GLUTEN AND CELIAC DISEASE

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**NO DISCLOSURES**
GLUTEN

- From Latin gluten, "glue"
- Protein composite found in wheat and related grains, including barley and rye (oats can be tolerated by most but cross-contamination or hypersensitivity may limit tolerability)
- Gluten is the composite of the storage proteins, gliadin and a glutenin
- Conjoined with starch in the endosperm of various grass-related grains
- True gluten, with gliadin and glutenin, is limited to certain members of the grass family
GLUTEN

- Bread flours are high in gluten
- Pastry flours have a lower gluten content
- Gluten is often the basis for imitation meats
- Gluten is often present in beer and soy sauce
- Stabilizing agent in food products such as ice cream and ketchup
- Gluten is also used in cosmetics, hair products, and other dermatological preparations
WHAT IS GLUTEN?

It is a protein that is primarily found in grains:

- Wheat
- Rye
- Barley
- *Oats
THICKENER
- Sauces
- Soups
- Gravy
- Stock cubes
- Marinades
- Processed food

MEAT
- Sausages
- Vienna's
- Burger patties
- Processed meat

WHEAT
- Baked goods
- Pasta
- Bread
- Pastry
- Pizza
- Crumbed food
- Battered food

CEREAL
- All bran flakes
- Corn flakes
- Barley
- Semolina
- Spelt
- Rye
DEFINITIONS

- Non-celiac gluten sensitivity (gluten intolerance)
- Wheat allergy
- Celiac disease (gluten sensitivity)

* No evidence suggests negative side effects occur with gluten consumption outside of the small percentage of the population having gluten sensitivity.
NON-CELIAC GLUTEN SENSITIVITY (GLUTEN INTOLERANCE)

- Syndrome of gastrointestinal responses to gluten different from the immune response characteristic of celiac disease
- No scientific consensus exists to confirm gluten intolerance is a definable pathological condition
- Frequently, symptoms arise in individuals as a result of undiagnosed celiac disease
- Due to a reaction to other components of wheat, such as short-chain, fermentable carbohydrates called FODMAPs
Fermentable Oligo-, Di-, Mono-saccharides and Polyols
WHEAT ALLERGY

- A wheat allergy causes the immune system to abnormally respond to a component of wheat that it treats as a threatening foreign body.
- This immune response is often self-limiting and does not cause lasting harm to body tissue.
- **Wheat allergy and celiac disease are different disorders.**
CELIAC DISEASE

- First described by Samuel Gee in 1888
- Recognized by Dutch pediatrician WWII food shortage
- Celiac lesion in proximal small bowel first described 1954
- Intestinal reaction to alpha-gliadin in gluten resulting in a loss of intestinal villi and a disruption of absorption
- Gluten sensitive enteropathy, also called nontropical sprue
CELIAC DISEASE

- Classic definition includes the following three features:
  - Villous atrophy
  - Symptoms of malabsorption such as steatorrhea, weight loss or other signs of nutrient or vitamin deficiency
  - Resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods (usually weeks to months)
CELIAC DISEASE: EPIDEMIOLOGY

- Multisystem disease
- 1% or 1/133 persons of US
- 1:70 to 1:300 in most countries
- Primarily in whites of Northern European ancestry
- Not specific to age or gender
- Familial (70% twins and 10% first degree family member)
Celiac Disease is one of the most common genetic autoimmune diseases on the planet!

313,000,000
Million Americans

1 in 133
People have Celiac Disease

97%
don’t know they have it

9 Years
Average delay in adult diagnosis

www.GlutenFreePrairie.com
CELIAC DISEASE: GENETICS

- Intra familial occurrence and close association with HLA-DQ2 and/or DQ8 gene loci provide basis of current understanding.
  - Immune disorder triggered by an environmental agent (gliadin) in genetically predisposed individuals.
- HLA-DQ2 (95% of patients) and HLA-DQ8 (5% of patients); Absence of the DQ gene rules out celiac disease with 99% confidence.
  - Presence of one of these markers is necessary but not sufficient for diagnosis.
- DQ2 and 8 are present in 30-40% of the general Western population, suggesting other factors play a role.
Investigators do not know every detail of how the immune system wreaks havoc with the intestinal lining of celiac patients, but they have identified a number of likely processes (below). Colored arrows indicate events that might be blocked by interventions now being investigated [see table on opposite page].

1. Indigestible fragments of gluten induce enterocytes to release the protein domain, which loosens tight junctions.
2. Indigestible gluten fragment
3. Damaged area
4. Tissue transglutaminase (TG), an enzyme released by the damaged cells, modifies the gluten.
5. Antigen-presenting cell
6. The gluten induces enterocytes to secrete interleukin-15 (IL-15), which arouses immune cells called intraepithelial lymphocytes against enterocytes.
7. T cell secretions (Chemokines and cytokines)
8. Help T cells that recognize the complexes secrete molecules that attract other immune cells and can directly damage enterocytes.
9. Helper T cells interact with enterocytes to destroy them.
10. The various accounts disable and kill enterocytes.

