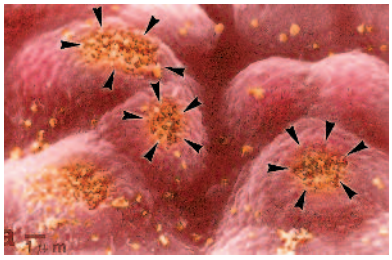
Intestinal Permeability Assessment



Damaged intestinal microvilli

Overview

The small intestine has the paradoxical dual function of being a digestive/ absorptive organ as well as a barrier to permeation of toxic compounds and macromolecules.[1-3] Either one of these functions may be disrupted by various mechanisms, resulting in local as well as systemic problems.

Defect in barrier functions

The distal intestine contains numerous dietary and bacterial products with toxic properties. These include viable bacteria, bacterial cell wall polymers, chemotactic peptides, bacterial antigens capable of inducing antibodies which cross-react with host antibodies, and bacterial and dietary antigens which can form systemic immune complexes.[4]

Abnormalities of the immune or mechanical barriers lead to enhanced uptake of inflammatory luminal macromolecules and pathogenic bacteria. With clinical intestinal injury, mucosal absorption of normally-excluded substances increases dramatically. Intestinal inflammation enhances the uptake and systemic distribution of potentially injurious macromolecules.[5] Peters and Bjarnson, in an excellent review of the uses of permeability testing, noted: "Measurement of intestinal permeability will play an increasing role in clinical investigation and monitoring of intestinal disease."[6]

Clinical significance

Increased permeability of the intestinal mucosal barrier appears to correlate with a number of frequently seen clinical disorders, while decreased permeability appears as a fundamental cause of malnutrition, malabsorption and failure to thrive.

Increased permeability is seen in disorders such as:[4]

- Inflammatory bowel disease
- Crohn's disease
- Inflammatory joint disease
- Food allergy
- Celiac disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Reiter's syndrome
- Chronic dermatological conditions
- Schizophrenia
- Allergic disorders

Several of these disorders are discussed in detail in the following sections.

Inflammatory bowel disease

Increases in permeability have consistently been reported with small bowel inflammation.[7] In 1972, Shorter proposed that a breach of the intestinal barrier is fundamental to the development of intestinal inflammation.[8] Now, most hypotheses about the pathogenesis of Crohn's disease posit the prime importance of mucosal integrity in maintaining a healthy state and suggest that increased mucosal permeability underlies the inflammatory process.

What this test does:

This test determines underlying problems linked to GI function.

This test directly measures how well two nonmetabolized sugars permeate the intestinal mucosa.

Turn-around Time 7 days

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Permeability studies show Crohn's disease to be more extensive than sometimes apparent using macroscopic approaches.[9] Pearson showed a sixfold increase in permeability in people with Crohn's disease.[10] When patients with Crohn's disease were placed on an elemental diet, their permeability improved significantly, coinciding with marked clinical improvement.[11]

Inflammatory joint disease

The concept that the underlying etiology of inflammatory arthritides (including rheumatoid arthritis) is related to pathology in the gut has become more accepted by researchers.[12,13] All material that traverses the mucosa is inspected by the immune system, and it is here that the immune system may have its greatest antigenic exposure. Increased gut permeability can permit exogenous antigens to enter the systemic circulation. If the antibodies generated towards gut antigens cross-react with the body's own immunologically similar tissues, the resulting process may manifest itself as an autoimmune disease.[14]

Studies have demonstrated that patients with ankylosing spondylitis, rheumatoid arthritis and vasculitis have increasedintestinal permeability, which may be an important factor in the pathogenesis of these disorders.[13,15-17]

There is a major association between enteric infection and Reiter's syndrome or reactive arthritis. Intestinal infections of Shigella, Salmonella, Yersinia, and Campylobacter are known to cause this type of disorder. It is suggested that the arthritis from these infections may be due to tissue deposition of circulating immune complexes arising from increased permeability of source antigens.[18,19] Darlington, after studying the influence of diet on arthritis concluded: "The mechanism by which fasting leads to improvement of rheumatoid arthritis may be a reduction in gut permeability."[20] Findings by Mielants show that in spondylarthropathies the joint disease is triggered through the gut.[15,21]

