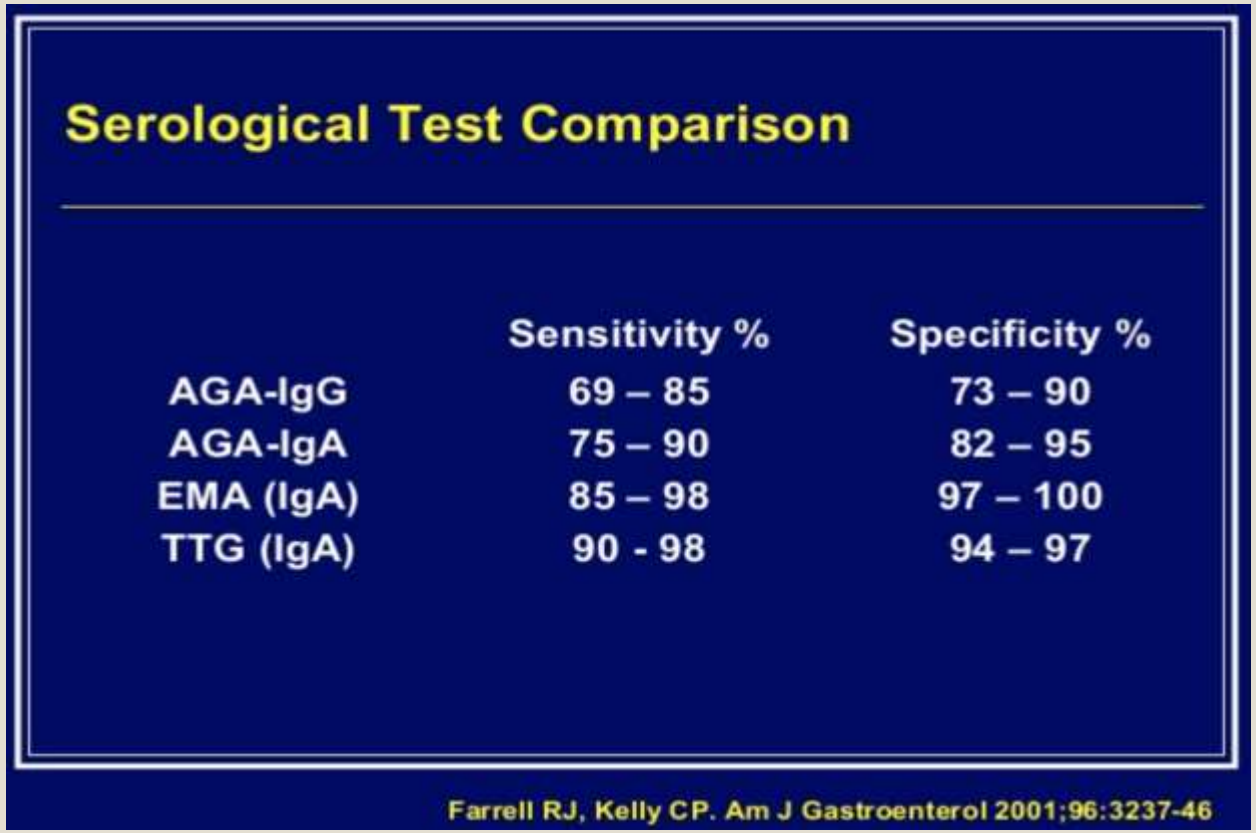
Pathophysiology of Celiac Disease



Diagnosis

- Serology
- Endoscopy with histology
- Response to gluten free diet

Serology



2% of the population is IgA deficient

Other tests I order

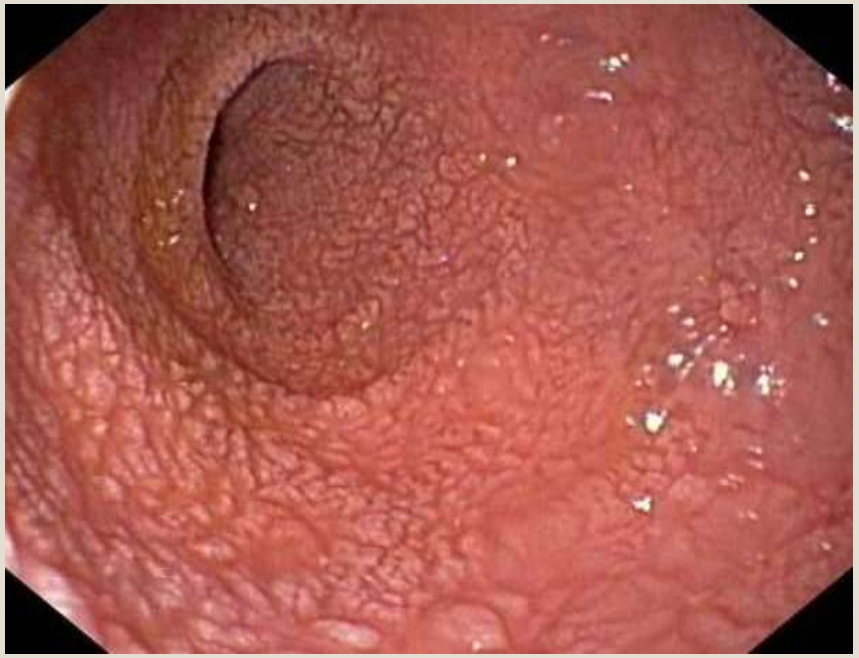
- CBC and ferritin, Vitamin B12
- C- reactive protein
- Fecal calprotectin
- TSH

