Leaky Gut and Inflammation

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Disclosures

I have no relevant financial relationships to disclose

I will not discuss any off-label use and/or investigational use in my presentation
Objectives

- 1. Determine the importance of the microbiome to health
- 2. Describe the factors causing intestinal permeability and inflammation
- 3. Understand importance of treating intestinal permeability to restore health

The Gut in Our Lives

- To have a gut feeling
- To have a gut response
- Go with your gut
- Have a gut reaction
- Have a strong stomach
- Have a knot in your stomach
- To have guts
- My gut tells me
- Like a kick in the guts
- Gut wrenching
- Gut instinct
- No guts, no glory
Enlightenment and the Gut

“Having awoken to unsurpassed, perfect enlightenment—I am endowed with a stomach whose digestion is regular, by means of which everything I eat, drink, chew and enjoy is digested with perfect ease, and I am free of disease and have left illness behind”

Patient Terminology

Doc, I think I have leaky gut with systemic candidiasis making me feel achy and causing brain fog and fatigue. Can you help me?
Medical Terminology

Doc, I think I have increased intestinal permeability allowing bacteria and endotoxin translocation through damaged tight junctions causing a chronic inflammatory response. Can I repair this?

Intestinal Function

- Nutrient absorption
  - transcellular and paracellular transport
- Barrier to antigens and pathogens
- Secretion of enzymes and hormones
- Neuroendocrine function
- Immunologic function
Epithelial Barrier Composition

- Lining of enterocytes, turnover every 4–5 days, just a single layer
- Barrier between the external environment and internal milieu by tight junctions between cells
- Mucus Layer
- Bacterial layer
Claudin proteins are considered to be the structural backbone of TJ

Claudins determine the selective permeability of the barrier

Zonula occludens are the intracellular scaffold for the tight junction
Mucus Layer

Goblet cells secrete mucin glycoproteins and MUC2

MUC2 is the major mucin making up the mucus coat of the intestinal epithelium

Microflora

- Friend, foe and bystander
- Host and microbe interactions bidirectional
- Immune modulators, nutrition, inflammation
- Diet is the primary modifier of the microbiota
**Bacterial Layer**

- Inhabited by $10^{14}$ microbes
- Competes with pathogens for nutrients
- Fermentation of non-digestible carbohydrates to Vitamin K, biotin, folate, riboflavin, cobalamin
- Production of SCFA butyrate and acetate
- Improved tight junctions
- Improved UGI motility
- Production of satiety hormones

**Bacterial Colonization**

- Colonization begins at birth, lactobacillus from the vaginal canal
- The infant is exposed to several environmental sources of bacteria (e.g. skin, mouth, mother’s milk)
- Gut microbiota has fully matured by the first 1–2 years of life
- 5–day course of oral antibiotics modifies human gut microbiota for up to 4 weeks
Gut Bacteria

- **Firmicutes (~75%)**
  - Tolerates pH < 5.5, produces butyrate
- **Bacteroidetes (~20%)**,
  - Tolerates pH > 6.5
- **Lesser contributions from Proteobacteria and Actinobacteria**
- **Lowering carbohydrate/soluble fiber reduces butyrate production**
Degradation of bacteria and antigens by gastric acid, bile acids and digestive enzymes

Commensal bacteria inhibit colonization of pathogens by production of antimicrobial substances, enhance enterocyte function by producing SCFAs acetate and butyrate

Water, glycocalyx, and mucus layer prevent bacterial adhesion and produce antimicrobial substances
GALT

Gut–associated lymphoid tissue (GALT) is comprised chiefly of aggregated (Peyer’s patches, PPs) and isolated lymphoid follicles (ILFs)

70% of the immune tissue is in the gut

Oral Tolerance

- At birth the intestines have high permeability
- Exclusive breast feeding provides protection over the next 6 months of maturation
- During this time the immune system is maturing, recognizing self and commensal bacteria
- Thought that exposure to immunogenic foods at this time can initiate food allergies
Intestinal Permeability

- Loss of the tight junctions and the epithelial layer
- Bacteria and endotoxins translocate through the paracellular route
- Then detected by dendritic cells
- Immune reaction in Peyer’s patches
- General inflammatory reaction
- Possible autoantibody production or antibody cross reaction with self

Serious Causes/Consequences

- Cause of sepsis and death in burn patients
- Cause of sepsis in post-op patients
- Seen in HIV
- Observed in inflammatory bowel disease
Disruption of the Barrier

- Food allergies
- Bile acid malabsorption
- High-fat diet
- Stress and inflammation,
  - Mast cell receptors to cortisol
  - Genetic predisposition to increased inflammatory response
- Dysbiosis
  - Impair through release of inflammatory mediators
- Smoking breaks down the barrier
- Alcohol breaks down the barrier

Factors affecting mucosal immune system resulting in intestinal barrier dysfunction, autoimmunity and nervous system abnormalities