Modified: Gluten fragments cross the intestinal lining in abundance and accumulate under epithelial cells (enterocytes.).
CELIAC DISEASE

- Associated disorders (many autoimmune)
  - Endocrine (DM I, autoimmune thyroid, Addison’s, Osteopenia)
  - Mixed connective tissue disease (Sjogren's, RA)
  - Cardiopulmonary (Asthma, Sarcoid, Carditis, pulmonary hemosiderosis, fibrosing alveolitis)
  - Neurological (Seizures, Dementia, Peripheral neuropathy, Psychiatric disorders)
CELIAC DISEASE

- Associated disorders (many autoimmune)
  - Skin (Dermatitis, Atopy, Psoriasis)
  - Malignancy (Lymphoma, Esophageal, Oropharyngeal)
  - Gastrointestinal (GERD, EoE, IBD-UC>CD, microscopic colitis)
  - Reproductive (Amenorrhea, Infertility, recurrent spontaneous abortion)
  - Immunologic (IgA deficiency)
  - Down syndrome
What are the Symptoms of Celiac Disease?

Have these symptoms? Don’t wait, get tested.

**Oral**
- Bad breath
- Gum disease
- Mouth sores
- Mouth ulcers
- Swollen gums
- Tongue sores
- Tooth enamel erosion

**Behavioral**
- ADD
- Anxiety
- Brain fog
- Depression
- Irritability
- Irrational anger
- Loneliness/isolation
- Loss of interest in activities
- Memory loss
- Mood swings
- Night terrors
- Panic attacks
- Short tempers
- Suicidal

**Female-specific**
- Breast tenderness
- Early menopause
- Frequent miscarriages
- Hormonal level swings
- Heavy, painful periods
- Infertility
- Swollen bladder/cervix

**Intestinal**
- Acid reflux
- Bloating
- Constipation
- Diarrhea
- Gas that would clean a room
- Loss of appetite
- Nausea
- Stomach pain

**Skin**
- Acne
- Brittle nails
- Bruising
- Burning scalp
- Dandruff
- Dark circles under the eyes
- Eczema
- Flaky skin around the eyes
- Hives
- Itchy rash
- Skin cancer
- Skin rashes

**Joint/Muscle**
- Ataxia
- Back pain
- Burning sensation in the joints
- Joint pain/stiffness/swelling
- Leg cramps
- Muscle spasms
- Swelling in hands and feet

**Vitamin deficiencies**
- Anemia (low iron)
- Low calcium
- Low vitamin B12
- Low vitamin D

**Miscellaneous**
- Asthma
- Bladder infections
- Blurred vision
- Chills & fevers
- Chronic fatigue
- Dandruff
- Coughing
- Dizziness/vertigo
- Fatigue
- Fluctuating weight
- Gerd
- Hair loss
- Headaches
- Heartburn
- Hemorrhoids
- High blood pressure
- Hypothyroidism
- Irregular heartbeat
- Low blood sugar
- Migraines
- Night sweats
- Racing heart
- Seizures
- Sinus pressure
- Sleeping issues

*Symptoms in red were mentioned the most often*

Source:
These symptoms were provided by over 180 people currently living with celiac disease. Only symptoms that were mentioned more than once were listed. To see all of the responses, go to: http://glutendude.com/celiac/what-are-your-specific-celiac-symptoms/
CELIAC DISEASE: CLINICAL MANIFESTATIONS

- May be confused with IBS due to non-specific symptoms
- Malabsorption (diarrhea, foul smelling stools, weight loss, cramps, fatigue)
- Multisystemic
  - Oral (dental enamel, aphthous ulcerations)
  - Labs (IDA, elevated transaminases ALT>AST (~42% of pts with celiac and normalize with gluten free diet), low albumin)
  - Dermatitis herpetiformis
  - Neuropsychiatric disease (HA, peripheral neuropathy, ataxia, depression, anxiety, epilepsy)
CELIAC DISEASE: CLINICAL MANIFESTATIONS

- Higher prevalence osteoarthritis (relationship unknown)
- Metabolic bone disease (osteopenia and osteoporosis)
  - Secondary hyperparathyroidism likely d/t vit D deficiency
- Hyposplenism (mechanism unknown)
  - Prophylactic pneumococcal vaccination suggested
- Kidney disease - glomerular IgA deposition, but rarely have manifestations
- Idiopathic pulmonary hemosiderosis (Lane-Hamilton syndrome)
  - Introduction of gluten-free diet assoc with remission of pulmonary symptoms
DENTAL ENAMEL HYPOPLASIA
DERMATITIS HERPETIFORMIS

- Intensely pruritic papulovesicular rash
- Typically on extensor surface
- Represents intestinal sensitivity to gluten
- Biopsy show granular IgA deposits in the papillary dermis (pathognomonic)
- Responds to gluten-free diet
- Dapsone may help with healing of skin
DERMATITIS HERPETIFORMIS
CELIAC DISEASE: WHO SHOULD BE TESTED?