- I do not order stool cultures routinely

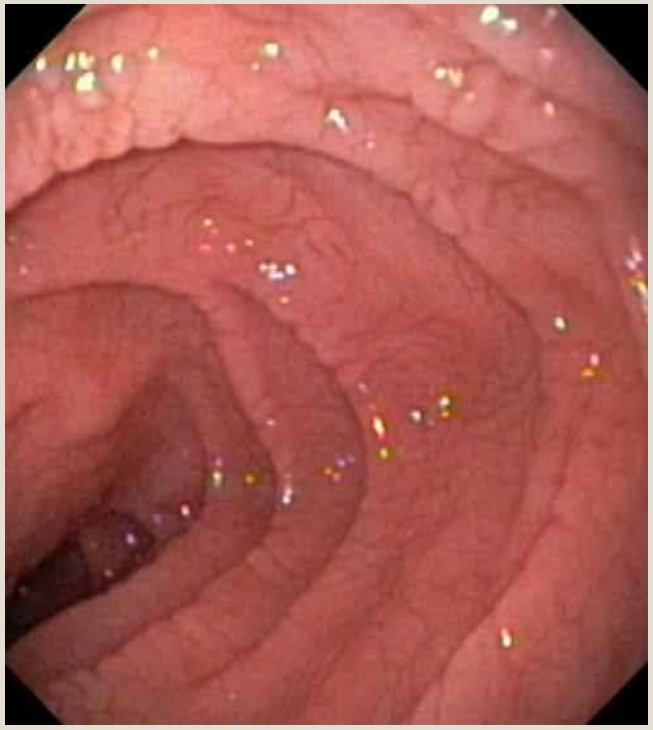
Fecal Calprotectin

- Calprotectin is a major protein found in inflammatory cells that can be measured in a fecal sample
- Levels over 250 ug/g stool is suggestive of IBD while a level below 50 ug/g stool is normal
- It could be elevated in severe celiac disease