Food allergy

Development of food allergies depends on heredity, intestinal permeability, immune responsiveness and exposure to food.[22] "Food sensitivity" is used to refer to all adverse reactions to the ingestion of food, including allergic, idiosyncratic, toxic, metabolic and pharmacological. Food "allergies" are distinguished by being mediated by an immunologic mechanism, consistently reproduced by blinded food challenge and causing functional changes in target organs.[23]

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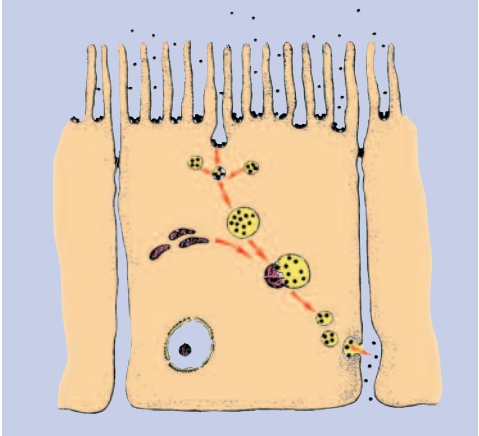

Figure 1

When this mechanism is ineffective, antigens are allowed to enter the system in excessive amounts, which leads to sensitization of the immune system in some individuals. Increased permeability is implicated in Type I, Type III and Type IV allergies.[22]

Andre, in a study of food allergy, concluded that "evaluation of intestinal permeability provides an objective means of diagnosing foodallergy and assessing the effectiveness of anti-allergic agents."[24]

A number of studies by Andre showed that people with food allergy had increased permeability during a fasting state and that the permeability further increased after ingestion of an offending allergen.

Andre concluded that using lactulose and mannitol to measure intestinal permeability allowed objective diagnosis of food allergy. Andre also observed that permeability increases even after ingestion of an amount of food that is not large enough to cause a clinical reaction.[25]

Magnusson studied children with cow's milk allergy and found that the majority of children displayed changes in permeability after challenge and that pretreatment with sodium cromoglycate diminished the changes.[26] Cromoglycate may stabilize mast cells and IgE producing plasma cells in the lamina propria of the gut and thus reduce the local inflammation which contributes to the increased intestinal permeability.

Causes of changes in permeability

- Nonsteroidal anti-inflammatory drugs
- HIV infection
- Intestinal infection
- Intestinal dysbiosis
- Maldigestion/malabsorption
- Alcoholism
- Aging
- Deficient sIgA
- Giardiasis
- Ingestion of allergic foods
- Ingestion of offending chemicals
- Trauma and endotoxemia
- Decreased permeability may be caused by chemotherapy and gastroenteritis.

Urticaria and atopic dermatitis can be caused by the ingestion of certain foods.[27] Andre showed that people with atopic dermatitis and those with urticaria demonstrated increased permeability when given an oral challenge of food that provoked symptoms.[25]

Coeliac disease

Intestinal permeability has been studied in patients with coeliac disease.1[0,28-30] In children with coeliac disease, Pearson demonstrated a significant alteration in permeability due to reduced absorption.[10] After exposure to a single oral dose of gluten, the intestinal permeability of people with coeliac disease became transiently abnormal, returning to normal within one week.[28] Hamilton concluded that the sugar ratio test is of value in assessing the response to gluten withdrawal and in monitoring patients who are already established on a gluten-free diet by detecting dietary lapses and "non-responders."

In another study, Bjarnason strongly suggested that a persistent functional and/or structural abnormality of the small intestine is associated with coeliac disease along with possible etiological implications.[29]

In certain disease states of the small intestine, such as gluten-sensitive enteropathy, permeability to large molecules may increase while permeability to small molecules decreases.

The explanation of this apparent paradox lies in the different routes of entry for readily absorbed, water-soluble molecules such as mannitol and normally excluded molecules like lactulose. Transcellular uptake of mannitol relies on properties of the luminal cell membrane, a relatively huge area compared to the minute intercellular junctional complexes or "tight junctions."

Increased porosity of tight junctions has little effect on mannitol uptake, but villous atrophy decreases mannitol diffusion into mucosal cells. Thus, decreased transcellular permeability to small, water-soluble molecules may lead to malnutrition. In contrast, increased porosity of junctional complexes may lead to increased uptake of food antigens and bacterial toxins, correlating with increased susceptibility to food allergies and autoimmune conditions such as rheumatoid arthritis.

