

Intestinal Permeability & Rejuvenation

WHAT IS LEAKY GUT SYNDROME?

Sometimes referred to as leaky gut syndrome, increased intestinal permeability (IP) refers to a loss of selective permeability across the paracellular pathway of the small intestine. This has diverse pathological consequences due to the extremely complex role of the intestinal barrier in coordinating digestive, absorptive, motility, neuroendocrine, and immunological/protective functions.

The gastrointestinal (GI) epithelium is the largest mucosal surface in the body, and represents the greatest interface with the external environment. This mucosal barrier must be semi-permeable to absorb nutrients from food; at the same time, it must protect against invasion of microbes and toxins with pathogenic capacities—a dual role sometimes referred to as the “dilemma of opposing functions.”¹ Indeed, unlike other mucosal surfaces which typically have only one of the above functions, the intestinal mucosa must balance the needs for a barrier against a hostile environment with the necessity of active and passive transport. An intact intestinal barrier is, therefore, critical to normal physiological function and prevention of disease.²

Given the complexity of this challenge, a number of defence mechanisms have evolved in the gut, including the secretion of toxins known as defensins and mucins, the preference of commensal flora to pathogenic organisms, enhanced sophistication of adaptive immunity, molecules which recognize antigen patterns and can regulate immunological responses, and tight junctions which regulate passage between cells.³ It is this last mechanism which has received considerable attention, likely because it is the rate-limiting step for paracellular transit, but certainly because tight junction dysfunction has been associated with a number of clinical syndromes and disease. While once viewed as extracellular cement which formed an absolute barrier, it is now apparent that tight junctions are extremely dynamic structures made up of a complex network of proteins; these proteins are involved in several key functions of the intestinal epithelium under both physiological and pathological circumstances.⁴

WHAT ARE THE CONSEQUENCES OF INCREASED INTESTINAL PERMEABILITY?

Perhaps of greatest consequence to abnormal IP is the passage of luminal antigens across the intestinal barrier, which would normally be denied access through functional tight junctions (See Figure 1). As a result, immune cells are exposed to intact antigens which disrupt several physiological functions, including immune homeostasis to pathogens (bacteria, viruses, fungi, and parasites), recognition and tolerance of self-antigens, tolerance to commensal flora, and tolerance as well as sensitization and desensitization to foods.⁵

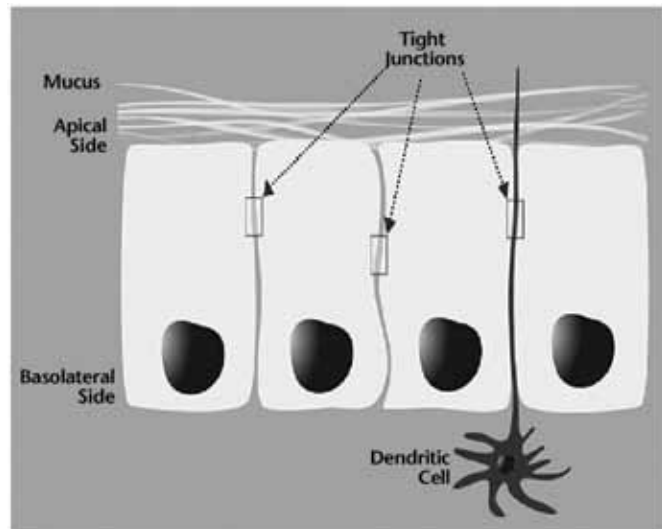


Figure 1* Structure of the mucosal barrier. Tight junctions link adjacent colon epithelial cells. The processes of dendritic cells pass between epithelial cells. The dendritic cells sample and process antigen material for presentation to other immune cells. Mucus produced by epithelial cells serves an additional physical barrier to prevent penetration of luminal antigens.