Endoscopy



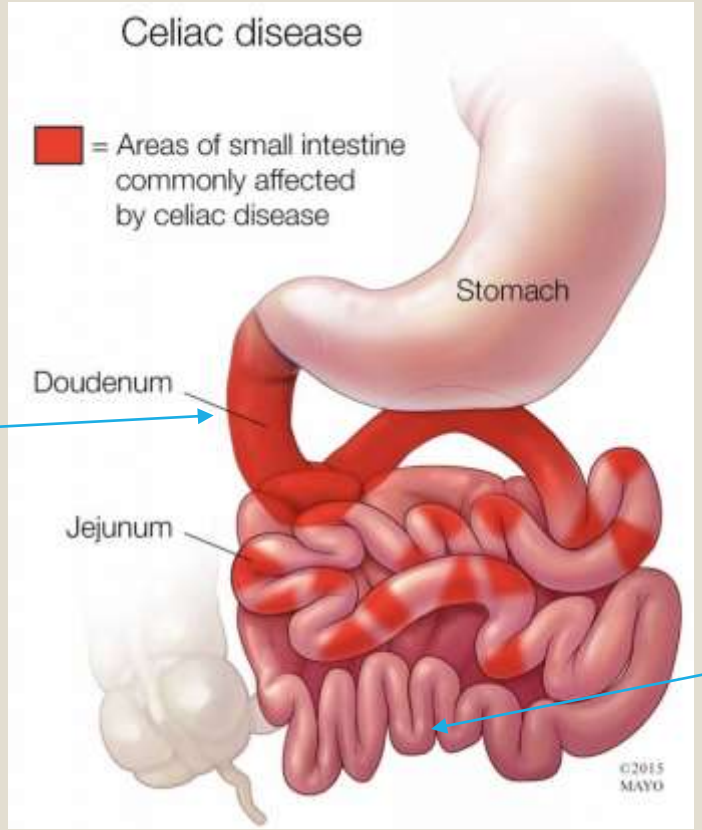
Mucosal fissuring



Scalloping

Distribution of Celiac disease

Iron, folate, calcium, vitamin D absorption as well as lactose, fructose

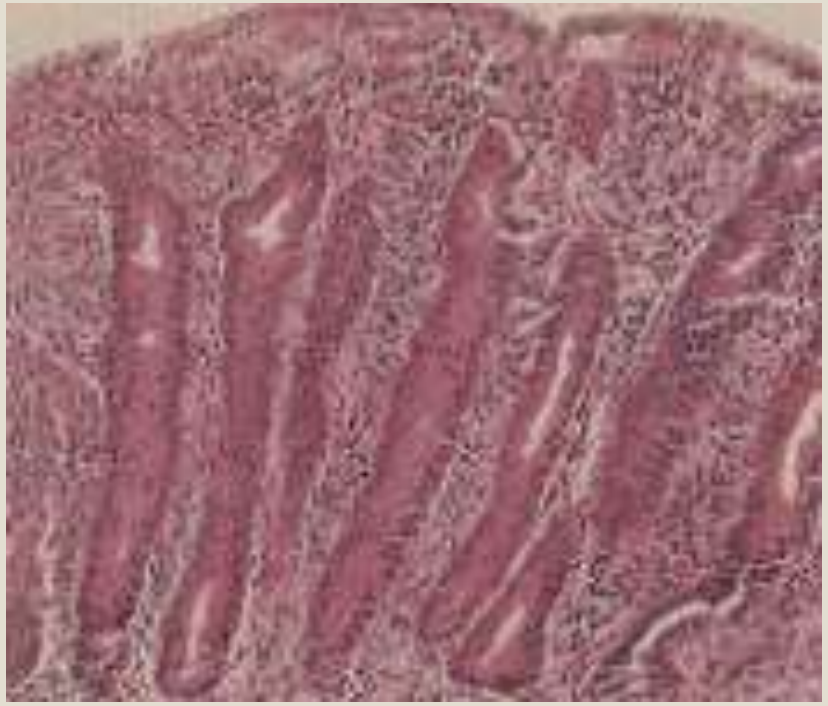


Vitamin B12 absorption as well as bile recirculation

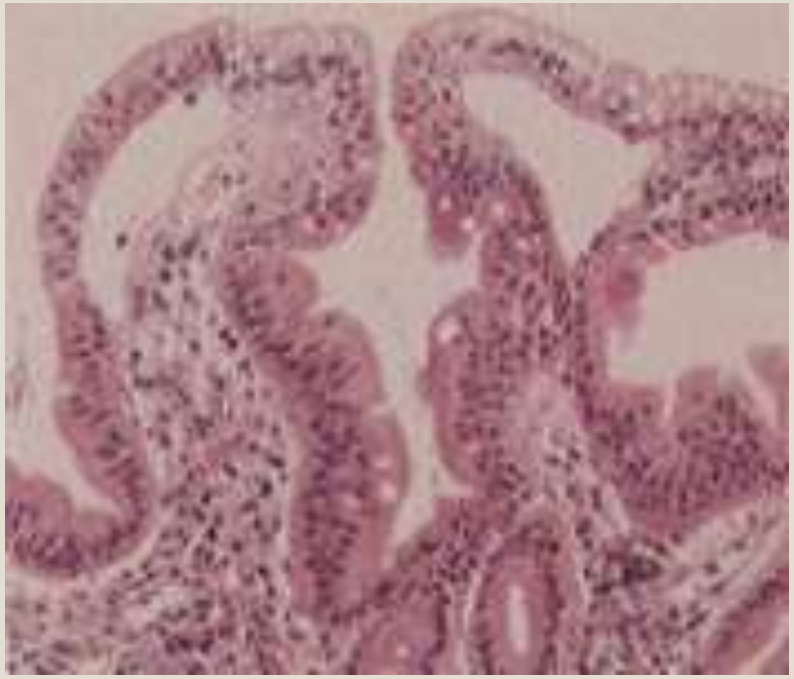
Malabsorption in Celiac disease

- **General nutrient malabsorption**
  - damaged absorbing surface
  - Inadequate mixing of nutrients, bile, and pancreatic enzymes from rapid intestinal transit
- **Fat malabsorption**
  - impaired enterohepatic bile circulation (impaired micelle formation)
- **Carbohydrate malabsorption**
  - Impaired brush-border hydrolase activity