Nonsteroidal anti-inflammatory drugs

Numerous studies have shown that NSAID usage disrupts the intestinal barrier function and causes increased permeability.[31-33] This is of particular importance in those peo-ple with arthritis who are being treated with NSAIDs because the increased permeability may be a key factor in their disease process.

The hypothesis that various bacterial and viral intestinal infections can cause altered permeability is well supported.[34,35] Studies show that host responses to infections are related to increased passage of microorganisms and endotoxins into the systemic circulation.[36] Several authors have claimed that this breach of the mucosal barrier is an important aspect in both acute and chronic systemic effects of intestinal infection.

Deitch reported that bacteria translocate across the mucosal barrier and cause systemic infections and various immunologic sequelae.[37] Factors that promote translocation of bacteria include disruption of the ecologic balance of normal indigenous microflora (dysbiosis), bacterial overgrowth, impaired immune defense, trauma and endotoxemia.

HIV infection and AIDS

Investigation has begun into intestinal permeability in patients testing positive for human immunodeficiency virus and patients with acquired immunodeficiency lsyndrome. In a recent study, Tepper looked at intestinal permeability in asymptomatic HIV-positive patients and AIDS patients with and without diarrhea.

This study indicates that patients with both AIDS and diarrhea have altered intestinal permeability and this alteration could allow increased transmucosal passage of opportunistic pathogens. Mannitol recovery decreased incrementally in

HIV-positive groups, suggesting that as HIV disease progresses, there is loss of functional absorptive surface, possibly contributing to the malnutrition that often characterizes advanced stages of AIDS.[38]

Pancreatic insufficiency

Intestinal permeability was studied recently in patients with well-characterized cystic fibrosis or with pancreatic insufficiency.[39] Compared to controls, lactulose permeation increased with exocrine pancreatic insufficiency. The degree of increased intestinal permeability correlated with the level of duodenal trypsin and with the degree of undigested fat in the stool. The authors suggested that urinary lactulose might be useful in evaluating exocrine pancreatic function.

Malabsorption, malnutrition

Recent studies show that damage to the small intestine mucosa (resulting in decreased permeability) is linked to poor growth rates and failure to thrive in children. The intestinal damage is typically a result of infection and resulting diarrhea.[40-41]

Alcoholism

A number of very interesting studies were performed by Bjarnason with alcoholic individuals.[42] He showed that alcoholics had elevated intestinal permeability. In many people, the abnormality persisted for up to two weeks after cessation of drinking.

This increased permeability may account for some of the extra-intestinal tissue damage common in alcoholics. Bode reported that gut-derived endotoxins might play a role in the initiation and aggravation of alcohol-induced liver disease.

Aging

In an intriguing study on aging, Hollander concluded that "the intestinal barrier to the absorption of potentially harmful environmental substances may be less efficient in aging animals."[43]

Various studies show that aging rats have diminishing capacity to prevent larger size molecules from penetrating the intestinal mucosa, possibly allowing antigenic or mutagenic compounds to reach the systemic circulation.[44]

Chemotherapy

Cytotoxic treatment has been shown to decrease permeability, a possible factor in malnutrition of cancer patients.[45]

Measuring permeability

Some of the noninvasive permeability techniques are simple and reliable such that they may be utilized to assess many clinical conditions.[46]

The permeation of water-soluble molecules through the intestinal mucosa can occur either through cells (transcellular uptake), or between cells (paracellular uptake). *(Figure 2)*

Small molecules (glucose, mannitol, etc.) readily penetrate cells and passively diffuse through them. Larger molecules such as disaccharides (e.g. lactulose) normally are excluded by cells. The rate-limiting barrier in this case is the tight junction between cells. Thus, tight junctions help maintain epithelial integrity.

The Intestinal Permeability Test directly measures the ability of two nonmetabolized sugar molecules—mannitol and lactulose—to permeate the intestinal mucosa.

Mannitol, a monomer, is readily absorbed and serves as a marker of transcellular uptake. Lactulose, a dimer, is only slightly absorbed and serves as a marker for mucosal integrity. To perform the test, the patient mixes premeasured amounts of lactulose and mannitol and drinks the challenge substance. The test measures the amount of lactulose and mannitol recovered in a 6-hour urine sample.

