Celiac Disease: Past, Present and Future

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Celiac Disease in the Past

➢ 50 A.D. - Aretaeus the Cappadocian “If the stomach be irretentive of the food and if it pass through undigested and crude, and nothing ascends into the body, we call such persons koeliacs”

➢ 1888 - Samuel Gee separates celiac disease from non-diet responsive chronic malabsorption. “On the Coeliac Affection...if the disease is to be cured at all it must be by means of diet”

Celiac Disease in the Present: Three Breakthrough Discoveries

➢ 1950 - Dicke publishes his medical school thesis: ‘Investigation of the harmful effects of certain cereals on patients with celiac disease’

➢ 1970’s –HLA DQ2 associated with celiac disease/dermatitis herpetiformis

➢ 1997 - The role of tissue transglutaminase in celiac disease identified
Pathophysiology

Step 1: Gluten Entry into the Submucosa
Step 2: Deamidation of Gluten by Tissue Transglutaminase (tTG)
Step 3: Immune Activation
Only HLA DQ2 and DQ8 are able to bind gluten!

Dermatitis Herpetiformis: Model for Celiac Disease Outside the Gut

Antibodies to TG3 or T cells primed to react to TG
Antibodies deposit at Dermal-Epidermal junction
Dapsone / sulfapyridine

Celiac Disease is a Multi-System Autoimmune Disorder

Hadjivassiliou et al. Lancet, Neuro 2010
Lane Hamilton Syndrome
IgA Nephropathy
MPGN
Cardiomyopathy
IHD
Fertility

Classic Celiac + Manifestations in:
Lung, Liver, Kidney, Blood Vessels, Placenta, etc
Changing Prevalence

What happened here?
IgA TTG serology > 95% accurate

United States
Finland

Lohi et al. APT 2007, Rubio-Tapia Gastro 2009

Mortality Risk in Celiac Disease


Current Epidemiology of Celiac Disease in the United States

Rubio-Tapia et al. AJG 2012

On Gluten Free Diet ~2 million
Seroprevalence of celiac disease ~2 million
Diagnosed with celiac disease and on a gluten free diet ~300,000
Current Definitions

- Celiac disease is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.

vs.

- Non-Celiac Gluten Sensitivity (NCGS) relates to one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded.


Initial Studies Suggest an Immune Mechanism for NCGS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Gluten Exposure (n=19)</th>
<th>Placebo Exposure (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4.1 (SD 0.0)</td>
<td>3.5 (SD 0.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>3.9 (SD 0.0)</td>
<td>3.2 (SD 0.0)</td>
</tr>
<tr>
<td>Thinness</td>
<td>3.1 (SD 0.0)</td>
<td>2.8 (SD 0.0)</td>
</tr>
</tbody>
</table>

VAS, visual analog scale.

*P values for analyses at weeks 1 and entire study period.

Gluten Exposure in Individuals without Celiac Disease reporting Gluten Responsive GI symptoms

Mean Change in Symptoms Over 6 Weeks

16g Gluten vs. Placebo
No Effect of Gluten on Symptoms

Role of alpha amylase/trypsin inhibitors (ATIs)

Current Paradigm

IBS
- Visceral Hyperalgesia
- ↑↓ Altered permeability
- ↑↓ Motility disturbance
- ↑↓ Low grade inflammation

NCGS
- Gluten related alterations in:
  - Intestinal permeability
  - Motility
  - Inflammation

Celiac Disease
- Intestinal and adaptive immune activation
- Auto-antibodies
- Destructive mucosal inflammation
Refractory Celiac Disease

• Less than 300 cases published from referral centers (10% nonresponsive CD)
• Females (2:1), >50 years old
• Population-based cohorts
  • 5 (0.7%) of 713 CD patients from Derby (UK)
  • 3 (1.4%) of 204 CD patients from Olmsted County
  • 8 (1.7%) of 480 CD patients from Boston
• Incidence 0.06 (95% CI: 0.0-0.12) per 100,000 persons years

Rubio-Tapia A et al, Gut 2010
West J. Gastroenterology 2009 136:02
Roshan B, Leffler DA et al AJG 2011

Abnormal IELs (CD3ε+ CD8-) in refractory sprue

Celiac Disease / Type 1 Refractory Sprue

Type 2 Refractory sprue

CD3 CD8

Cellier et al, Lancet 2000

Prognosis by Refractory Celiac Disease Classification

Al-toma et al, Gut 2007

Graph showing survival times for different types of refractory celiac disease.
Let Thy Food Be Thy Medicine

Hippocrates, 400 AD

- Strict gluten free diet is the only accepted treatment for celiac disease
- The GFD is one of the more challenging treatments we assign patients
- Involves avoidance of all wheat, rye and barley products
- Less than 50 mg of gluten (1/30th of a slice of bread) can cause significant, sustained mucosal inflammation
- Untreated celiac disease increases risk of malignancy, infection, and results in a 2-3 fold increase in mortality