For example, a recent trial found increased IP in all subjects with adverse reactions to food, with the severity of the clinical symptoms correlated with the degree of permeability.⁶ One explanation is the loss of tolerance to food antigens, because these intact antigens are allowed to interact more directly with immune cells.⁷

Another of the most significant consequences of IP may be its link with autoimmunity. A recent review described this paradigm shift in thinking about autoimmune disease. The authors note that increased IP seems to precede autoimmune disease, likely because an abnormality in antigen delivery triggers the process which leads to an autoimmune response. This theory also suggests that autoimmune disease may be reversible, if the IP is restored.⁸ This is most clearly seen with celiac disease, although it may apply to other autoimmune diseases as well (See Figure 2).

Inflammatory bowel disease (IBD), which has a strong association with intestinal integrity, may also be triggered by the same mechanism. Defective function of the mucosal barrier is thought to be a necessary factor in the etiology of IBD; it allows bacterial antigens to come in contact with the innate and adaptive immune cells, which then generate inflammatory responses.⁹ Irritable bowel syndrome (IBS) has also been shown to have altered IP.¹⁰

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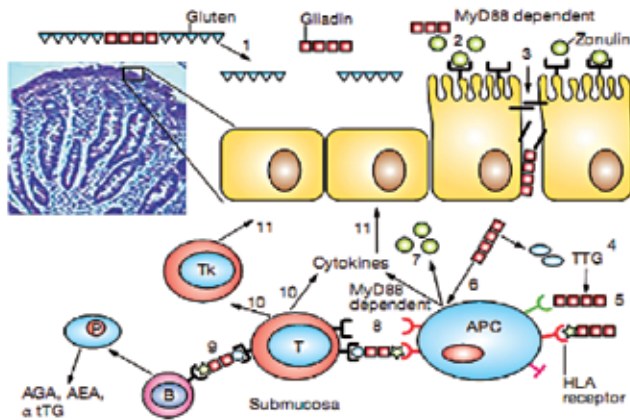


Figure 2 Proposed role of abnormal intestinal permeability in the pathogenesis of celiac disease. Gliadin and its immunomodulatory/inflammatory fragments are present in the intestinal lumen 1], which induces MyD88-dependent zonulin release 2]. Zonulin release causes opening of tight junctions and gliadin passage across the tight junction barriers in subjects with dysregulation of the zonulin system 3]. After tissue transglutaminase deamidation 4], gliadin peptides bind to human leukocyte antigen receptors present on the surface of antigen-presenting cells 5]. Alternatively, gliadin can act directly on antigen-presenting cells 6], causing MyD88-dependent release of both zonulin and cytokines 7]. Gliadin peptides are then presented to T lymphocytes 8], which process is followed by an aberrant immune response, both humoral 9], and cell-mediated 10], in genetically-susceptible individuals. This interplay between innate and adaptive immunity is ultimately responsible for the autoimmune process targeting intestinal epithelial cells, leading to the intestinal damage typical of celiac disease 11]. AEA, anti-endomysium antibodies; AGA, anti-gliadin antibodies; APC, antigen-presenting cell; tTG, anti-tissue transglutaminase; B, B lymphocyte; P, plasma cell; T, T lymphocyte Tk, lymphocyte T killer; TTG, tissue transglutaminase.

The effects of IP are not just confined to the gut. Individuals with asthma, atopic dermatitis, fibromyalgia, chronic regional pain syndrome, and possibly autism have also been shown to have an increase in IP.^{11, 12, 13, 14} Those with some types of arthritis may be susceptible as well. In a study of 40 children with various subtypes of juvenile arthritis, all subjects had an increase in IP.¹⁵

Very recently, a connection between chronic heart failure and IP was established. It is unclear if an increase in IP is the primary event that causes systemic inflammation leading to heart disease. However, most likely in patients with pre-existing heart disease, hypoperfusion of the intestinal microcirculation triggers intestinal dysfunction and inflammation, creating a vicious cycle.^{16, 17}

Recently, Type 1 diabetes has been shown to be associated with leaky gut. Even pre-diabetic normoglycemic individuals with signs of beta cell autoimmunity have been shown to have increased IP and inflammation. Interestingly, treatment of leaky gut in animals has been shown to modulate development of Type 1 diabetes, suggesting potential for prevention in humans.¹⁸

Lastly, those with chronic liver disease have been shown to have increased IP, including some individuals without cirrhosis.¹⁹ While alcohol is a known risk factor for damaged intestinal epithelium, individuals with non-alcoholic steatohepatitis have been shown to

have increased permeability in response to aspirin compared to controls, suggesting other risk factors also contribute.²⁰

WHAT ARE THE CAUSES OF INCREASED INTESTINAL PERMEABILITY?

