Understanding Leaky Gut and how Chiropractic can help in Treatment

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Abstract

Introduction: Leaky Gut Syndrome is a condition in which the intestinal mucosal lining has somehow been damaged or altered (1, 2, 22, 23). This paper will explore the current concepts in "Leaky Gut" syndrome.

Discussion: It is not a diagnosis but is a term used to describe a collection of symptoms caused by increased intestinal permeability (1, 2, 8). The damaged or altered mucosal lining exhibits increased permeability allowing substances such as toxins, microbes, undigested food particles or bacterial metabolic waste to leak through into the body through the blood (1, 2, 3, 22, 23). It has been determined that the tight junctions, originally thought to be static are actually very dynamic and change or are altered depending on the intestinal milieu (1, 2, 6, 8, 10, 12, 14). One endogenous protein that has been found to regulate the paracellular pathway through its effect on tight junctions is zonulin (5, 6, 11). Consequences of a leak gut have wide spread effects throughout the body such as intestinal bacterial overgrowth, bacterial translocation, autoimmune diseases, increased inflammation and cancer (6, 7, 9, 13, 15, 16)

Conclusion: The role of the chiropractor is to educate patients, evaluate lifestyle including diet and exercise and then put together a treatment program to allow a patient in a step by step manner to improve their health. Increased intestinal permeability can be improved by making some simple but often difficult changes such as elimination diets, adding a probiotic (15,16), addition of moderate exercise, all of which are geared towards raising a patients overall health better enabling their bodies to let the innate healing capabilities to do their jobs (21, 22, 23)

Understanding Leaky Gut Syndrome and how Chiropractic can help in Treatment

Introduction

Leaky Gut Syndrome is a condition in which the intestinal mucosal lining has somehow been damaged or altered (1, 2, 22, 23). The damaged or altered mucosal lining exhibits increased permeability allowing substances such as toxins, microbes, undigested food particles or bacterial metabolic waste to leak through into the body through the blood (1, 2, 3). The purpose of this paper is to review some of what is known about this phenomenon thus far and to relate the phenomenon to the development of diseases related to the gastrointestinal system. The paper will also consider what treatments could be offered through Chiropractic care. The paper will open with a brief review of the physiology of the intestinal mucosal lining, followed by what research has elicited so far on the mechanism of intestinal permeability involving tight junctions. To further understand leaky gut syndrome, this paper will also look at the effects to the body of increased intestinal permeability. And finally, a focused look on the role a chiropractor can take to aid patient's suffering from this syndrome.

Leaky Gut Syndrome is not a diagnosis but is a term used to describe a collection of symptoms caused by increased intestinal permeability (1, 2, 8). However, according to Dr. Bernard Brom (1, 2), leaky gut is a well-recognized and common diagnosis within the community of integrative doctors. He proposes that this is because the integrative medical focus is not on the disease, but more on the functional dysregulation behind disease. Dr. Brom states that "Leaky gut is regarded as the harbinger of a great deal of ill health and the later

development of many chronic diseases, such as food intolerance, inflammatory bowel disease, rheumatoid arthritis and other autoimmune diseases." Dr. Brom also states that the mucosa lining of the intestinal tract is a protective layer between the contents of the intestine and the inside of the body. And when dysfunctional, it becomes the entry point of pathogens and micro-toxins and becomes a source and origin of ill health (1). More than 30 years ago an earlier version of a "leaky gut hypothesis" was proposed by a man named Jacob Fine. According to Michael P. Fink, MD in his editorial called Leaky Gut hypothesis: A historical perspective (2), Fine proposed the "idea that irreversibility in several forms of shock results from the systemic absorption of gut-derived bacterial endotoxins in the setting of impaired host resistance lipopolysaccharide (LPS), the latter phenomenon being due to the adverse effects of shock on the normal functioning of the reticuloendothelial system." In his editorial Fink reports that there are two kinds of leakiness currently considered likely. The first type of leakiness is increased permeability to macromolecules, specifically bacterial toxins. Fink reports from an article by Van Deventer et al (1988) that there is considerable evidence supporting the idea that systemic absorption of gut-derived endotoxins is increased in certain disease states. The second type of leakiness reported by Fink is the loss of the normal barrier to the movement of viable microbes from the gut lumen also known as translocation. To understand leaky gut, it is important to have an understanding of the digestive system and so a brief review the digestive system is in order.

