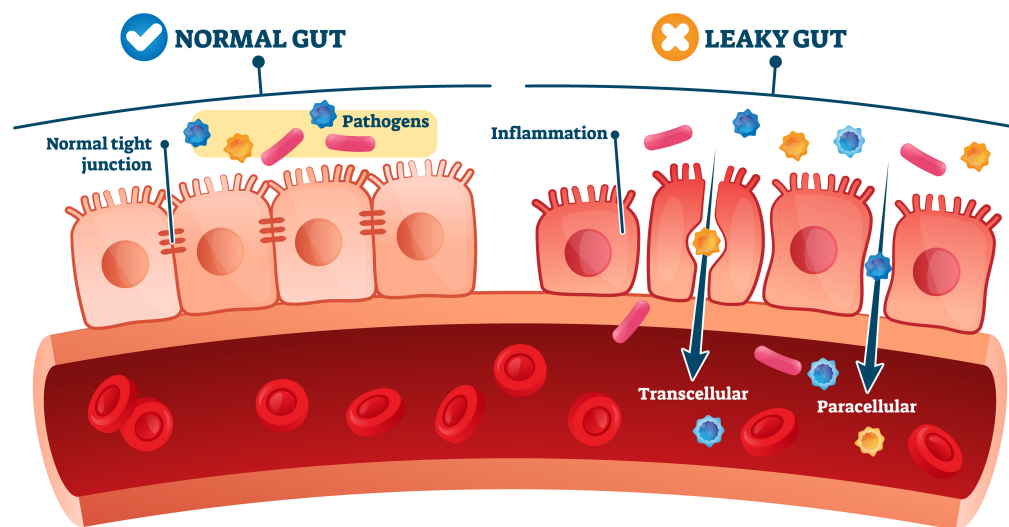


Zonulin is a protein molecule involved in the regulation of intercellular tight junctions between epithelial cells in the intestinal wall. When it binds to specific receptors on the cell surface, the tight junctions open and as a result increase the permeability of the intestinal epithelial cells. Increased permeability in the intestines can leak bacteria and their byproducts (lipopolysaccharides LPS), yeast and large protein molecules and other compounds into the bloodstream which leads to allergic responses and other immune activation. Inflammatory compounds released from immune cells is now recognized as a major source of chronic inflammation leading to metabolic disruption and are regarded as a major factor in aging and chronic health issues. Causes of increased expressions of zonulin includes certain pathogens, damaged intestinal mucosal layer, microbiome disruption, chronic stress or dietary issues like low fiber and high fat choices and contact with gliadin. The invasion of foreign antigens and cell components eventually trigger GUT-Immune dysregulation, which has far reaching negative health consequences

Increased levels of zonulin is indicative of GUT mucosal barrier disruption and leaky gut. The consequences of increased zonulin include related conditions below:

LEAKY GUT



ASSOCIATED CONDITIONS:

- ADHD
- Adult glucose intolerance
- Aging
- Ankylosing spondylitis
- Asthma
- Autism
- Celiac disease
- Chronic fatigue syndrome
- Colitis
- Gestational diabetes
- Glioma
- Hyperlipidemia
- HIV
- Inflammatory bowel disease
- Major depression
- Multiple sclerosis
- Non-celiac gluten sensitivity
- Nonalcoholic fatty liver disease
- Rheumatoid arthritis
- Type I and 2 diabetes; insulin resistance

RECOMMENDED MANAGEMENT OPTIONS:

- IgE, IgG, IgG4 and C3 b/d complement food testing.
- Removal of foods sensitivities – elimination diet based on lab results
- Stool testing - Identification of pathogens, enzyme deficiencies and gut flora that could be altering Zonulin dependent tight junction regulation.
- Oral immunoglobulins - block Zonulin from binding to gut mucosal receptors and prevent tight junctions from opening up.
- Probiotics-Bifidobacterium and Saccharomyces have been reported in the literature to decrease leaky gut and help improve immune response. ,
- L-Glutamine to help to inhibit inflammation and oxidative stress linked to tight junctions and to support mucosal integrity.

