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Imbalances in Zonulin, histamine, DAO and LPS are associated with intestinal permeability, often referred to as, "leaky gut."

When the gut barrier is weakened, a person is more vulnerable to food antigens, toxins, and unfriendly microbes. A leaky gut tears down the body's defenses and opens up the system to increased inflammation. There are many possible causes of damage to the GI lining and subsequent leaky gut.

Common causes of intestinal permeability are bacterial overgrowth, food sensitivities including gluten sensitivity, NSAIDs, and alcohol consumption.

Reducing inflammation and healing the GI lining can help restore the GI barrier and normalize Zonulin, DAO, histamine, and LPS.

## High Zonulin

High plasma zonulin is associated with intestinal permeability. Zonulin is a protein that leads to the break-down of tight gap junctions in the GI lining. These junctions are critical for a healthy barrier against the outside world.

When the gut barrier is weakened, a person is more vulnerable to food antigens, toxins, and unfriendly microbes. A leaky gut tears down the body's defenses and opens up the system to increased inflammation.

Increased levels of zonulin may be a contributing factor in the development of celiac disease, autoimmune disorders, insulin dependent diabetes, multiple sclerosis and rheumatoid arthritis. Higher zonulin levels have been reported in patients with active celiac disease compared to non-celiac patients.

<sup>1-3</sup>Zonulin levels elevate 2-5 years before diabetes, autoimmune conditions, and allergies. Zonulin may therefore be an early marker of disease processes.

## Histamine Intolerance

Histamine intolerance can develop when a person has abnormal levels of histamine and the histamine-degrading enzyme, diamine oxidase (DAO). Typical symptoms of histamine intolerance are headache, diarrhea, migraine, and engorged or dripping nose.

Histamine intolerance might be more obvious with specific food triggers leading to asthma and arrhythmia, hypotension, urticaria, and dysmenorrhea. When DAO or histamine is imbalanced, the main focus of treatment is to increase DAO, reduce histamine, and heal the gut.

## High Histamine

- Anaphylaxis
- Gas
- Low muscle tone
- Painful menstruation
- Circadian rhythm
- High blood pressure
- Shortness of breath
- Body temperature
- Dizziness
- Congestion
- Runny nose
- Food intake
- Nausea, vomiting
- Food intake
- Hives
- Memory
- Diarrhea
- Flush
- Locomotion
- Stomach Ache
- Itching
- Cramps
- Abnormal heart rate
- Headache
- Sneezing



## Histamine

Histamine balance is a critical factor in patients with allergic and gastrointestinal symptoms. Histamine was first discovered for its role in anaphylactic allergy. A specific allergen can trigger the degranulation of mast cells, subsequently releasing histamine. This can lead to severe, life-threatening symptoms. When the gut barrier is weakened, a person is more vulnerable to food antigens, toxins, and unfriendly microbes. A leaky gut tears down the body's defenses and opens up the system to increased inflammation.

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Classic symptoms of high histamine are tachycardia, headache, flushing, urticaria, pruritis, hypotension, bronchospasm, and cardiac arrest. However histamine can have far-reaching impacts and lead to many atypical symptoms because it binds cells throughout the body in the gastrointestinal tract, respiratory tract, skin, cardiovascular system, and central nervous system, among others.

Gut permeability can also increase histamine. Leaky gut activates T cells and triggers degranulation of histamine-containing mast cells. In addition to histamine made in the body, we consume histamine in varying amounts in foods. An excellent full text review of this topic is available.<sup>1</sup>

After extreme histamine exposure, like in anaphylactic shock, levels of both diamine oxidase and histamine will be elevated. Low histamine levels may cause fatigue or depression. Alterations of histamine have been noted in sleep-wake disorders such as narcolepsy, as well as other neurological and psychiatric diseases. Brain levels of histamine are decreased in Alzheimer's and low histamine has been seen in cases of convulsions and seizures.

## High Histamine Foods

**Very High:** Aged or fermented foods: kimchi, sauerkraut, yogurt or kefir, kombucha, aged cheese, alcohol of any kind, vinegar, and cured meat. Fish and seafood, especially canned or smoked fish.

**Medium:** Spinach, eggplant, mushrooms, tomatoes, canned vegetables, dried fruit, avocados, strawberries, papaya, pineapple, and leftovers.

## DAO

Diamine oxidase (DAO) is histamine's vital counterpart and the primary enzyme responsible for keeping histamine levels in check. DAO degrades extracellular histamine and is mainly produced in the microvilli of the small intestine. When diamine oxidase is low it means the patient cannot properly break down histamine. Histamine-N-methyl-transferase (HNMT) is the secondary enzyme involved in histamine break down.

Low diamine oxidase is associated with headaches, fatigue, hives, any allergy symptom, dysmenorrhea, estrogen dominance, arrhythmia, inflammation, arthritis, and certain neurologic conditions such as multiple sclerosis. Symptoms of low DAO are essentially identical to symptoms of histamine excess because they are two sides of the same coin.