Discussion

As described in the Textbook of Medical Physiology (12th edition) by Guyton and Hall (3) and power point notes from physiology classes by Dr. A. Ignatov (4), the digestive system is made up of the alimentary canal, also called the gastrointestinal (GI) tract, which consists of a long tube that runs from the mouth all the way down to the anus. It also includes some accessory organs consisting of teeth, tongue, salivary glands, liver, gallbladder, and the pancreas. The functional segments of the gastrointestinal (GI) tract consist of the mouth, esophagus, small intestine and the large intestine and involve six basic processes. The processes are: 1. ingestion – the intake of food into the mouth; 2. secretion – consisting of release of water, acid, buffers and enzymes into the lumen mixing in with the food ingested; 3. mixing and propelling the food through the lumen; 4. digestion – mechanical by way of the mixing and propelling and chemical catabolism by way of exposure to digestive enzymes; 5. absorption – which refers to the transfer of digested products from the GI tract to the blood and lymphatics for distribution to cells; and finally, 6. defecation – which is the emptying of indigestible substances out through the rectum. The small intestine is where chemical and mechanical digestion takes place along with most of the absorption of nutrients through the mucosal lining (3, 4). The lining of the GI tract and more specifically of the small intestine is made up of four layers going from the inside (lumen) out are called: 1. Mucosal layer, 2. Submucosa layer, 3. Muscularis layer, and 4. Serosa layer. For the purposes of this paper, the focus will be on the mucosal layer (3, 4). The mucosa is made up of the epithelium layer,

lamina propria layer and muscularis mucosae layer (3, 4). In the small intestine the epithelium consists of a single layer of simple columnar cells called enterocytes that has the apical side facing the lumen of the GI tract and is connected to each other via tight junctions (3, 4, 6). This epithelium layer of simple columnar cells that makes up the microvilli, also known as the brush border, secretes enzymes for chemical digestion and absorbs the needed nutrients into the blood capillaries and lymphatic lacteals located within the villi (3, 4). The next layer is the lamina propria which contains the blood vessels and lymphatic tissues (3, 4). The lymphatic tissues are part of MALT which is mucosa-associated lymph tissue (3, 4). The nutrients are absorbed into the blood and lymphatic tissues at this point and are only now considered to be in the body and being made available for use. There is only a single layer of cells separating the external environment from the internal milieu (3, 4, 6). The last part of the mucosa layer is called the muscularis mucosae and is a layer of smooth muscle which creates folding in the mucosa (3,4). This folding of the mucosa layer increases local movements which in turn increases absorption because of greater exposure of the surface epithelium to the contents within the lumen (3,4, 8).

Mechanism of the intestinal barrier function (tight junctions)

The lining of the GI tract not only performs the function of absorbing the needed nutrients, it also provides a barrier function (3, 4, 5). The intestinal epithelial barrier with its intercellular tight junctions together with the gut-associated lymphoid tissue (MALT) and the neuroendocrine network controls the equilibrium between tolerance and immunity to non-self antigens. (3, 4, 5, 6) In the anatomical structure of the epithelial barrier the enterocyte balances