There appear to be numerous causes of abnormal IP. Among them are nutritional deficiencies, stress,²¹ food allergy/intolerance, any source of increased inflammatory cytokines, noxious environmental toxins,²² microorganisms,²³ and unknown causes. Certainly in patients with celiac disease increased permeability is caused by gluten consumption, but a recent *in vitro* study suggests that wheat germ agglutinin (WGA) may have some ability to damage GI epithelium by different mechanisms.²⁴ Exercise, when accompanied by dehydration, may also increase GI permeability. A small study of 20 runners found that one hour of exercise increases leaky gut if no fluid is consumed during the activity.²⁵

Non-steroidal anti-inflammatory drugs (NSAIDs) are a well-known cause of increased IP in both the short- and long-term, causing significant morbidity and mortality.²⁶ Aspirin was recently shown to increase the susceptibility to "gut leakiness" in patients with non-alcoholic steatohepatitis (NASH), particularly in the large intestine.²⁷ Given the important role of microflora in determining GI integrity, antibiotic use is also thought to increase IP by altering the balance between commensal and pathogenic flora.

Lastly, immune dysfunction is an established component of at least some of the cases of intestinal damage. In addition to autoimmune disorders, immune dysregulation may lead to increased intestinal inflammation, which is at least partly mediated by mast cell activation. Mast cells are key regulators of the integrity and function of the gastrointestinal barrier.

HOW IS EXCESSIVE INTESTINAL PERMEABILITY DIAGNOSED AND MONITORED?

Laboratory assessment of small IP is done primarily with the lactulose/mannitol test. After drinking a pre-measured amount of these two sugars, the amount recovered in the urine indicates the degree of absorption of each, and is an index of permeability. Monosaccharides, such as mannitol (or L-rhamnose), are absorbed through the transcellular pathway and reflect the degree of absorption of small molecules. Disaccharides, such as lactulose (or cellobiose) are absorbed through the paracellular junction complex, which corresponds to the permeability of larger molecules.²⁸ The efficacy of treatment may also be monitored with this same test.

WHAT ARE THE BASIC PRINCIPLES OF TREATMENT?

The principles of treating leaky gut can be broken down into several steps.

1. Removing sources of intestinal damage

This can be accomplished by eliminating medications known to increase permeability when possible, reducing or eliminating alcohol consumption, and identifying and avoiding allergenic foods. Adopting an elimination/challenge diet is one of the most effective ways to identify problematic foods. Additionally, screening for known causes of intestinal damage such as celiac disease should be considered as a complement to a traditional elimination diet.

Conditions associated with (IP)	Relationship	References
Food allergy	Increased IP creates self-perpetuating cycle in which antigens penetrate the mucosa and induce allergic inflammation	7
Celiac disease	Gluten triggers opening of tight junctions through up-regulation of zonulin	8
Inflammatory bowel disease	Increased IP precedes disease development, allowing for contact with bacterial antigens	9
Irritable bowel syndrome	Increased colonic permeability, particularly those with diarrhea predominant IBS (IBS-D)	10
Asthma	Increased paracellular permeability documented in children and adults	11
Atopic dermatitis	Increased IP, improvement seen with <i>Lactobacillus</i> species	12
Fibromyalgia	Both gastroduodenal and small intestine permeability increased	13
Chronic regional pain syndrome	Both gastroduodenal and small intestine permeability increased	13
Autism	Increased IP, possibly due to pathological inflammation	14
Juvenile arthritis	All subtypes studied displayed increased IP	15
Heart failure	Increased IP as well as augmented bacterial biofilm documented in chronic heart failure	16,17
Type 1 diabetes	Increased IP found in Type 1 diabetes, as well as those normoglycemia and beta-cell autoimmunity	18
Liver disease	Increased IP in those with advanced liver disease, NASH, as well as those without cirrhosis	19,20

Table 1* Relationship between increased intestinal permeability and associated disorders.