Histology

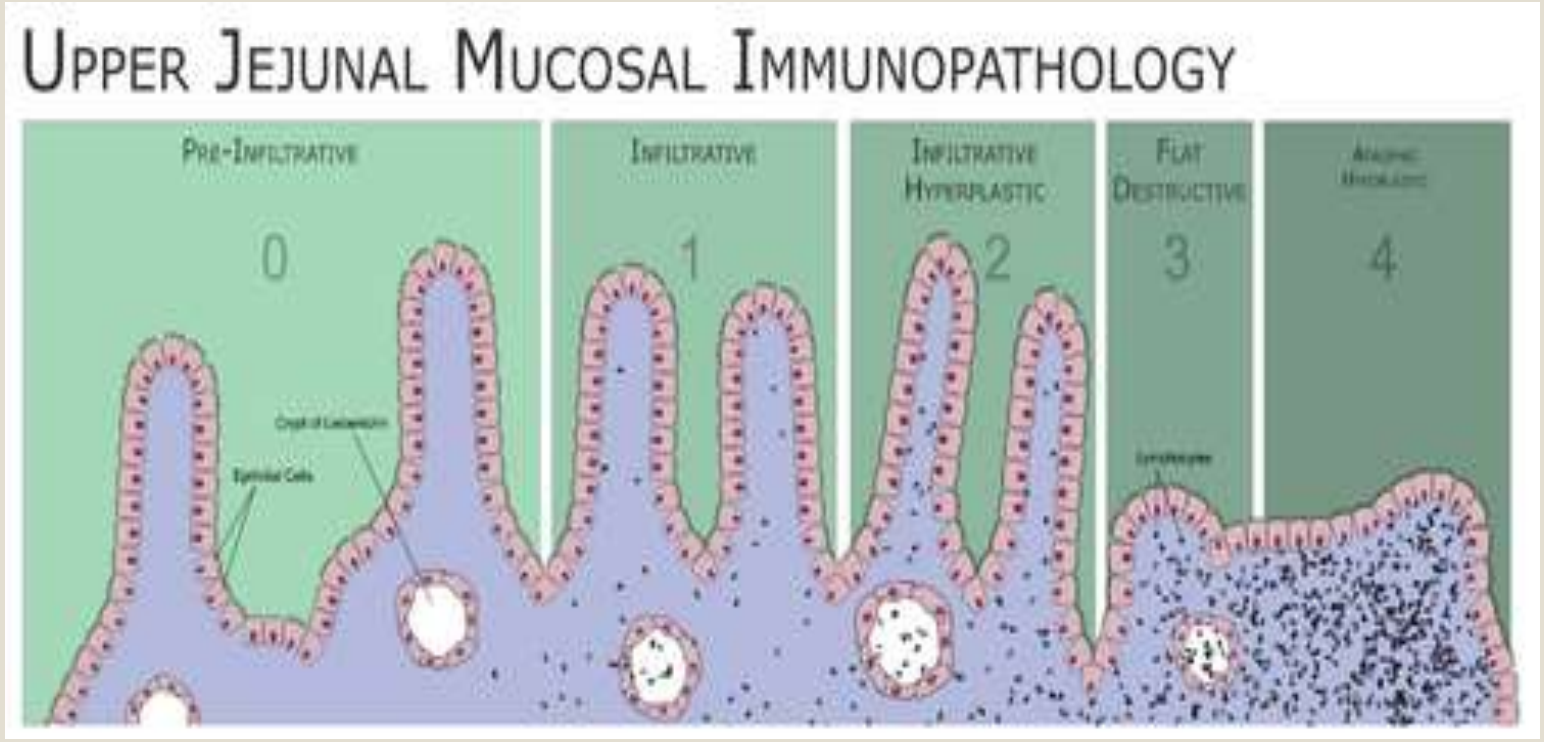


Villous atrophy with lymphocytosis



Normal

Marsh Classification

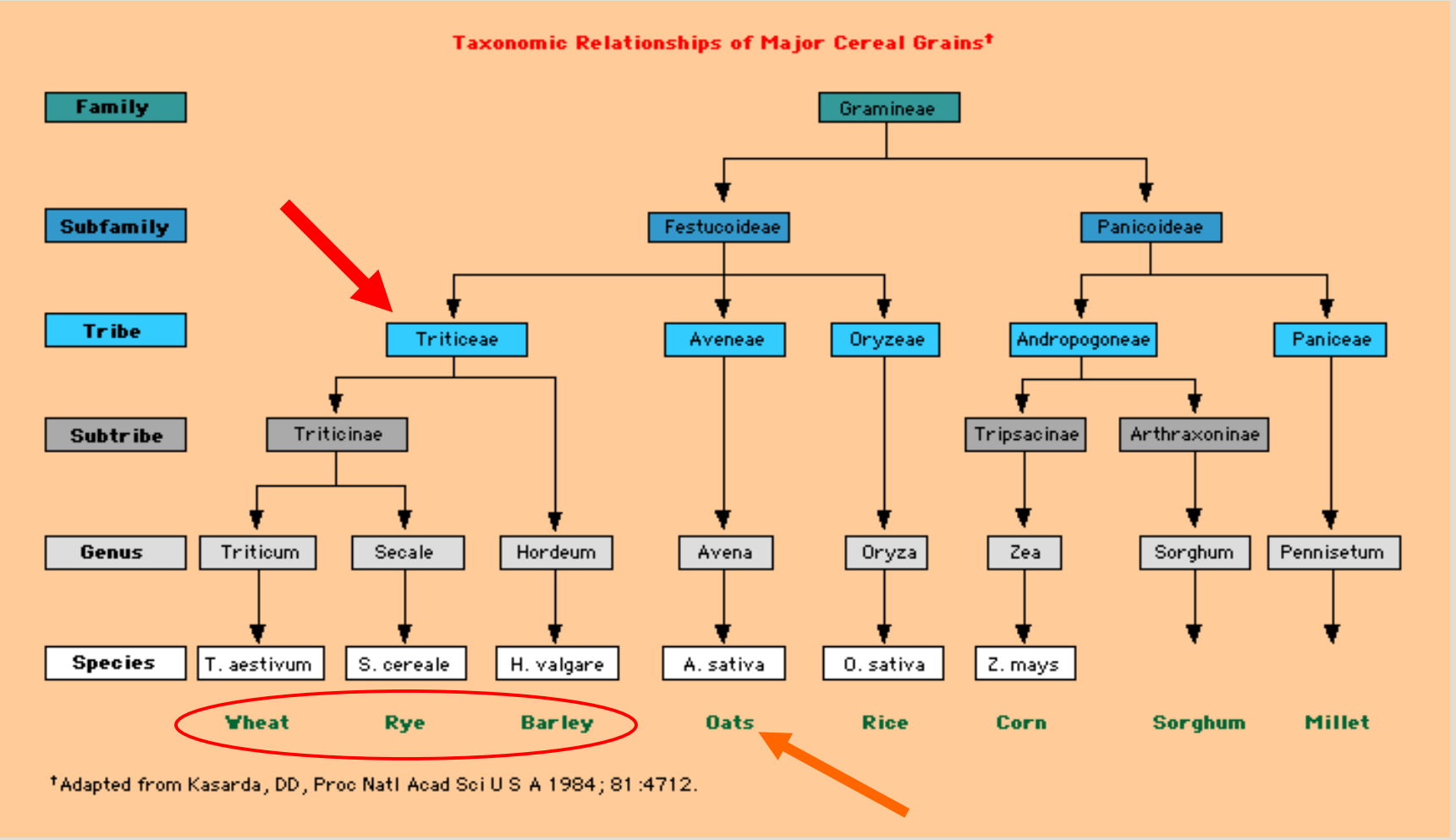


Case continued

- She tells you that in the past 3 months she has been strictly gluten free and has felt somewhat better

- **Does this information hurt or help us?**

Cereal Family



Gluten-free Grains, Flours, and Starches	Gluten-containing Grains, Flours, and Starches
Amaranth	Barley
Arrowroot	Bulgar
Bean flours (garbanzo, fava, romano)	Cereal binding
Buckwheat	Chapatti flour (atta)
Corn	Couscous
Fava	Dinkel
Flax seed	Durum
Garbanzo beans	Einkorn
Garfava[a] flour (garbanzo+fava bean)	Emmer
Hominy	Farina
Mesquite flour	Farro
Millet	Fu
Montina[b] flour	Gluten, gluten flour
Nut flour and nut meals	Graham flour
Oats (uncontaminated)	Kamut
Peas flour	Malt (malt extract, malt flavoring, malt syrup, malt vinegar)
Potato flour, potato starch	Matzoh meal
Quinoa	Oats (most commercial brands, oat bran, oat syrup)
Rice, all forms (brown, white, sweet, wild, jasmine, basmati, glutinous rice, rice polish, rice bran)	Orzo
	Rye
Sago	Seitan (aka wheat meat)
Sorghum flour	Semolina
Soy flour	Spelt
Tapioca (manioc, cassava, yucca)	Triticale
Teff (or tef) flour	Wheat (bran, germ, starch)