Low levels of DAO correlate with poor mucosal integrity and indicate poor gut function. Atrophy of the microvilli can cause low DAO. Patients suffering from diseases like urticaria, Crohn's, or celiac disease are reported to show low DAO activity in serum or plasma.<sup>4,5</sup> Low DAO can also be a trigger for depression or anxiety. Low diamine oxidase in plasma can be used to diagnose histamine intolerance. Individuals with an inability to break down histamine may seem to "react to everything," or improve on anti-histamines. Those with anaphylactic reactions often have lower DAO activity. Following a histamine-free diet can result in a significant reduction, or even disappearance, of symptoms within a few weeks.

Many medications inhibit DAO or damage the gut lining, reducing DAO production. Alcohol and its degradation product, acetaldehyde, are inhibitors of DAO.

## DAO: Histamine Ratio

The DAO: Histamine Ratio helps detect subtle imbalances between histamine and DAO levels. Even if the DAO enzyme level is normal, symptoms can occur when histamine is high. A low ratio indicates that there may not be enough of the DAO enzyme relative to the amount of histamine in your body.

Treatments to normalize DAO or histamine will also improve this ratio.



## High LPS

An elevated lipopolysaccharide (LPS) reaction indicates intestinal permeability or “leaky gut.” Lipopolysaccharide is the immunogenic portion, as well as the major constituent, of the outer cell membrane of gram-negative bacteria. LPS is a bacterial endotoxin made by bacteria in the body.

When lipopolysaccharides are high in the blood, it means they are passing not only between intestinal cells, but also directly through the cells, potentially causing neuroinflammation<sup>6</sup> and brain injury.<sup>7</sup> When LPS is absorbed into systemic circulation it can elicit a strong immune response.

Elevated levels may be associated with bacterial infection, food sensitivities, chronic inflammation, autoimmune conditions, digestive disorders, and neurological conditions.

## High LPS

There is clinical importance to having a low immune reaction to LPS antibodies. Since there will always be some LPS present, there should be an immune response recorded. When a patient tests on the low end of the spectrum for an immune response for LPS IgG, LPS IgA and LPS IgM, this is a good indication that their immune system is not functioning as it should. When there is a low response this means immunoglobulin levels go down and bacterial levels stay up. Ongoing gut pain and flairs persist, as patients can no longer fight infections as they should and the higher level of bacteria in the gut causes irritation.

Conditions associated with low LPS antibodies are IBS, Crohns Disease and Colitis.

## Conditions Associated with Elevated Levels of LPS

- Shock
- Multiple Organ Dysfunction
- Depression
- Anxiety
- Sepsis
- Atherosclerosis
- Obesity
- Type 2 Diabetes
- Alzheimer’s
- Autoimmunity
- Infertility
- Hypogonadism
- Leptin Resistance
- Chronic Constipation
- Mood and Appetite Disorders
- Cognitive Decline
- Anorexia
- Parkinson’s
- Chronic Pain

Analytes	Low Levels
Zonulin	Low Zonulin is not clinically significant.
DAO	Low DAO is a result of atrophied microvilli demonstrating gut permeability. This will also result in an inability to degrade histamine creating sensitivity and symptoms associated with histaminosis. See High Histamine for Treatment.
Histamine	Low levels can be associated with fatigue depression and certain types of schizophrenia. Histadine and accessory amino acids can be given to raise levels.
DAO: Histamine	A high ratio shows that the gut lining is in balance between its ability to make and degrade histamine.
LPS IgA, IgM, IgG	Low LPS Antibodies are associated with an immune system that is chronically worn down. IBS and IBD can both be a result of an infection that was chronic and that has resulted in little to no immune reserve. Immunoglobulins are an excellent intervention. Adequate Vitamin A and D as well as adequate protein can also help to increase levels.



Analytes	High Levels
Zonulin	<p>Possible bacteria, yeast, gluten.</p> <p>Treatment:</p> <ul style="list-style-type: none"> <li>• Treat dysbiosis with berberines from Golden Seal or Oregon grape, garlic, and oregano.</li> <li>• Immunoglobulins sourced from colostrum, egg, or serum because immunoglobulins block Zonulin from binding to tight junctions.</li> </ul>
DAO	<p>DAO will increase initially to compensate for higher levels of histamine from dysbiosis, immune dysregulation of foods. It is a compensatory response due to challenge of histamine. Treat by lowering histamine. Higher levels may also just be associated with healthy microvilli and a robust production.</p>
Histamine	<p>Increased levels are secondary to antigens causing mast cell degranulation. Also, certain bacteria can create histamine and certain foods are higher in histamine.</p> <p>Treatment involves increasing DAO to degrade histamine; consider Omega 3 fatty acids, Vitamin C, Copper, B6 and Sacchromyces. SAME to increase methylation of histamine, or B5 to acetylate histamine.</p> <p>Other therapies to decrease degranulation of mast cells or histamine producing cells include: Quercetin, Vitamin C and Omega3 fatty acids.</p>
DAO: Histamine	<p>When the ratio is elevated it means you do not have enough Diamine oxidase to degrade histamine. See Histamine above for treatment.</p>
LPS IgA, IgM, IgG	<p>This indicates that the immune system is actively fighting bacterial overload. Treatments include antimicrobials to lower bacterial load.</p>
LPS High IgM: Low IgG	<p>A high IgM with a Low IgG means there was poor seroconversion to a matured response to LPS. Antimicrobial therapies and immunoglobulins will support improvement in these areas.</p>

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