2. Re-establish a healthy flora

Perhaps the greatest factor in determining intestinal integrity is the health of the microbial flora. Healthy microbial balance is essential to the maintenance of healthy digestion as well as disease prevention, the production of essential vitamins and co-factors, cidal activity against pathogenic bacteria, enhancement of intestinal barrier function through modulation of cytoskeletal and tight junctional protein phosphorylation, metabolism of toxins, reduction of GI inflammation, and the maintenance of immune homeostasis within the gut-associated lymphoid tissues (GALT).²⁹

RestorX™ contains the shelf-stable probiotic *Bifidobacterium Longum* (patented BB536), which has shown significant clinical benefit. It has been shown to prevent damage to intestinal cells caused by enterohemorrhagic *E. coli*,³⁰ to increase production of tight junction cell proteins (zonula occludens-1 and myosin light-chain kinase),³¹ and improve intestinal integrity in children with atopic dermatitis.³²

3. Stimulate intestinal rejuvenation by providing healing nutrients

A number of nutrients have been shown to repair damaged intestinal lining, and regulate the integrity of tight junctions:

- *L-glutamine* – long known to be the primary amino acid source for intestinal cells, glutamine has recently been shown to regulate intercellular junction integrity.³³
- *N-acetyl glucosamine (NAG)* – given the breakdown of glycosaminoglycans that occurs with leaky gut, this nutrient³⁴ provides a substrate for repair of these tissues. A trial in children with IBD showed significant potential for this nutrient.

- *Zinc* – zinc deficiency has been shown to disrupt tight junctions, alter membrane permeability, impair immune function, and cause intestinal ulceration.³⁵
- *Antioxidants* (such as vitamin C, vitamin E, beta carotene, grape seed extract, and milk thistle extract)—not only protect the GI from oxidant damage, but also help with hepatic detoxification of compounds associated with intestinal dysfunction.
- *Quercetin* – this antioxidant appears to be critical to intestinal integrity, and acts through a number of mechanisms. These have been shown to include the assembly of a number of tight junction proteins (zonula occludens (ZO)-2, occludin, claudin-1, and claudin-4).^{36, 37} Quercetin has also long been known to stabilize mast cells, which are important regulators of intestinal function and tight junction integrity.³⁸
- *Highly-digestible, low-allergy protein (from organic-sprouted brown rice), and water-soluble fibre*—nutrients known to restore intestinal health, while eliminating sources of damage.

In addition to containing many important daily vitamins and minerals, RestorX™ contains the nutrients shown to have specific benefits in restoring intestinal integrity.

WHAT IS THE RESTORX™ INTESTINAL REPAIR PROGRAM?

The RestorX™ Intestinal Repair Program is based upon the principles above for restoring intestinal integrity. RestorX™ is taken twice per day for seven days as the primary source of sustenance, providing the nutrients that are necessary to stimulate the healing of the in-

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testines. RestorX™ is mixed with water or juice (fresh vegetable juice is preferred), or it can be made up as a fruit smoothie with added essential fatty acid oil such as OptiMega-3™ or flaxseed oil for additional intestinal nutrition, as well as additional anti-inflammatory activity. Fresh or steamed vegetables and small amounts of fruit can be eaten when hungry. One simple meal is prepared in the evening with steamed vegetables, fish high in omega-3 fatty acids and low in mercury, such as wild salmon or halibut, and brown rice (cooked beans, split peas or lentils along with brown rice can be used as a vegetarian alternative). A lightly-sautéed stir fry can also be prepared for this meal. This food can be seasoned with natural herbs and small amounts of flax oil.

The RestorX™ Intestinal Repair Program may also be combined with a food allergy elimination diet. After the seven-day program, on day eight, foods that are potential allergens are introduced one per day, while one continues to take RestorX™ twice per day. Any food causing a reaction (which can occur up to 24 hours later) is removed from the diet. See the RestorX™ handout for details about elimination and challenge.

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FIGURES

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