Figure 2. Gluten-free and gluten-containing grains, flours, and starches. [a]Originally developed by Authentic Foods Company, Gardena, CA. [b]Amazing Grains Grower Cooperative, Ronan, MT. Adapted from Case S. *Gluten-Free Diet: A Comprehensive Resource Guide*. Regina, Saskatchewan, Canada: Case Nutrition Consulting; 2006, with permission, and Raymond N, Heap J, Case S. The gluten-free diet: An update for health professionals. *Pract Gastroenterol.* 2006;30:67-92, with permission.

Genetics: HLA II Genes

- Approximately 25% to 30% of individuals of European descent carry HLA-DQ2 susceptibility, but only about 4% of these individuals will develop celiac disease in their lifetime.
- In a large European collaborative study, only 4 of 1008 patients (0.4%) fulfilled criteria for celiac disease but did not carry DQ2 (including half-heterodimer) or DQ8.

HLA DQ2 and DQ8 testing

1. In the presence of an equivocal biopsy,
2. When someone is already on the diet,
3. To determine which family members should be screened for celiac disease.

- Remember that being positive for HLA DQ2 or DQ8 does **not** mean you have celiac disease

Case continued

- Her HLA DQ2 is positive but her anti-transglutaminase antibody level is 12 (mildly positive)

- **Can we say she has celiac disease?**
- **Do we need to do more testing?**

Duodenal biopsy may be avoided when high transglutaminase antibody titers are present

Figure 2 Histopathological differences between children and adults according to Marsh classification.

