Zonulin: Key to Leaky Gut Pathogenesis and a Factor in Inflammation, Autoimmune Disease and Cancer

Over the past 15 years, an accumulation of published research has continued to support the hypothesis that Zonulin, a protein compound is a key modulator of the tight junctions between enterocytes in the intestine.

Here is a quick overview of Zonulin From Wikipedia:

Zonulin

Zonulin is a protein that modulates the permeability of tight junctions between cells of the wall of the digestive tract. Initially discovered in 2000 as the target of zonula occludens toxin, secreted by cholera pathogen Vibrio cholerae,[1] it has been implicated in the pathogenesis of coeliac disease[2] and diabetes mellitus type 1.[3] It is being studied as a target for vaccine adjuvants.[4] ALBA Therapeutics is developing a zonulin receptor antagonist, AT-1001, that is currently in phase 2 clinical trials.

Gliadin (glycoprotein present in wheat) activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules. [5]

An article by Dr. Jill Carnahan, MD (IFM certified in Functional Medicine) provides a good overview on this topic:

An amazing discovery a few years ago revolutionized our ability to understand the gut and permeability and how this impacts a wide range of health conditions from cancer to autoimmune disease to inflammation and food sensitivities.
Zonulin is the “doorway” to **leaky gut**

Zonulin opens up tight junctions in the intestinal wall: that normally occurs, in order for nutrient and other molecules to get in and out of the intestine.

However, when leaky gut is present, the tight junctions between the cells open up too much allowing macromolecules to get into the bloodstream where an immunologic reaction can take place. Once that happens, the body is primed to react to those proteins each and every time they appear.

It can also cause leakage of intestinal contents, like bacteria into the immune system creating inflammation and overloading the liver’s ability to filter out this garbage.

**Triggers that open the zonulin doorway**

**Based on Dr. Fasano’s research, we know that the two most powerful triggers to open the zonulin door are gluten and gut bacteria in the small intestine.**

**Gliadin causes zonulin levels to increase both in those people who have celiac disease and those who do not.** As the zonulin level rises, the seal between the intestinal cells (tight junctions) diminishes, opening up spaces between the
enterocytes that allow all sorts of things to pass right through. This is called “leaky gut”.

The immune system may be primed to think that these are foreign invaders and will mount an immune response leading to food sensitivities. In addition this immune activation leads to more damage to the enterocytes and the gut becomes more inflamed and more permeable or “leaky”. As the damage continues, the microvilli that line the intestines and absorb nutrients become damaged, leading to other nutrient deficiencies.

**Top causes of increased zonulin and development of leaky gut:**

1. Overgrowth of harmful organisms, like bacteria or yeast in the intestine
   1. SIBO (small intestinal bacterial overgrowth)
   2. Fungal dysbiosis or candida overgrowth
   3. Parasite infections
2. Gliadin in the diet (from gluten containing foods)

However, a study published in the Scandiavian Journal of Gastroenterology in 2006 clearly showed that gliadin can affect zonulin **even in people without the gene for celiac**. The researchers concluded that

*Based on our results, we concluded that gliadin activates zonulin signaling irrespective of the genetic expression of autoimmunity, leading to increased intestinal permeability to macromolecules.*

The significance of this is that gluten affects intestinal permeability in all persons to different extents. It also means that 100% of patients with autoimmune disease or leaky gut could potentially benefit from a gluten-free diet.