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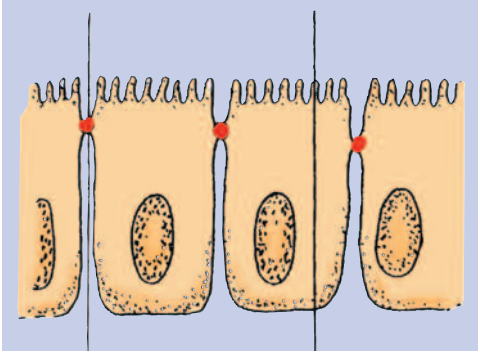

Figure 2

Genova Diagnostics' Intestinal Permeability Assessment Interpretation

Low levels of mannitol and lactulose indicate malabsorption. Elevated levels of lactulose and mannitol are indicative of general increased permeability and "leaky gut" phenomena. Permeability to lactulose can increase, indicative of "leaky gut," while permeability to mannitol may decrease, indicative of malabsorption of small molecules. The lactulose/mannitol ratio is a useful parameter. An elevated ratio indicates that the effective pore size of the gut mucosa has increased, allowing access (to the body) of larger, possibly antigenic molecules.

Patient preparation

The Intestinal Permeability Test requires an overnight fast. Nothing, including water, should be consumed after 11 p.m.

Sample requirements

Two urine samples are required. The first is a random urine pretest sample. The second is a sample drawn from a 6-hour urine collection after ingesting the challenge drink.

Report form

The Intestinal Permeability Report includes lactulose percent recovery, mannitol percent recovery, and the ratio of lactulose to mannitol.

Other tests to consider

Genova Diagnostics' Intestinal Permeability test is particularly useful in combination with **Comprehensive Digestive Stool Analysis, Parasitology Profile** and **Food Antibody Assessment**. These studies provide strong evidence as to initiating processes which affect intestinal permeability. The **Detoxification Profile** can be an important area to investigate as well, with impaired intestinal permeability causing increased demands on the liver's detoxification capacity.

Clinical therapeutics

There are a number of therapeutic substances, some of which are listed below, that can be used to normalize intestinal permeability. In determining which substance to use, it is helpful to understand the proposed mechanism of action.

For more information, refer to our **Intestinal Permeability Interpretive Guidelines**.

To provide nutritional support:

1. Glutamine and L-arginine, single amino acids, have been shown to both prevent and reverse intestinal mucosal damage from various insults.

Glutamine is the principle fuel used by the upper intestinal tract. It has also been shown to decrease bacterial translocation after intestinal insult.[47,48]

2. Butyric acid, a short chain fatty acid manufactured in the lower intestines as a by-product of bacterial fermentation of fiber, is the main energy source for lower intestine and colon epithelial cells.

It has been shown to be involved in the repair and regeneration of damaged cells.[49,50]

3. Some intestinal mucosal damage is due to oxygen-derived free radicals, potentiated by vasoconstriction.[31]

Administration of free radical scavengers has been suggested as being beneficial. Some common natural ones include vitamin E, beta-carotene, ascorbic acid, zinc, selenium and superoxide dismutase.

4. Agents that help stimulate protective mucus secretion appear to be beneficial.

To lower toxic load:

1. Bentonite clay, a colloidal aluminum silicate, is a well-known intestinal adsorbent which absorbs numerous toxins, endotoxins and bacteria.

Its value in permeability alterations may result from lowering the toxin load in the lumen, thus facilitating repair.

2. Lactobacillus has been shown to provide protection against increased permeability by enhancing antigen-specific immune defense.

3. HCl and digestive enzymes such as plant enzymes, pepsin and pancreatin might help to lessen the antigenic and the macromolecule load being presented to the intestinal mucosa.

To counter inflammation:

1. Cromolyn sodium inhibits the release of mediators from sensitized mast cells.

It has been used in many clinical trials to reduce the increased permeability caused by oral ingestion of a food allergen. Quercitin, a natural bioflavonoid, is molecularly similar and also stabilizes mast cells.[24,25]

2. Gingko biloba extract has been shown to prevent the action of various mediators of ischemic mucosal damage.

It protects the intestinal mucosa by reducing neutrophil infiltration and lipid peroxidation.[52]

3. Prostaglandin E2 and E1 (Misoprostol) has intestinal mucosal protective and trophic properties.[12]

Studies by Bjarnason have shown that Misoprostol reduces the increased permeability caused by indomethacin.[31] *(Note: Misoprostol is a potent abortifacient.)* Natural PGE2 precursors, such as certain fatty acids, also may prove to be beneficial.

How do I order this test?

For Intestinal Permeability kits or information, please call a Client Services representative at 800-522-4762 or order online at www.GDX.net.

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