Pathogenesis of Gluten Sensitivity: Translational Evidence of Innate Immunity

Ciarán P. Kelly, M.D.

Medical Director, Celiac Center
Beth Israel Deaconess Medical Center

Professor of Medicine
Harvard Medical School
Boston MA
Evidence of Innate Immunity in vitro & ex vivo studies

- Upregulation of inflammatory cytokine production in leukocytes & other cell types:
  - IL-1β, IL-2
  - IL-4, IL-12
  - IL-13, IL-23
  - TNFα, GM-CSF

- Modulation of the junctional complex, zonulin & permeability

Human trials in NCGS show ... ....

**Celiac disease versus Gluten Sensitivity versus Control**

**Intestinal permeability by lactulose and mannitol excretion**

**Genes involved in barrier function and immunity in mucosal biopsies**

**Gluten Sensitivity**
- No increased intestinal permeability
  - (in fact, significantly reduced compared with controls (P = 0.03))
- Increased expression of claudin 4 (P = 0.03)
- No increase in IL-6 or IL-21
- Innate immunity marker TLR-2 increased (P = 0.03).
- T-regulatory cell marker FOXP3 reduced in GS (P = 0.03)

“characterization of Gluten Sensitivity as a condition associated with gluten-induced activation of innate, rather than adaptive, immune responses in the absence of detectable changes in mucosal barrier function”.


“Overall symptoms” shown: Similar & significant differences for: Abdominal pain, bloating, tiredness & satisfaction with stool consistency

“There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability.”

On Gluten:

- More bowel movements per day (P = .04)

- Permeability effects:
  - Higher SB permeability (0-2 h mannitol & lactulose:mannitol ratio)
  - Small decrease in expression of zonula occludens 1 in SB mucosa
  - Significant decreases in expression of zonula occludens 1, claudin-1, and occludin in rectosigmoid mucosa

- Effects were greater in HLA-DQ2/8 positive patients

- No significant effects on transit or histology
No effects of gluten in patients with self-reported NCGS after dietary reduction of fermentable, poorly absorbed, short-chain carbohydrates.


- Double-blind cross-over trial of 37 subjects with NCGS and IBS.
- Low FODMAP diet followed by
  - high-gluten (16 g/d),
  - low-gluten (2 g/d and 14 g whey protein/d)
  - control (16 g whey protein/d)
- GI symptoms - improved on low FODMAP diet
- GI symptoms – worsened on gluten and on whey – no specific gluten challenge effect seen

“CONCLUSIONS: In a placebo-controlled, cross-over rechallenge study, we found no evidence of specific or dose-dependent effects of gluten in patients with NCGS placed diets low in FODMAPs.”
Variable Results of Gluten in Human Studies of NCGS & IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Symptoms</th>
<th>Permeability</th>
<th>Inflammatory markers</th>
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<tbody>
<tr>
<td>Sapone et al, BMC Med 2011</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Biesiekierski et al, Gastro 2011</td>
<td>No</td>
<td>Not studied</td>
<td>No</td>
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<tr>
<td>Vazquez-Roque et al, Gastro 2013</td>
<td>Yes</td>
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**Effects not confined to Gluten activity**
- FODMAPs - Fructans, galactans
- Prebiotic effects
- Wheatgerm agglutin (lectin)
- Amylase trypsin inhibitors (ATIs)

**Is NCGS the correct term?**