- Gi symptoms (diarrhea, malabsorption, weight loss, distension or bloating) mimicking IBS or lactose intolerance
- Individuals without other explanations for IDA, folate or B12 deficiency, persistent elevation in serum aminotransferases, and physical manifestations previously discussed
- Patients with Type I DM, 1st degree relatives of individuals with celiac disease
CELIAC DISEASE: LABORATORY STUDIES

- Anti Gliadin IgG: 75% sensitivity, 97% specificity
  - May also be found in 10-20% of patients with other disease that affect the small intestinal mucosa
  - Helpful for monitoring outcome: always becomes negative with the regrowth of jejunal villi in patients after gluten-free diet

- Anti Endomysial IgA: 97-100% specificity, 85% sensitivity (untreated patients)
  - Can persist in low titers in 10-25% of patients who are treated despite normal histology, or become negative with adherence to gluten-free diet
**CELIAC DISEASE: LABORATORY STUDIES**

- **Anti-transglutaminase IgA (tTG IgA):** 100% specificity, 90% sensitivity - best sensitivity and specificity

- Endomysial and transglutaminase can be false negative in those with IgA deficiency (approximately 2.5% of the population; therefore IgA level should always be ordered with serology) and children less than 2 years old

- Any serological tests for celiac disease should be confirmed with a small bowel biopsy
Celiac disease diagnostic testing algorithm

High probability (>5 percent)

- Duodenal biopsy
  - TTGA IgA

  - Both negative: Celiac disease unlikely
  - Both positive: Celiac disease
  - Biopsy/serology disagreement:
    - HLA DQ2 and DQ8 genotyping
    - Measure IgA level ± TTGA/DGP IgG
    - Work-up for other causes of villous atrophy

Low probability (<5 percent)

- TTGA IgA ± IgA level
  - Positive TTGA
  - Negative TTGA
    - Low IgA
    - Normal IgA
      - Duodenal biopsy
        - TTGA IgG ± DGP IgG
          - Any positive
          - All negative
        - Celiac disease unlikely

DGP: deamidated gliadin peptide; HLA: human leukocyte antigen; Ig: immunoglobulin; TTGA: tissue transglutaminase antibody.
Pts on gluten free diet

- HLA DQ2/DQ8 tests if pt genetically susceptible
- Positive HLA testing with negative baseline histology should undergo modified gluten challenge
# The Marsh–Oberhuber Classification

<table>
<thead>
<tr>
<th>Marsh Type</th>
<th>Intraepithelial Lymphocytes per 100 Enterocytes</th>
<th>Crypts</th>
<th>Villi</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;40</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>&gt;40</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>&gt;40</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;40</td>
<td>Increased</td>
<td>Mild atrophy</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;40</td>
<td>Increased</td>
<td>Marked atrophy</td>
</tr>
<tr>
<td>3c</td>
<td>&gt;40</td>
<td>Increased</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Type 0: Normal mucosa; CD highly unlikely.

Type 1 (Infiltrative lesion): Seen in patients on a gluten-free diet (suggesting minimal amounts of gliadin are being ingested); patients with DH; and family members of patients with CD. However, these patients need to be followed because they may convert to a Type 3 lesion.

Type 2 (Hyperplastic type): Very rare; seen occasionally in DH.

Type 3 (Destructive lesion): Spectrum of changes seen in symptomatic CD (38, 39).
CELIAC DISEASE ENDOSCOPY AND HISTOLOGY
CELIAC DISEASE: HISTOLOGY

- Modified Marsh Classification
  - Type 1: increased intraepithelial lymphocytes but no villous atrophy
  - Type 2: villi still present but shortened
  - Type 3: mild to marked villous atrophy
  - Type 4: lamina propria hypoplasia; no villi
### Causes of small intestinal villous atrophy other than celiac disease

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Small intestinal bacterial overgrowth</td>
</tr>
<tr>
<td>Crohn disease</td>
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<tr>
<td>Cow’s milk or soy protein intolerance (children)</td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Giardiasis</td>
</tr>
<tr>
<td>Intestinal lymphoma</td>
</tr>
<tr>
<td>Peptic duodenitis</td>
</tr>
<tr>
<td>Post-gastroenteritis</td>
</tr>
<tr>
<td>Tropical sprue</td>
</tr>
<tr>
<td>Zollinger-Ellison syndrome</td>
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<tr>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)</td>
</tr>
<tr>
<td>Medications (eg, olmesartan)</td>
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<tr>
<td>Whipple disease</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Intestinal tuberculosis</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
</tr>
</tbody>
</table>
Diagnostic algorithm for small intestinal villous atrophy