its dual functions of absorption and barrier by having embedded transporter systems and channels within the membrane for water soluble compounds going from lumen into the internal environment (5, 6). Some of the routes are: transcellular route for trafficking lipophilic and small hydrophilic compounds; transcellular routes via aqueous pores which traffic small hydrophilic compounds; active carrier-mediated absorption trafficking nutrients, electrolytes, and some exogenous substances, such as peptidomimetic antibiotics; and endocytosis, followed by transcytosis and exocytosis for larger peptides, proteins, and particles as referenced by M Camilleri et al (7) from AV Keita, *Neurogastroenterol Motil* 2010. However, there is also another potential route for solute traffic that is not regulated by the brush border membrane transporter channels located to the sides of the individual enterocytes (5,6). This is a paracellular route. There are a series of intercellular junctions along the lateral margins of the epithelial cells. Closest to the luminal surface lies the tight junction and underneath is the adherens junction, which is more basally situated. (8,9) The barrier function is performed by the surface of the mucosa that forms a barrier which separates the external environment, i.e., the gut lumen, from the protected internal milieu. According to Shen, Le, and Jerrold R. Turner, "each cell in the epithelium is encircled at the apicolateral boundary by the tight junction which seals the paracellular space."(10) Originally it was thought that the tight junctions provided a static barrier and were meant to only allow the passage of solutes paracellularly from lumen to blood according to size and charge. It is now believed that tight junction function and structure is very dynamic and can be regulated and so can become dysfunctional (5, 6, 8, 9, 10).

These junctions are complex and are made up of lipid and protein constituents. Arrieta et al state that, "an ever expanding family of proteins are found in the vicinity of theses

junctions, forming fibrils that cross the plasma membrane to interact with proteins from the adjoining cell."(8). The authors explain that the proteins are also interacting intracellularly with an actomyosin ring that encircles the enterocyte at the level of the tight junction through numerous smaller proteins. "The fibrils between cells consist of at least two types of tetraspanning membrane proteins, Occludin and members of the Claudin family." (8) These protein fibrils make up part of the structure of the tight junction complex spanning the intercellular space. On the intracellular side of the membrane the carboxy terminal end of these proteins spanning between cells interacts with the intracellular scaffold-like tight junction proteins ZO-1, ZO-2, and ZO-3 (8,9). Underneath and connecting to the junctional complex via actin filaments lies the ring of actin microfilaments and it is thought that contraction of this actin microfilament ring is what regulates the paracellular permeability. Tight junctions originally thought to be static are now considered to be incredibly dynamic (5, 6, 7, 8). According to the authors "the tight junctions open and close to a variety of stimuli such as dietary state, humoral or neuronal signals, inflammatory mediators, mast cell products, and a variety of cellular pathways that can be usurped by microbial or viral pathogens." (8) The actin cytoskeleton is a primary target of immune-mediated epithelial barrier dysfunction. (10) Permeability of the paracellular pathway via tight junction complexes can also be modulated by transcellular absorptive processes as well.(7, 8) In other words, substances being absorbed through the transporter channels embedded in the enterocyte cellular membrane can also affect the permeability state of the tight junction paracellular pathway. (7, 8, 11) According to M. Camilleri et al (7), "tight junctions are continually being monitored and regulated by both intra- and extracellular signals." "Signaling molecules that control the assembly and

disassembly of tight junctions through phosphorylation and dephosphorylation reactions include myosin light chain kinase, Rho GTPases, protein kinase C, and mitogen-activated protein kinases."(7)

Modulation of Tight Junctions and barrier dysfunction

One substance that has been found to regulate the paracellular pathway through its effect on tight junctions is zonulin. Zonulin is an endogenous protein that can bind to an apical membrane receptor on the enterocyte leading to activation of the intracellular/paracellular pathway resulting in actomyocin contraction and increased paracellular permeability (11). The Zonulin pathway or Zonulin System is of particular relevance to disease pathogenesis because up regulation of zonulin secretion from a lamina propria source into the lumen of the intestine seems to be a common pathophysiological event. (8) The zonulin pathway appears to be involved in several functions which include tight junction regulation responsible for the movement of fluid, macromolecules, and leukocytes between the blood stream and the intestinal lumen. Intestinal zonulin may also have a potential protective role against microorganism colonization of the proximal intestine involving innate immunity according to an article written by Alessio Fasano. (6) Through additional research done by A Fasano, zonulin was identified to be the same compound as Pre-Haptoglobin 2, a molecule that, to date has only been regarded as the inactive precursor for Haptoglobin 2 (HP2) which is one of the two genetic variants (together with HP1) of human Haptoglobins (HPs). The only function assigned to HPs so far is to bind free hemoglobin (Hb) to form stable HP-Hb complexes and so preventing Hb-induced oxidative tissue damage.(6) There have been several potential intestinal stimuli

