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A Dual Mechanism Hypothesis for Celiac Disease: Intraluminal Pressure-Induced Villous Compression and Nitrate-Driven Motility Impairment

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Abstract

Background: Celiac disease (CD) is an immune-mediated enteropathy triggered by gluten ingestion in genetically predisposed individuals, resulting in villous atrophy, crypt hyperplasia, and mucosal inflammation. While immunologic mechanisms are well characterized, the role of mechanical and biochemical factors in disease onset remains underexplored.

Objective: To propose a novel dual-pathway hypothesis for CD pathogenesis that integrates mechanical compression from intraluminal pressure and biochemical disruption from nitrate-derived nitric oxide accumulation.

Methods: A conceptual model was developed through synthesis of published data on intestinal gas dynamics, microbial nitrate metabolism, nitric oxide signaling, and mucosal immunity. This hypothesis combines insights from gastrointestinal physiology and immunopathology to suggest new mechanistic pathways.

Results: Hypothesize that (1) excessive intraluminal gas exerts mechanical stress on villi, altering their structure and function; and (2) nitrate-derived nitric oxide disrupts epithelial motility and barrier integrity. These two mechanisms may act synergistically to enhance translocation of gliadin peptides and microbial antigens into the lamina propria, promoting inflammation and tissue injury.

Conclusion: This dual mechanism hypothesis offers a new perspective on CD by highlighting underrecognized non-immunologic contributors to disease progression. It may suggest novel therapeutic targets focused on intestinal gas modulation, microbial ecology, and nitrate handling.

Limitations: This hypothesis has not been tested experimentally due to current limitations in funding and research resources, which restrict *in vivo* and clinical validation.

Keywords: Chronic functional abdominal pain, Crohn's disease, Crohn's disease, Gastroenterology, Gastrointestinal endoscopy, Inflammatory bowel disease

Introduction

Celiac Disease (CD) is a chronic autoimmune enteropathy driven by dietary gluten in individuals carrying HLA-DQ2 or HLA-DQ8 alleles. The hallmark features include villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis, mediated by both adaptive and innate immune responses. However, many patients report gastrointestinal symptoms such as bloating and distention, which suggest a potential role for physical forces and intestinal motility disturbances in disease manifestation and progression.

While the immune mechanisms of CD are well characterized, there is a need to explore non-immune contributors to mucosal damage. This paper proposes a novel hypothesis integrating two underappreciated factors: (1) mechanical

compression of intestinal villi due to gas accumulation and intraluminal pressure, and (2) biochemical disruption via microbial or dietary nitrate-derived nitric oxide, which may impair villous motility and barrier function.

Hypothesis

We propose that in celiac disease:

1. **Mechanical pressure–induced villous compression:** Excess gas in the small intestine increases intraluminal pressure, mechanically flattening villi and stretching epithelial tight junctions. This physical disruption may compromise barrier integrity and increase antigen translocation.

2. **Nitrate-induced villous motility impairment:** Nitrates from dietary or microbial sources are converted to nitric oxide, a known smooth muscle relaxant. Nitric oxide may inhibit the motility and structural dynamics of villous smooth muscle or stromal contractile cells, reduce absorptive efficiency and compromise epithelial regeneration.

3. **Amplified permeability and immune activation:** The combined mechanical and biochemical insults increase intestinal permeability, allowing gliadin peptides and microbial products to reach the lamina propria, where they activate dendritic cells, trigger cytokine cascades (e.g., tumor necrosis factor (TNF)-α, interferon (IFN)-γ), and amplify inflammation.

4. **Microbial composition and lipopolysaccharides (LPS) contribution:** In addition to mechanical and nitrate-induced disruption, the role of microbiota particularly the balance between gram-negative and gram-positive bacteria, may amplify or mitigate villous injury. Gram-negative bacteria release LPS, potent endotoxins that activate intestinal immune pathways and increase epithelial permeability. In CD, where mucosal integrity is already compromised, LPS translocation may exacerbate inflammatory cascades. Moreover, gram-negative species contribute to fermentation and gas production, reinforcing intraluminal pressure. Conversely, gram-positive commensals often produce short-chain fatty acids like butyrate, which can strengthen epithelial barriers. Thus, microbial composition is a key determinant of how mechanical and biochemical pathways influence CD progression.

Supporting Evidence

- **Gas and pressure in gastrointestinal disorders:** Elevated intraluminal pressure can disrupt tight junctions and epithelial integrity. Conditions like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) demonstrate barrier dysfunction under distention [1,2].

- **Mucosal sensitivity in CD:** CD patients exhibit enhanced mucosal reactivity and increased epithelial turnover, rendering villi more vulnerable to mechanical and oxidative stress.

- **Microbial dysbiosis and gas:** CD-associated dysbiosis increases fermentation gases (hydrogen, methane, CO_2), exacerbating pressure [3].

- **Nitrates and nitric oxide:** Nitrate-derived nitric oxide affects gastrointestinal smooth muscle and can impair barrier function by altering blood flow, motility, and signaling [4,5].

Experimental Approaches

1. ***In vitro* gut-on-chip models:** Simulate intraluminal pressure and nitrate exposure; assess epithelial integrity, cytokine release, and villous structure.

2. **Animal models:** Use gluten-sensitive mice to examine effects of controlled gas distention and dietary nitrate modulation on villous morphology and immune markers.

3. **Clinical imaging correlation:** Correlate imaging markers of bloating/distention with mucosal damage in CD patients using ultrasound or magnetic resonance imaging.

Conclusion

This hypothesis introduces a dual mechanical-biochemical model for villous disruption in celiac disease. If validated, this concept may broaden our understanding of CD pathophysiology and lead to novel therapeutic strategies targeting gas accumulation, microbial metabolism, and dietary nitrate intake.

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