**Elevated zonulin levels and leaky gut are also associated with the following:**

1. Crohn’s disease
2. Type 1 Diabetes
3. Multiple Sclerosis
4. Asthma
5. Glioma
6. Inflammatory Bowel Disease

In conclusion the article states:

*Genetic predisposition, miscommunication between innate and adaptive immunity, exposure to environmental triggers, and loss of intestinal barrier function secondary to the activation of the zonulin pathway by food-derived environmental triggers or changes in gut microbiota all seem to be key ingredients involved in the pathogenesis of inflammation, autoimmunity, and cancer.*

*This new theory implies that [once this path is activated] it can be... reversed by preventing the continuous interplay between genes and the environment.*

*In a recorded interview with Chris Kresser, L.Ac., Dr. Fasano indicated the significance of upregulated zonulin levels on a variety of health issues:*

Upregulated zonulin levels can be present even after individuals have adopted a gluten-free diet. This is true not only for celiac patients, but also for other people with different kinds of autoimmune diseases:

*Dr. Alessio Fasano:*

We have seen this in celiac disease and type 1 diabetes and multiple sclerosis. When we discovered what zonulin is all about in terms of genes, now we know that zonulin is the precursor of a molecule, a protein called haptoglobin 2, so we know what kind of molecule it is.

And using that as a biomarker, we see that there are three major categories of conditions that see zonulin upregulated or present in a mutated fashion.

*These are autoimmune diseases, and besides the three that I just mentioned, it has been proven in Crohn’s disease, for example, and in another category there are tumors ovarian cancer, pancreatic cancer, glioma, these kinds of cancers, and then in diseases of the nervous system, including schizophrenia and autism.*
The significance of Zonulin and its impact on not only Leaky Gut but a variety of other potentially significant health issues cannot be underestimated and it reinforces the importance of reviewing the impact that grains in our modern diet have on our overall health.

Now Available:

**Daily Body Restore: Revolutionary Probiotic plus Digestive Enzymes Formulation**

(Featuring 10 digestive enzymes plus 9 human strain probiotic bacterial species (13 billion CFU’s))

Key Biotics products that impact on gut health include the following:

- L-Glutamine Powder
- L-Glutamine Caps
- Beta Plus
- Beta-TCP
- Betaine Plus HP
- Hydro-Zyme (HCl & Enzymes)
- BioDoph-7 Plus
- BioDophilus-FOS
- BioDophilus Caps
**Gastrazyme**

**Categories:**

AntiInflammatory, Digestion, Gall-Bladder-Support, Gastrointestinal, NPN, Vegetarian

**Description:**

Gastric inflammation and Morning Sickness

**Indications:**

Methionine (derived from cabbage) an amino acid, has historically been referred to as 'vitamin U' in the European research literature, is known for it's Gut Healing properties

**IPS (Intestinal Permeability Support)**

**Categories:**

Allergies, AntiInflammatory, Digestion, Energy-Boost, Gastrointestinal, H-Pylori, Immune-Support, NPN, NeoNatal-Glandulars

**Description:**

Leaky Gut Support

**Indications:**

For Irritable Bowel Syndrome, leaky gut, colitis, Crohn’s disease, allergies, intestinal mucosa repair, and gut detoxification. Lays down a new mucosa layer on the inside of the gut wall, inhibits food leakage thus reduces allergic reactions

**Ingredients:**

Proprietary, broad-spectrum formula (650 mg) including Jerusalem artichoke, glutamine, porcine intestine concentrate, Tillandsia (Spanish Moss), glucosamine sulfate, gamma oryzanol, glutathione and catalase
A.D.P. (Anti-Dysbiosis Product)

Categories:

Allergies, Anti-Inflammatory, Antimicrobial, Blood-Cleansing, Detoxification-Liver, Digestion, Gastrointestinal, H-Pylori, Microemulsified, NPN, Respiratory, Virus-Support

Description:

Oregano Oil - Standardized Emulsified Sustained Release 50 mg/tab

Indications:

To BREAK DOWN BIOFILMS.

Gut dysbiosis, toxic bowel syndrome, candida, intestinal parasites, yeast, fungus, genital-urinary tract infections and for antimicrobial action with upper respiratory bacterial or viral infections, especially in the case where there is antibiotic resistance. ADP can be used with Liquid Iodine or Liquid Iodine Forte™ Always follow up with probiotics after use over 2 weeks. Use BioDoph FOS (if constipated) BioDoph 7 Plus (if diarrhea) or Lactozyme (vegetarian).