that can trigger the release of zonulin. Two powerful triggers are exposure of the small intestine tissue to bacteria and exposure to gluten. (5, 6, 7, 15, 16) According to A Fasano, enteric infections have been implicated in the pathogenesis of several pathological conditions, including allergic, autoimmune, and inflammatory diseases, by causing dysfunction to the intestinal barrier. Evidence was generated that supported that zonulin was secreted when the small intestine was exposed to enteric bacteria. (6, 15, 16)

Another possible pathway of modulation of intestinal permeability involves the enteric nervous system (ENS). (12) The ENS forms a neuronal network that is embedded within the gastrointestinal wall in the submucosa layer. It is composed of the myenteric (Auerbach's) plexus and the submucosal plexus (3, 4, 12). Additionally, "the submucosal plexus is composed of three different plexus: 1. The plexus of Meissner located immediately under the mucosa; 2. The intermediary plexus located in the plane of the mucosal blood vessels; and 3. The plexus of Henle, which is in contact with the circular muscle" according to Neunlist M et al (12) referenced from Timmermans JP et al 1997. Results of a study done by Neunlist M et at (12) is that Vasoactive Intestinal Peptide – ergic (VIP-ergic) submucosal pathways were involved in the control of the intestinal epithelial permeability. They showed that VIP released after activation of enteric neurons decreased paracellular permeability. (12). Their study also "provides the first evidence that the activation of the ENS and that VIP were able to regulate the expression of ZO-1 in intestinal epithelial cells, both at the mRNA and protein level. This action on ZO-1, which is a key regulator of tight junctions, could explain, in part the regulatory effect of submucosal neurons on epithelial permeability. Effects of VIP released after activation of submucosal neurons on ZO-1 expression were at least partly mediated by a direct action of VIP on epithelial

cells."(12). In another review article by M Camilleri et al the potential neuroimmune modulation of intestinal barrier function is summarized as "the extrinsic vagal and/or sympathetic efferents or enteric nerves influence the mucosal barrier through direct effects via acetylcholine or vasoactive intestinal polypeptide on epithelial cells, tight junction protein expression or through interaction with immune (e.g. mast or plasma) cells." (7) The authors also referenced materials that suggested that "during stress and inflammation, mast cell mediators such as TNF-α, tryptase [via protease-activated receptor type 2 (PAR-2)], nerve growth factor, and interleukins may affect paracellular permeability by altering expression of claudins in the tight junctions or the transcellular uptake route by increasing macro-pinocytosis which disrupts the barrier to antigens and bacteria." (referenced articles M Arrieta et al 2006; Neunlist M et al 2003; C Jacob et al 2005; L Bueno et al 2008). As mentioned above, stress is known to effect mast cells. In a study by J Demaude et al, it was found that acute stress induced a three day delayed increase in colonic paracellular permeability which involved mast cell degranulation and overproduction of INF-$_{\gamma}$. The colonic epithelial barrier was morphologically altered and expression of mRNA encoding tight junction proteins ZO-2 and occludin was decreased. The authors concluded that the data highlight new mechanisms whereby acute stress acts on the gastrointestinal tract by inducing alteration in colonocyte differentiation and decreased expression of mRNA encoding tight junction proteins. And so this could open the door towards stress related intestinal disorders. (12,13)