Histamine is an organic nitrogenous compound which naturally occurs in the human body, where it acts as neurotransmitter and is involved in immune responses and the regulation of physiological functions. A major cause of histamine production is through degranulation of mast cells located in many tissues in the body. In an allergic reaction, the immune system releases a high level of histamine, leading to inflammatory reactions which are responsible for typical allergic symptoms. High histamine has far reaching consequences over and above traditional allergic response symptoms. Those who are intolerant to histamine can even have similar reactions from an oral intake of histamine containing foods

The Histamine Intolerance test (HIT) measures Histamine levels in the blood. Histamine intolerance is thought to be related to a build-up of histamine. In a healthy individual, histamine is broken down by two enzymes – diamine oxidase (DAO) and histamine N-methyltransferase (HNMT). Symptoms may occur when one of these enzymes are not working correctly or if histamine production is triggered through gene activation due to chronic immune activation. DAO is manufactured in the intestinal cells. Erosion of intestinal epithelial cells from changes in gut permeability or dysbiosis can result from not having enough DAO to break down histamine. In addition, excessive allergic response can compromise DAO levels. When this occurs, histamine levels increase triggering a wide variety of symptoms.

HIGH HISTAMINE FOODS:

- Alcohol, especially red wine and sparkling wine
- Cultured dairy - Aged Cheeses, yogurt, sour cream, buttermilk
- Processed meats / smoked meats (chorizo, salami, ham, bacon, jerky)
- Fish, shellfish and fish sauces
- Certain vegetables (eggplant, tomatoes, chickpeas and spinach)
- Certain fruits (olives, citrus, dried fruits, avocados, grapes, strawberries, pineapple and banana)
- Peanuts, walnuts
- Coffee, vinegar
- Chocolate
- Fermented foods – pickles, vinegar, soy sauce, fish sauce, miso, etc.
- Sourdough bread, yeast, marmite
- Leftovers
- Reduce canned food intake

Decreased DAO levels may explain why histamine intolerance symptoms are more common in individuals with gut disorders such as inflammatory bowel disease (IBDs), irritable bowel syndrome (IBS), celiac disease, ulcerative colitis and small intestinal bacterial overgrowth (SIBO). DAO activity can also be blocked by over 90 medications, which 20% of our population takes on a daily basis. This list includes:

- Acetylsalicylic acid (aspirin)
- Antibiotics
- Antidepressants - TCAs
- Antimalarial drugs
- Antipsychotics - haloperidol
- Antituberculosis drugs
- Benzodiazepines – diazepam
- Bronchodilators, such as theophylline
- Cardiovascular medications – antihypertensives, dobutamine, antiarrhythmic
- Diuretics – furosemide (Lasix)
- Expectorants/Mucolytics – guaifenesin
- Gastrointestinal motility medicines – metoclopramide (Reglan)
- Muscle relaxants
- nausea and gastroesophageal reflux disease, GERD
- NSAIDs – ibuprofen, naproxen
- Pain medications - opioids
- Ulcer medications – H2 blockers cimetidine, ranitidine, etc.

FOODS REPORTED TO BLOCK THE DAO ENZYME:

- * Alcohol – aggressively attacks DAO
- Black tea
- Energy drinks
- Mate tea

HIGH HISTAMINE SYMPTOMS INCLUDE:

- Abdominal discomfort/cramps
- Abnormal heart rate
- Anaphylaxis
- Asthma, shortness of breath
- Body temperature variations
- Circadian rhythm
- Congestion
- Constipation
- Diarrhea
- Dizziness
- Flushing
- Increased food intake
- Gas
- Headache
- High or low blood pressure
- Hives
- Insomnia
- Itching
- Low muscle tone
- Memory
- Menstrual disturbances
- Nausea, vomiting
- Painful menstruation
- Runny nose
- Sleep issues
- Sneezing
- Tachycardia and arrhythmia
- Vaginal dryness
- Watery eyes