Ingredients:

Micro-emulsified standardized sustained release oregano oil 50 mg/tab
Regards,

Rob Lamberton

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**Abstract:**
The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and to electrolytes and water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens.

*Zonulin is the only physiological modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the finely tuned zonulin pathway is deregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune, inflammatory, and neoplastic disorders can occur.*

This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by reestablishing the zonulin-dependent intestinal barrier function. This review is timely given the increased interest in the role of a “leaky gut” in the pathogenesis of several pathological conditions targeting both the intestine and extraintestinal organs.
“Besides celiac disease, several other autoimmune diseases, including type 1 diabetes, multiple sclerosis, and rheumatoid arthritis, are characterized by increased intestinal permeability secondary to non-competent tight junctions that allow the passage of antigens from the intestinal flora, challenging the immune system to produce an immune response that can target any organ or tissue in genetically predisposed individuals,” Fasano wrote in the February 2012 issue of *Clinical Reviews in Allergy and Immunology*.2

3. ^ Sapone, A; De Magistris, L; Pietzak, M; Clemente, MG; Tripathi, A; Cucca, F; Lampis, R; Kryszak, D; Carteni, M; Generoso, M; Iafusco, D; Prisco, F; Laghi, F; Riegler, G; Carratu, R; Counts, D; Fasano, A (2006). "Zonulin upregulation is associated with increased gut permeability in subjects with type 1 diabetes and their relatives". *Diabetes* **55** (5): 1443–9. doi:[10.2337/db05-1593](https://doi.org/10.2337/db05-1593). PMID [16644703](https://pubmed.ncbi.nlm.nih.gov/16644703/).
5. ^ Drago, Sandro; El Asmar, Ramzi El; Di Pierro, Mariarosaria; Grazia Clemente, Maria Grazia; Tripathi, Amit Tripathi Anna; Sapone, Manjusha; Thakar, Giuseppe; Iacono, Antonio; Carroccio, Cinzia D'Agate Tarcisio; d'Agate, Lucia; Not, Catassi; Zampini, Alessio; Catassi, C; Fasano, A (2006). "Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines". *Scandinavian Journal of Gastroenterology* **41** (4): 408–419. doi:[10.1080/00365520500235334](https://doi.org/10.1080/00365520500235334). PMID [16635908](https://pubmed.ncbi.nlm.nih.gov/16635908/).

**Leaky Gut & Autoimmune Diseases (Zonulin)**

The effects of perioperative probiotic treatment on serum zonulin concentration and subsequent postoperative infectious complications after colorectal cancer surgery: a double-center and double-blind randomized clinical trial

The measurement and clinical significance of intestinal permeability

Coeliac Disease: Early effects of gliadin on enterocyte intracellular signalling involved in intestinal barrier function

**Zonulin, regulation of tight junctions, and autoimmune diseases**

Intestinal Permeability and Its Regulation by Zonulin: Diagnostic and Therapeutic Implications

**Physiological, Pathological, and Therapeutic Implications of Zonulin-Mediated Intestinal Barrier Modulation**

A Comparison of Antibody Testing, Permeability Testing, and Zonulin Levels with Small-Bowel Biopsy in Celiac Disease Patients on a Gluten-Free Diet

Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer

Regulation of Intercellular Tight Junctions by Zonula Occludens Toxin and Its Eukaryotic Analogue Zonulin

**Intestinal zonulin: open sesame!**

Host-dependent zonulin secretion causes the impairment of the small intestine barrier function after bacterial exposure
Zonulin Upregulation Is Associated With Increased Gut Permeability in Subjects With Type 1 Diabetes and Their Relatives

Gliadin, zonulin and gut permeability: Effects on celiac and non-celiac intestinal mucosa and intestinal cell lines

Human zonulin, a potential modulator of intestinal tight junctions

Circulating zonulin, a marker of intestinal permeability, is increased in association with obesity-associated insulin resistance

Circulating Zonulin, a Marker of Intestinal Permeability, Is Increased in Association with Obesity-Associated Insulin Resistance