Measurement of Intestinal Permeability

Measurement of intestinal permeability is an important testing procedure for many reasons. Permeability testing could be used to determine the possibility of emerging disease processes, or in detection of gastrointestinal damage, or for determining the effectiveness of different types of treatments, or screening for damaging effects of a variety of drugs, or for research to evaluate the permeability properties of the paracellular pathway (14). It seems that there has been a lot of effort that has gone into development of a simple non-invasive means of evaluation. Movement across the paracellular pathway occurs by a non-carrier mediated process and so depends on several features such as: 1.The concentration gradient across the barrier; 2.The surface area of the epithelium; 3.The time available for permeation to take place; and 4.The intrinsic permeability properties of the barrier (8,9). It is important to keep the first three variables as steady as possible because the intrinsic permeability properties of the barrier are the variables of interest with regard to the study of leaky gut. Although there have been many different probes that have been utilized to measure permeability, there are some features that should be considered. The size of the probes should be similar and they should be easily assayed in a urine sample in order to allow for more meaningful comparison (14). In addition to being small in size, the probes should be water soluble, non-charges compounds that are not destroyed in the gut, are non-toxic, not metabolized or sequestered once absorbed, and quantitatively cleared by the kidney into the urine (8). According to J Meddings and I Gibbons in their efforts to develop a method for more site specific permeability measures determined that “an ideal screening test for gastrointestinal damage, based on altered permeability, would consist of a single drink containing non-radiolabeled probes that selectively measured damage in the proximal, mid, or distal gastrointestinal tract.” (14) The results of their

study determined that a single drink containing sucrose to study gastroduodenal region permeability, lactulose and mannitol to study permeability in the small intestine and sucralose to study colonic permeability provided effective screening. The authors utilized sucralose to evaluated damage to the colon as opposed to using Cr-labeled ethylenediaminetetraacetic acid (Cr-EDTA) because it is a radiolabeled marker and so reduced its acceptability. Sucrose is rapidly hydrolyzed by sucrose-isomaltase and therefore permeation of intact sucrose across the gastrointestinal mucosa must occur in the most proximal regions of the gut. (8) The small intestinal probes lactulose and mannitol are degraded by the bacterial flora of the large intestine and so give no information regarding colonic permeability characteristics. (8). Sucralose probes remain stable throughout the gastrointestinal tract and so are useful to provide information about colonic permeability. (8) According to M Arrieta et al, small intestinal permeability is traditionally expressed as the ratio of the fractional excretion of a larger molecule (lactulose) to that of a smaller one (mannitol). This has to do with the distribution of “aqueous pores” along the crypt-villus axis of the small intestine. At the tips of the villus are relatively abundant small channels for transport of compounds such as the smaller mannitol, while in the crypts there exist larger channels but in lower abundance for transport of larger compounds such as lactulose. And so, interpretation of permeability data, expressed as a lactulose : mannitol ratio, is the amount of epithelial damage as a proportion of mature small intestinal surface area (8). Mature small intestinal surface area is indicated by increased absorption of mannitol in the tips of the villi through the increased numbers of aqueous pores. Damage is indicated by an increase in lactulose absorption in the crypts area and a decrease in

mannitol absorption because the tips of the villi must be damaged. And so a drink containing sucrose, lactulose, mannitol and sucralose can be effective probes to measure gut permeability.

Consequences of a Leaky Gut / Intestinal Permeability and Disease

Intestinal Bacterial Overgrowth and Bacterial Translocation

Bacterial translocation is defined as the passage of viable bacteria from the gastrointestinal tract to extra intestinal sites, such as the mesenteric lymph node complex, liver, spleen, kidney, and blood stream. According to Yaron Ilan, bacterial translocation, the innate immune system and toll-like receptors play a role in the pathogenesis of liver damage. (15) Intestinal bacterial overgrowth and increased bacterial translocation of gut flora from the intestinal lumen predispose patients to bacterial infections. As stated earlier the intestinal epithelial barrier with its intercellular tight junctions together with the gut-associated lymphoid tissue (MALT) and the neuroendocrine network controls the equilibrium between tolerance and immunity to non-self antigens such as enteric bacteria. (6) Note that immune tolerance describes a state of unresponsiveness of the immune system to substances or tissue that has the capacity to elicit an immune response. It is suggested that impaired gut epithelial integrity (leaky gut) due to alterations in tight junction proteins may be the pathological mechanism underlying bacterial translocation. (15,16) Yaron Ilan references in his article on bacterial translocation and leaky gut from information gathered by (I Hritz et al *Hepatology* 2008) that liver inflammation and chronic damage are mediated by innate immune responses that are regulated by toll-like receptors. He references from A Mencin et al, *Gut* 2009 that the toll-like receptors recognize pathogen-associated molecular patterns to detect the presence of