INTESTINAL BARRIER DYSFUNCTION
- FOOD ALLERGY & INTOLERANCE
- IMMUNE SYSTEM ABNORMALITIES
- AUTOIMMUNITY

INFLUENCE ON THE BLOOD-BRAIN BARRIER AND NEUROAUTOIMMUNITY
Intestinal Permeability

- Increased intestinal permeability is implicated as a cause of autoimmune, inflammatory, and atopic diseases
- Increased with aging and stress
- Combination of genetics and antigens
- Associated with deficiencies of Vitamin D, Zinc, Magnesium, Calcium, B12, and Vitamin A

Gastrointestinal Disease

- Ulcerative colitis, Crohn’s disease, celiac disease and irritable bowel disease are examples of diseases of the GI tract with increased permeability
Disease Associations

- Crohn’s
  - seronegative spondyloarthropathy, erythema nodosum, autoimmune hemolytic anemia, uveitis
- Ulcerative Colitis
  - seronegative spondyloarthropathy, erythema nodosum, autoimmune hemolytic anemia, uveitis
- Celiac Disease
  - diabetes mellitus type 1, non-Hodgkin's lymphomas
- Irritable Bowel Disease
  - interstitial cystitis, fibromyalgia, endometriosis

Diseases Associated with Increase Intestinal Permeability

- Diabetes mellitus type 1
- Multiple sclerosis
- Rheumatoid arthritis
- Ankylosing spondylitis
- Irritable bowel disease
- Schizophrenia
Type 1 Diabetes

- ~50% have increased serum zonulin levels associated with increased intestinal permeability
- 25% of unaffected family members have increased zonulin levels
- Suggests loss of intestinal permeability a part of this process, but needs an exposure to antigen
- Association of Ab to Glo-3a wheat protein and islet cell auto-immunity

Progression to Disease

- The host must have a genetic susceptibility
- The host must be exposed to the antigen in the intestinal lumen
- The antigen must be presented to the GALT through paracellular transit
- The permeability of the intestine must be altered to allow this
- The key modulator is upregulation of zonulin, opening the gates previously closed by tight junctions
Intestinal Permeability and Autoimmune Diseases

- Autoimmune diseases involve a miscommunication between innate and adaptive immunity
- The continuous stimulation by nonself-antigens seems to be necessary to perpetuate the process
- Loss of the protective function of mucosal barriers that interact with the environment is necessary for autoimmunity to develop

Celiac Disease as an Example

- Genetic predisposition through HLA genes
- The gliadin antigen
- A highly specific humoral autoimmune response against tissue transglutaminase auto-antigen
- An early loss of tight junctions mediated through increase of zonulin
- Reversed with the removal of the environmental antigen
Toll-like receptors activated by bacterial lipopolysaccharides
TLR present in adipocytes, immune cells, epithelial cells and create an inflammatory response
Diet alters the gut microbiota: protein vs. vegetables
Altered gut microbiota, increased gut permeability

Mediterranean diet decreases inflammatory disease without weight loss

Bacterial lipopolysaccharides cause inflammation in the obesity state
High-fat meals increase intestinal permeability through changes in occludin and zonulin
Bacterial lipopolysaccharides increased after a high fat meal via translocation
Increase in inflammatory markers such as NF-kB
IBS and Permeability

- Studies have shown increased permeability
- Increased number of mast cells in IBS
- Mast cells have corticotrophin releasing factor receptors
- Increased permeability as measured by L:M ratios correlated to increased severity of pain
- Increased number of mast cells correlated with fatigue
- Decreased glutamine synthetase in IBS

IBS and Inflammation

- An abnormal IL-10/IL-12 ratio in patients with irritable bowel syndrome is indicative of a proinflammatory Th-1 state; has been shown to be normalized by Bifidobacterium infantis
Atopy and Probiotics

- Lactobacillus given to pregnant women reduced atopy in infants
- Lactobacillus given to infants reduced the incidence of atopy
- Probiotics given to infants with atopy reduced the severity of disease

Treating Increased Permeability

- Probiotics
  - increase barrier function
  - butyric acid, acetic acid, propionic acid
  - Treat the dysbiosis

- Glutamine
  - energy source for the rapidly dividing enterocytes,
  - improves the tight junction
Elimination Diet, 4 weeks

- Oranges
- Egg
- Dairy
- Gluten
- Beef, pork, shellfish
- Soy
- Corn
- Alcohol, coffee, soda
- Sugars, artificial sweeteners

Conclusion

- The intestine is a barrier to antigens
- The microbiome improves this function and the health of the enterocytes
- 70% of the immune system lines the gut
- Integrity of the tight barriers prevent translocation of antigens and endotoxins
- These then can stimulate an innate or adaptive immune reaction
- Causing inflammation and subsequent disease
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