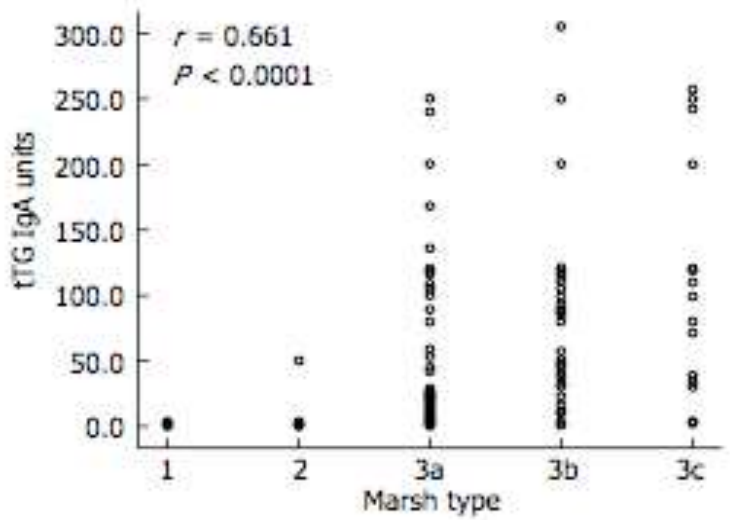


Figure 3 Serum tTG antibody levels *vs* Marsh classification. tTG IgA was significantly correlated with Marsh type.

World J Gastroenterol 2009 October 14; 15(38): 4775-4780

How Much Gluten leads to inflammation?

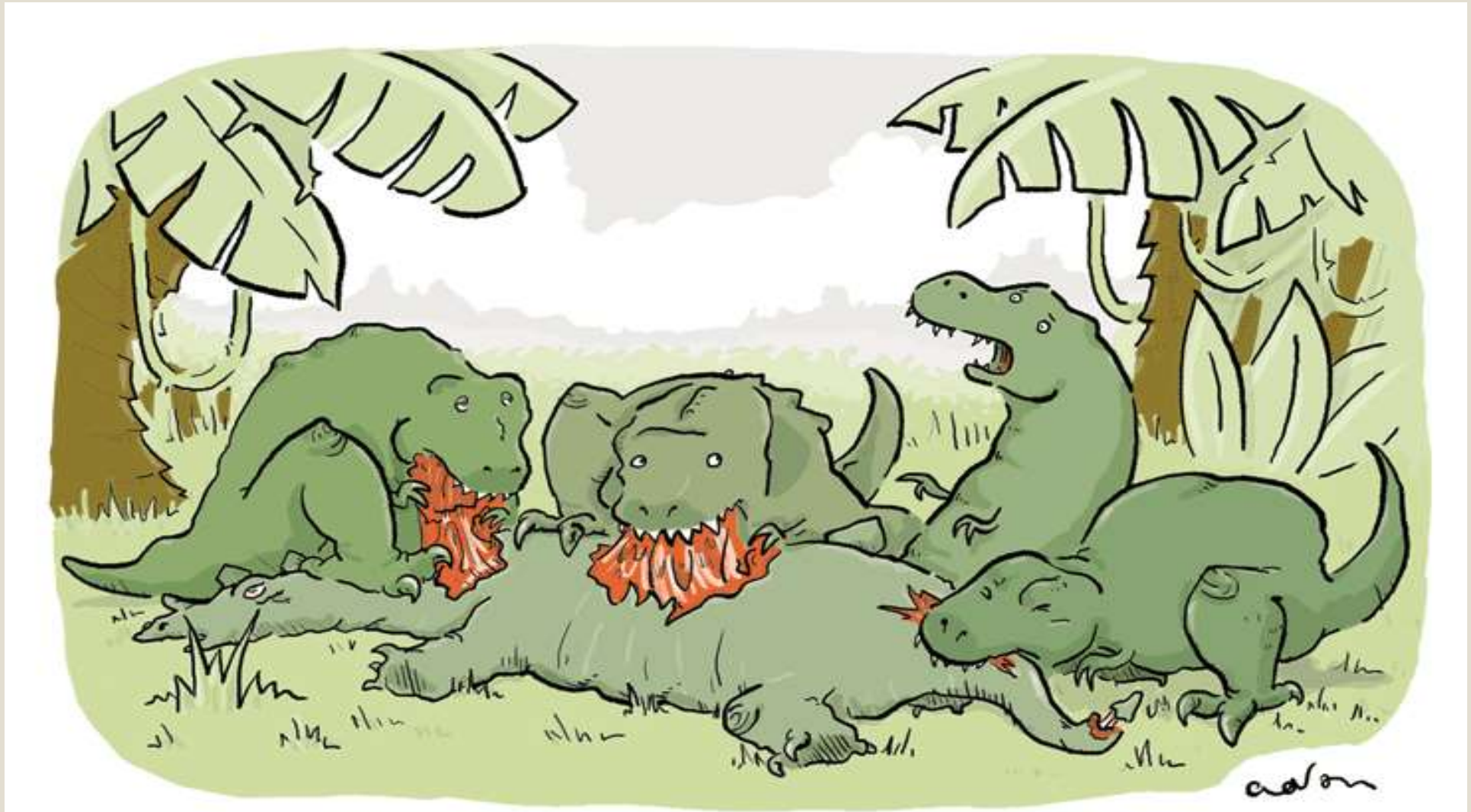
- There is conflicting data where some patients are reactive to as low as 10 mg while most can tolerate under 80 mg per day

- One slice of bread has about 5 grams of gluten

Case continued

- She is convinced to return of gluten for 6 weeks and do serology and a duodenal biopsy
- Both come back consistent with celiac disease?