Villous atrophy

- Check tTG-IgA

  - Negative
    - Review pathology; consider NCE
    - Non-diagnostic
    - Check serum immunoglobulin
      - Low IgA and normal IgG
        - Check IgG-DGP
          - Negative
            - Manage as NCE
          - Positive
            - Sero pathological and clinical response
      - Low IgG and IgA
        - Check serum albumin
          - Normal
            - Work up for CVID
          - Low
            - Manage as presumptive CD
      - Normal IgA and IgG
        - Check HLA
          - Positive
            - Manage as NRCD
          - Negative
            - Manage as NRCD

  - Positive
    - Manage as celiac disease
      - Poor or partial response
        - Check HLA
          - Positive
            - Manage as NRCD
          - Negative
            - Manage as NRCD

NCE: non-celiac enteropathy; tTG: tissue transglutaminase antibody; IgA: immunoglobulin A; IgG: immunoglobulin G; DGP: deamidated gliadin peptide; HLA: human leukocyte antigen; NRCD: non-responsive celiac disease; CVID: common variable immunodeficiency; CD: celiac disease.

CELIAC DISEASE: TREATMENT

- Gluten-free diet: removal of wheat, rye and barley; Nutrition consult for education
  - Oats do not contain gluten but are often contaminated with gluten during processing
  - Rice, corn, and millet do not contain gluten
- Lactose-free diet initially (the brush border contains lactate which is not functional with sprue)
- Those with continued diarrhea should be examined for other causes of diarrhea
- DDX of non-responders:
  - Incorrect diagnosis (IBS), Continuing gluten intake (restaurants), SBBO, IBD/Microscopic colitis, Pancreatic insufficiency, lactase deficiency, Lymphoma, Autoimmune enteropathy, Refractory sprue (rare)
CELIAC DISEASE: COMPLICATIONS

- Malignancy: Squamous cell cancer of esophagus, Small bowel adenocarcinoma, Intestinal and extraintestinal lymphoma (T-cell)
- Rarely a functional asplenia can occur, consider Pneumovax
- Risk of untreated Celiac disease: Infertility, Miscarriage, Epilepsy, Intestinal Lymphoma
Conditions to consider if previously responsive patients begin to deteriorate:

- Noncompliance: with gluten-free diet (most common)
- Lymphoma (T-Cell): most common malignancy complicating celiac disease; Requires high index of suspicion
  - Think about in patients not responding to diet therapy or recurrent weight loss despite diet therapy
  - EGD, CT & exploratory laparotomy may be necessary
Refractory Sprue: Patients do not respond to gluten-free diet, either at onset of diagnosis or becoming refractory with diet adherence

- No other cause found after thorough investigation
- Some respond to steroids, azathioprine and cyclosporine
- Severe complications include ulcerative jejunitis, collagenous sprue, and lymphoma
CELIAC DISEASE: COMPLICATIONS

- Collagenous Sprue: subset of Refractory Sprue; Usually refractory to all forms of therapy other than parenteral alimentation
  - Characterized by development of thick band of collagen-like material
- Other malignancies with increased risk
  - Non-Hodgkin’s lymphoma
  - Small bowel adenocarcinoma
  - Oropharyngeal and esophageal cancers
LEARN MORE ABOUT CELIAC DISEASE

https://celiac.org

Celiac Disease Symptoms and Conditions Checklist
What is Celiac Disease?
Dermatitis Herpetiformis
Gluten Sensitivity
Diagnosing Celiac Disease
Screening Diagnosis
Treatment and Follow Up
Poorly Responsive Celiac Disease

Celiac Disease and Vaccinations
Celiac Disease and Diabetes
Celiac Disease and Crohn’s Disease
Future Therapies for Celiac Disease
Research
Research Studies
Celiac Disease in the News

Celiac Disease Foundation
Featured in Time Magazine
July 30, 2015
CELIAC DISEASE FOR PRACTITIONERS

- https://celiac.org/celiac-disease/provider-directory
- Be Listed in the CDF Healthcare Practitioner Directory
- Earn CME in Celiac Disease
- Earn CME in Gluten-Related Disorders
Celiac disease effects 1% of healthy average Americans. That means at least 3 million people in our country are living with celiac disease. 97% of them are undiagnosed.
THANK YOU
clepane@hotmail.com

KEEP CALM
EAT
GLUTEN FREE