RECOMMENDED MANAGEMENT OPTIONS:

- Diamine Oxidase (DAO) supplements to help breakdown histamine in the body.
- Remove high histamine foods.
- Identification of gut flora that could be producing histamine (stool testing).
- Also consider the following as these have been reported to assist in the breakdown of histamine and decrease degranulation of mast cells.
- Vit C
- B6
- Zn/Cu
- Bromelain
- Magnesium
- Mangosteen fruit extract
- Quercetin
- Stinging nettle leaf (*Urtica dioica*) – freeze-dried optimal – leaf only
- *Tinospora* (*Tinospora cordifolia*)

REFERENCES

- Fasano A. Zonulin and its regulation of intestinal barrier function: the biological door to inflammation, autoimmunity and cancer. *Physiol Rev.* 2011;91(5):151-75.
- Hotamisligi GS. Inflammation, metaflammation and immunometabolic disorders. *Nature.* 2017;542:177-85.
- Sturgeon C, et al. Zonulin, a regulator of epithelial and endothelial barrier functions, and its involvement in chronic inflammatory diseases. *Tissue Barriers.* 2016;4(4):e1251384.
- Fasano A. All disease begins in the (leaky) GUT: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F10000 Res.* 2020;9:LF1000 Faculty Rev-69.
- Fasano A. All disease begins in the (leaky) GUT: role of zonulin-mediated gut permeability in the pathogenesis of some chronic inflammatory diseases. *F10000 Res.* 2020;9:LF1000 Faculty Rev-69.
- Uray NS, et al. Serum Bovine Immunoglobulins Improve Inflammation and Gut Barrier Function in Persons with HIV and Enteropathy on Suppressive ART. *Pathog Immun.* 2019;4(1):124-46.
- Terciolo C, et al. Beneficial effects of *Saccharomyces boulardii* CNCM I-745 on clinical disorders associated with intestinal barrier disruption. *Clin Exp Gastroenterol.* 2019;12:67-82.
- Ahmadi AR, et al. The Effects of Probiotic/Synbiotic on Serum Level of Zonulin as a Biomarker of Intestinal Permeability: A Systematic Review and Meta-Analysis. *Iran J Public Health.* 2020;49(7):1222-1231.
- Rapin JR, et al. Possible links between intestinal permeability and food processing: a potential therapeutic niche for glutamine. *Clinics (sao Paulo).* 2010;65(6):635-43.
- Thangam, EB, et al. The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets. *Front Immunol.* 2018;9:1873.
- Music E, et al. Serum diamine oxidase activity as a diagnostic test for histamine intolerance. *Wein Klin Wochenschr.* 2013;125(9-10):230-43.
- Sanchez-Perez S, et al. Biogenic amines in plant-origin foods: are they frequently underestimated in low-histamine diets? *Foods.* 2018;7(12):205.
- Manzotti G, et al. Serum diamine oxidase activity in patients with histamine intolerance. *Int J Immunopathol Pharmacol.* 2016;29(1):105-11.
- Sattler J, et al. Inhibition of human and canine diamine oxidase by drugs used in an intensive care unit: relevance for clinical side effects? *Agents Actions.* 1985;16(3-4):91-4.
- Schnedl WJ, et al. Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. *Food Sci Biotechnol.* 2019;28(6):1779-84.
- Comas-Baste O, et al. Histamine intolerance: the current state of the art. *Biomolecules.* 2020;10(8):1181.
- Schnedl WJ, et al. Diamine oxidase supplementation improves symptoms in patients with histamine intolerance. *Food Sci Biotechnol.* 2019;28(6):1779-84.
- Kettner L, et al. Evaluation of porcine diamine oxidase from the conversion of histamine in food-relevant amounts. *J Food Sci.* 2020; 85(3):843-52.
- Schink M, et al. Microbial patterns in patients with histamine intolerance. *J Physiol Pharmacol.* 2018;69(4): doi: 10.26402/jpp.2018.4.09.