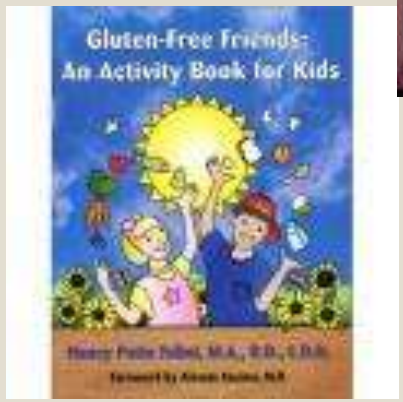
- **She asks: "What can I eat now?"**



"This is gluten-free, isn't it?"

Patients need good advice

- Patients should see a dietician with experience in celiac disease
  - Quebec Celiac Foundation
  - Canadian Celiac Association
- Involve patients in support groups
- Online resources are also available



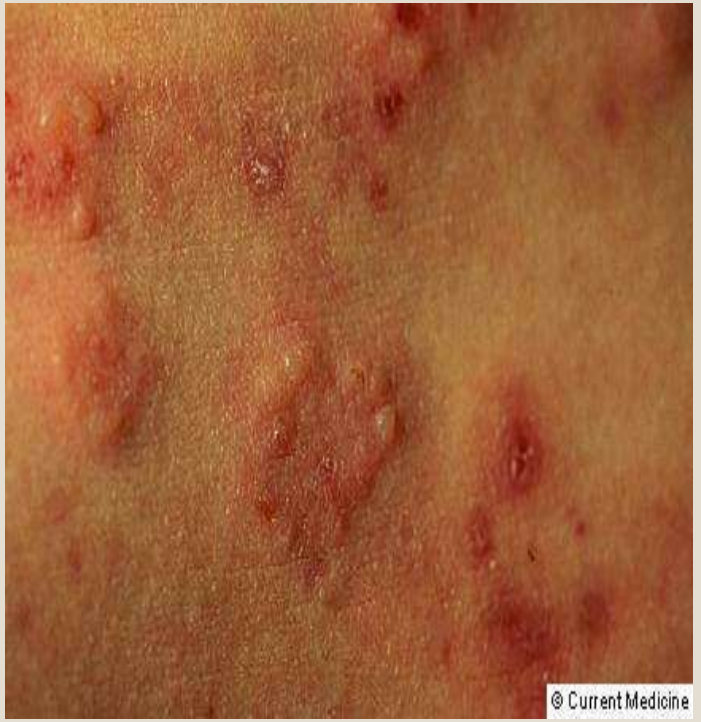
Case continued

- She is feeling good but still has trouble with dairy products. Repeat serology 12 months later is negative

- **She asks:**
  - **“why am I still lactose intolerant?”**
  - **“ if I feel better can go back to eating gluten?”**
  - **“do I need to repeat my gastroscopy?**

Extra Intestinal Manifestations

- Dermatitis Herpetiformis
  - Pruritic papulovesicular eruption on knees, elbows, buttocks and back
  - 90% will have small bowel enteropathy but seen in only 10% with celiac disease
  - Responds to gluten free diet but often delayed so other treatments may be needed



Hepatic Disorders

- Increased ALT or AST seen in up to 42%. Usually nonspecific and resolves with gluten free diet
- ALP rise is often related to secondary hyperparathyroidism from hypocalcemia due to malabsorption
- Autoimmune diseases such as PBC or AIH, as well as PSC, can be seen associated with celiac disease but it is a rare association.

Endocrine

- AATG antibodies found in 2-7% of type I diabetics
  - 60% were diagnosed at onset of DM
- 5-12% of patients with Addison's disease

Gastroenterol Clinic N Am 37:411

- Hypogonadism, amenorrhea
  - Due to altered sensitivity to testosterone
- Infertility, recurrent abortions

Table 1
Prevalence of celiac disease among arthritis patients

Study	Autoimmune disorder (number of patients)	Age (years)	Prevalence of celiac disease	Celiac disease diagnosis confirmation
Stagi, et al [18]	Juvenile idiopathic arthritis (151)	2.4 to 16.9 (median, 8.3)	6.7%	Positive anti-EMA and IgA tTg serology, SBBx
Lepore, et al [19]	Juvenile chronic arthritis (119)	2 to 16 (mean, 11.5)	2.5%	Positive anti-EMA serology, SBBx
Francis, et al [20]	Rheumatoid arthritis (60)	20 to 84 (mean, 61)	0.63%	Positive anti-EMA serology; SBBx not reported

Study	Autoimmune disorder (number of patients)	Age (years)	Prevalence of non-erosive arthritis	Effect of gluten-free diet
Lubrano, et al [21]	Previously diagnosed celiac disease patients (200)	18 to 65 (mean, 32.8)	26%	Higher prevalence of arthritis on regular diet 41% versus 21% on gluten-free diet

Abbreviation: SBBx, small bowel biopsy.