pathogens.(article 6) Some of these pathogen-associated molecular patterns include bacterial lipopolysaccharides, a component of gram-negative bacteria and bacterial DNA fragments. (article 6) "Bacterial lipopolysaccharide is an important structural component of Gram-negative bacterial cell walls, such as those of *Bacterioides* and the Enterobacteriaceae, and is highly inflammatory, being a pathogen-associated molecular pattern recognized by the innate immune system." (17) The toll-like receptors are located on many different types of cells. These are immune cells, Kupffer cells, endothelial cells, dendritic cells, biliary epithelial cells, hepatic stellate cells and hepatocytes as referenced from T Aoyama et al, *Gastroenterol Res Pract* 2010. (15) He also references an article by (M. úbeda et al *Hepatology* 2010) that innate immune cells can both initiate and maintain inflammation in the liver and that bacteria translocated from the gut activate lymphocytes after interacting at the mesenteric lymph nodes. (15) The bacteria translocated from the gut initiates an immune response with the sequence of events described by the following, bacterial translocation initiates a Th1 immune response in mesenteric lymph nodes leading to T-helper 1 (Th1) polarization and the production of tumor necrosis factor (TNF)-α by monocytes. (15) The re-circulation of these activated effector immune cells into the blood promotes systemic inflammation as referenced from L Muñoz et al*, Hepatology* 2005. A systemic inflammatory state with increased circulating TNF-α has been linked to increased susceptibility to bacterial infections as well as other diseases involving systemic inflammation. (15,16)

Autoimmunity

The body's immune system protects the body from disease and infection. Autoimmunity is when the body's immune system attacks its own healthy cells. Autoimmune diseases are characterized by tissue damage and loss of function due to miscommunication between innate and adaptive immunity leading to an immune response that is directed against specific organs. (18) According A Fasano, (*CRC Press, Inc.* 2001) referencing from earlier works, "a common denominator in autoimmune diseases is the presence of several pre-existing conditions that lead to an autoimmune process". Fasano, again referencing previous work, listed these conditions as 1. The genetic susceptibility of the host immune system to recognize, and potentially misinterpret, an environmental antigen presented within the gastrointestinal tract. 2. The host must be exposed to the antigen. 3. The antigen must be presented to the gastrointestinal mucosal immune system following its paracellular passage from the intestinal lumen to the gut submucosa. Note that this third condition is normally prevented by competent tight junctions. Fasano reports that current data suggests that altered processing by intra-luminal enzymes, changes in intestinal permeability, and activation of innate immunity mechanisms seems to precede the activation of the adaptive immune response. (18) "Although the diseases associated with increased permeability do differ in terms of pathogenesis and clinical presentation, there seems to be a common denominator: an altered barrier function is believed to facilitate increased exposure to antigens that can trigger immune reaction and autoimmune destruction and alterations of normal body function. (9)

Celiac Disease and Gluten Sensitivity

Celiac disease is an immune-mediated chronic enteropathy with a wide range of presenting manifestations of variable severity. It is triggered by the ingestion of gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible individuals with subsequent immune reaction leading to small bowel inflammation and with normalization of the villous architecture in response to a gluten-free diet.(5,6,18) Celiac disease is a complex genetic disorder, with HLA status appearing to be the strongest determinant of risk to developing the disease, that not only affects the gut, but is also a systemic disease that may cause injury to any organ. (18) The prevalence of celiac disease in the United States is 0.71% (1 in 141), which is similar to that found in several European countries. However, most cases of celiac disease were undiagnosed. (19)