Patient Satisfaction with the GFD is Low

- Controversial in the past
- Better scientific data and a more diverse celiac population → general acceptance

Treatment Burden is Second Only to Hemodialysis

*VAS: 0=Very Easy
100=Very Difficult

Shah S, Leffler DA, AJG 2014
Many Barriers to Staying Gluten Free

- Health concerns
- Cost
- Label reading
- Access to gluten-free foods
- Nutritional content
- Social and professional life
- Psychological well-being
- Medications
- Supplements
- Processed meats
- Frozen vegetables
- Soy sauce
- Seasonings
- Drink mixes

“Non-Responsive” Celiac Disease

Persistent or recurrent signs/symptoms occur in ~10-30% of patients

Histologic Recovery is Age Related
Current Recommendations for Celiac Monitoring

- Currently: No standard practice regarding need for and timing of clinical, serologic and histologic follow up
- Commonly recommended:
  - Clinical and serologic follow up Q3-6 months until normal than Q1-2 years
  - Histologic follow up: variable from repeat biopsy at 4-6 months to never if clinical and serologic response
  - DXA at least once

Available Biomarkers

- Excellent for diagnosis
  - tTG/DGP are >90% accurate
  - Biopsy confirmatory
  - Response to therapy supportive and typical
- Imperfect for monitoring
  - Drop in serologic titers after diagnosis is helpful
  - Repeat histology can be reassuring
  - Symptomatic improvement
  - BUT
  - Serology and symptoms are not predictive of mucosal healing
  - Histologic changes can be patchy and misleading and have differing responsiveness

Adriaanse, Leffler et al. in press, Adriaanse et al. Aliment Pharmacol Ther. 2013
Celiac Disease in the Future

Tight junctions are inter-cellular "gates" that open and close in response to internal and external stimuli.

Tight junction abnormalities trigger increased permeability and inflammation.

Modifying disease state epithelial permeability through the regulation of tight junctions – A potential paradigm shift in the treatment of immune mediated and inflammatory diseases.

Larazotide (Alba)

Phase 2a Larazotide Acetate: Prevention of Signs & Symptoms of Gluten Exposure During Two Week Gluten Challenge

- No differences in primary endpoint of LA:MA
- Prevention of immunological changes in PBMc (B cells)
- Daily diary: Reduction in frequency of bowel movements, abdominal discomfort & pain
- Safety comparable to placebo

ALV-003 (Alvine)

1. **Gluten Ingested**
   - Digestively Resistant Gluten Fragments

2. **Reaction**
   - Normal
   - Celiac Patient

3. **Triggers Immune Response and Inflammation in Small Intestine**
   - Gluten Peptide
   - Processed in the Mucosa
   - T Cell Activation
   - Celiac Specific Antigen Presentation

   Celiac Patient Immune Reaction

   Causes
   - Inflammation
   - Intestinal Mucosa

   Normal
   - No Immune Reaction

   Reaction 1

   Triggers immune response and inflammation in small intestine

   Reaction 2

   Triggers immune response and inflammation in small intestine

   Reaction 3

   Triggers immune response and inflammation in small intestine

   Phase 2a ALV-003: Prevention of Gluten Induced Mucosal Injury Exposure During 6 Week Gluten Challenge

   Nexvax (ImmunosanT)

   - Treatment shifts T cells from pro-inflammatory to tolerant response to gluten
   - Induces tolerance in a celiac mouse model
   - Phase 2a trials underway
   - Nexvax administration → symptoms mimicking oral gluten exposure

   Peptide library:
   - 18,117 13mers
   - 2,922 20mers
   - 3 16AA Proteins
   - Dominant peptides

   3 16AA Proteins
Non-Dietary (non-behavioral) Therapies: Transformative for Celiac Disease?

Case Study: Erectile Dysfunction

Though 1980 ED was considered an uncommon psychological disorder “all sexual dysfunctions are caused by a single factor: anxiety”

In the 1980s the first surgical/injectable ED treatments were approved →

1. “80% of ED cases stem from physical problems”
2. “The emergence of the urologist as the primary coordinator of care for the patient with sexual dysfunction”


Good Therapies → More Care and More Research

Conclusions

• In the past:
  – Celiac diagnosis/treatment limited to patients with classic symptoms and monitoring was non-existent
• In the present:
  – Diagnostic tools are excellent and diagnosis is improving
  – Histological recovery is slow/partial, recurrent symptoms are common and long term risks elevated
  – GFD is recognized as an imperfect therapy
  – Treatment and monitoring strategies are lacking which perpetuates reluctance to diagnose and follow
• In the future:
  – Novel therapeutics will significantly alter all aspects of celiac disease care, increasing diagnosis, encouraging monitoring and improving outcomes