Risk of Mortality

- older adults with undiagnosed CD had limited comorbidity and no increase in mortality compared with controls (Gastroenterology. 2009 Jul;137(1):88-93)
- undiagnosed CD was associated with a nearly 4-fold increased risk of death
- The overall risk of malignancy was not increased among antibody-positive cases in the follow-up of two decades (Gut 2009;58:643-647)
- Risk of death among patients with celiac disease, inflammation, or latent celiac disease is modestly increased (JAMA. 2009;302(11):1171-1178)

Risk of Malignancy

- US study of 381 patients *(Green P. et al Am J Med 2003)*
  - 11% diagnosed with cancer (43/381)
    - 9/43 after the diagnosis
    - 7/43 at the time of diagnosis
    - 27/43 before the diagnosis
  - Mean age at diagnosis of celiac = 44 ± 18
  - Average age at cancer diagnosis = 58 ± 10

The main cancer diagnosed is small intestinal adenocarcinoma and lymphoma

Follow-up

- Consider duodenal biopsy 6-12 months later
  - 80% of patients do not return to a normal mucosa (Lee SK. Gastointest Endosc 2003:57:187)
- Serology 6-12 months later and possibly yearly may be worthwhile
  - Routine yearly blood work

Case continued

- She has a two year old son

- **She asks:**
  - **“Should my son be tested?”**
  - **“Should he be on a gluten free diet?”**

Most children with potential celiac disease are healthy but one/third of them develop villous atrophy at 3 years follow-up

BACKGROUND AND AIM: The presence of celiac disease-associated autoantibodies (anti-endomysium and anti-tissue-transglutaminase [anti-TG2]) with normal jejunal mucosa indicate potential celiac disease. We performed a prospective, 3-year cohort study to determine the natural history of potential celiac disease in children.
RESULTS: Eighty-nine of the 106 patients entered the follow up study, with normal daily consumption of gluten. During the follow up antibodies disappeared in 14.6% and fluctuated in 32.6%. Villous atrophy was observed in 12/39 (30.8%) patients that underwent a repeat biopsy.
CONCLUSIONS. **After 3 years, approximately 30% of patients develop villous atrophy.**

Clin Gastroenterol Hepatol. 2010 Sep 16

Progression of celiac disease with antibodies against TG and normal duodenal biopsies

- Children 2-18 with positive serology were followed for 12 years while still on gluten containing diet
- !5% developed duodenal villous atrophy,
- 32% no longer tested positive

Gastro 2019:157:413

Screening for celiac disease in family members: is follow-up testing necessary?

Our goal was to determine if one-time screening of relatives is sufficient.

Of 171 family members with an initially negative endomysial antibody who were tested on more than one occasion, **6 (3.5%) were positive on repeat testing.**

The average time to seroconversion was 1.7+/-1.2 years (range, 6 months-3 years 2 months). None of the patients had a change in symptoms between testing.

Repeat testing should occur irrespective of the presence of symptoms.

Goldberg D - Dig Dis Sci - 01-APR-2007; 52(4): 1082-6

Is gluten hypersensitivity real?

- Difficulty to say
- Probably not but the data is conflicting

Fructan, Rather Than Gluten, Induces Symptoms in Patients With Self-Reported Non-Celiac Gluten Sensitivity

- double-blind crossover challenge of 59 individuals on a self-instituted gluten-free diet, for whom celiac disease had been excluded. Participants were randomly assigned to groups placed on diets containing gluten (5.7 g), fructans (2.1 g), or placebo, concealed in muesli bars, for 7 days. Following a minimum 7-day washout period (until the symptoms induced by the previous challenge were resolved), participants crossed over into a different group, until they completed all 3 challenges (gluten, fructan, and placebo).
- The overall GSRS-IBS score for participants consuming fructans was significantly higher than for participants consuming gluten There was no difference in GSRS-IBS scores between gluten and placebo groups

Gastro 2018 Feb;154(3):529

No effects of gluten in patients with self-reported non-celiac gluten sensitivity after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates.

- double-blind cross-over trial of 37 subjects (aged 24-61 y, 6 men) with NCGS and irritable bowel syndrome (based on Rome III criteria), but not celiac disease. Participants were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16 g gluten/d), low-gluten (2 g gluten/d and 14 g whey protein/d), or control (16 g whey protein/d) diets for 1 week, followed by a washout period of at least 2 weeks.
- In all participants, gastrointestinal symptoms consistently and significantly improved during reduced FODMAP intake, but significantly worsened to a similar degree when their diets included gluten or whey protein.

Gastro 2013 Aug;145(2):320

Small Amounts of Gluten in Subjects With Suspected Nonceliac Gluten Sensitivity: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial.

- 61 adults without celiac disease or a wheat allergy who believed ingestion of gluten-containing food to be the cause of their intestinal and extra intestinal symptoms. Participants were assigned randomly to groups given either 4.375 g/day gluten or rice starch (placebo) for 1 week, each via gastrosoluble capsules. After a 1-week gluten-free diet, participants crossed over to the other group.
- subjects with suspected NCGS, the severity of overall symptoms increased significantly during 1 week of intake of small amounts of gluten, compared with placebo.

Clin Gastroenterol Hepatol 2015 Sep;13(9):1604

FINAL QUESTIONS?