As mention above, gluten is one of the most powerful triggers to the release of zonulin. (6) Gluten is a complex molecule made of gliadin and glutenins. A Fasano referenced the work by MG Clemente, *Lab Invest* 2008, stating the gliadin portion of gluten affects the intestinal barrier function by releasing zonulin. A Fasano et al, *Gastroenterology* 2006 referenced materials that gliadin only increased intestinal permeability when administered on the luminal side of the intestinal tissue which led to the discovery and identification of the chemokine receptor CXCR3 as the target intestinal receptor for gliadin. (6) Data collected demonstrated that in the intestinal epithelium, CXCR3 is expressed at the luminal level and is overexpressed in patients with celiac disease. (A Fasano et al, *Gastroenterology* 2006) A Fasano referenced additional work by M. Nikulina et al, *J Immunol* 2004, that there are at least 50 toxic epitopes in gluten peptides exerting cytotoxic, immunomodulatory, and gut permeating activities. A Fasano has hypothesized the following as a sequence of events for celiac disease:

> "After oral ingestion, gliadin interacts with the small intestinal mucosa causing IL-8 neutrophils in the lamina propria. At the same time, gliadin-permeating peptides 111-130 and 151-170 initiate intestinal permeability through a MyD88-dependent release of zonulin (as we have recently confirmed by identifying CXCR3 as the receptor that releases zonulin in a MyD88-dependent manner, ref. KM Lammers et al, *Gastroenterology* 2008) that enables paracellular translocation of gliadin and its subsequent interaction with macrophages (through 33-mer and other immunomodulatory peptides) within the intestinal submucosa (ref. KE Thomas et al, *J Immunol* 2006). This interaction initiates signaling through a MyD88-dependent by TLR4- and TLR2-independent pathway, resulting in the establishment of a proinflammatory (Th1-type) cytokine mileu (ref. KE Thomas et al, *J Immunol* 2006) that results in mononuclear cell infiltration into the submucosa. The persistent presence of inflammatory mediators such as tumor necrosis factor (TNF)-α and interferon (INF)-γ causes further increase in permeability across the endothelial and epithelial layers (ref(s) JR Turner, *Nat Rev Immunol 9* 2009; C Zufferey et al, *Immunology* 2009), suggesting that the initial breach of the intestinal barrier function caused by zonulin can be perpetuated by the inflammatory process after the access of gliadin to the submucosa. In genetically predisposed individuals, this, in turn, may permit the interaction of T cells with antigen-presenting cells, including macrophages, leading ultimately to the antigen-specific adaptive immune response causing the autoimmune insult of the intestinal mucosa seen in patients with celiac disease. (B Jabri, LM Sollid, *Nat Rev Immunol 9* 2009; N Periolo et al, *Autoimmunity* [In Press]; D Schuppan et al, *Gastroenterology* 2009)" (6)

One other point that was made concerning research involving gliadin is that wheat gliadin has been implicated to be a dietary diabetogen (ref(s) DP Funda et al, *Diabetes Meta Res Rev* 2008; JT Visser et al, *Diabetologia* 2010)(5)(18,6)

Diabetes Mellitus (Type 1 and Type 2)

Clinical and experimental evidence suggests that both type 1 and type 2 diabetes are associated with an increased intestinal permeability. S de Kort et al in referencing work by S Wild et al, *Diabetes Care* 2004 states that in the past decades, the prevalence of both type 1 and type 2 diabetes mellitus has dramatically increased, resulting from changes in diet, reduced

physical activities and exposure to certain environmental factors. (9) Experimental data indicate that the protein zonulin appears also to play an important role in the pathogenesis of diabetes mellitus through modulation of intestinal permeability. (9) In looking at the connection between type 1 diabetes and increased intestinal permeability data suggests there is a significantly increased lactulose / mannitol ratio (the permeability measure for small intestine) in diabetic patients in comparison to controls, but that there was no significant correlation found with duration of disease or mean HbA1c values. (9) It was also found that prediabetic subjects had the greatest increase, suggesting that increased intestinal permeability precedes the onset of clinical diabetes. (6,9) Further evidence was presented by referencing Bosi et al, *Diabetologia* 2006 they observed no differences in enteropathy, measured by the lactulose / mannitol test, between preclinical and long-standing diabetes, suggesting that the duration of diabetes does not further influence intestinal permeability and an increased intestinal permeability precedes, rather than is caused by type 1 diabetes mellitus. (9) Data gathered from several different studies found that a subclinical inflammation, found in young diabetic patients and characterized by increased interleukin (IL)-4, TNF-α, INF-γ is possibly involved in compromising the integrity of epithelial barrier leading to increased intestinal permeability of the gut. (M Brewer et al, *FASEB J* 2005; Q Li et al, *Clin Immunol* 2008; O Vaarala, *Curr Opin Gastroenterol* 2008; M Westerholm-Ormio et al, *Diabetes* 2003) The author states that whether a subclinical inflammation precedes or is caused by increased intestinal permeability, more research is needed. (9) Either way, increased intestinal permeability makes the host inclined and more prone to immune reactions against antigens from various environmental, dietary, viral or bacterial origins. “These agents can then activate humoral responses and translocate to

lymphoid tissue surrounding the pancreas where they may trigger autoimmune reactions against insulin producing beta cells." (9) Type 2 diabetes mellitus is characterized by obesity and peripheral insulin resistance. Focusing in on type 2 diabetes, it was reported that "an important role for the gut microbiota and more specifically for lipopolysaccharide as a trigger molecule has been postulated in the onset of metabolic disorders associated with obesity and type 2 diabetes."(9) "High-fat and high-caloric diets have been shown to favor the colonization of the intestine with Gram-negative microbiota, leading to increased plasma lipopolysaccharide levels (metabolic endotoxemia), whereas the quantity of *Bacteroidestes* spp. decreases and that of *Firmicutes* spp. increases." (ref. RE Ley et al, *Pro Natl Acad Sci USA* 2005) "Furthermore, high-fat diet strongly increases intestinal permeability, probably mediated by reducing the expression of ZO-1 and occluding, favoring translocation of lipopolysaccharides through the intestinal wall." (ref. PD Cani et al, *Diabetes* 2008) Although findings mention in this article support a role of increased epithelial permeability, altered intestinal microbiota and subsequent metabolic endotoxemia as possible causal factors in type 2 diabetes, more research is needed. (article 9) To summarize, the increased exposure to luminal antigens due to increased intestinal permeability can possibly result in an autoimmune destruction of pancreatic beta cells as has been proposed in type 1 diabetes (article 9, 18,6,5) or in an increased peripheral insulin resistance as a consequence of increased cytokine production as has been postulated for type 2 diabetes. (9)

Functional GI Disorder – Irritable Bowel Syndrome (IBS)

There is evidence of increased permeability in patients with IBS. Evidence presented by M Camilleri et al indicates that both GI infections and chronic psychological stress in susceptible individuals appears to decrease epithelial barrier function. The associated immune activation may well contribute to the elevated cytokines, fatigue, and non-GI symptoms that are characteristic of IBS. (7) Another aspect of intestinal permeability and IBS has to do with the utilization of glutamine. Glutamine is a major energy source for the rapidly dividing cells of the intestinal mucosa. Depletion of intestinal glutamine results in epithelial atrophy of intestinal cells and a subsequent increase in permeability of the intestinal barrier. (7) The mucosa epithelial cells lining the gastrointestinal tract have a relatively small free glutamine pool and so must rely on glutamine synthetase to maintain adequate levels. Glutamine synthetase is a key intestinal enzyme that catalyzes the conversion of glutamate and ammonia to glutamine. (7) "Decreased levels of intestinal glutamine synthetase present in certain conditions may lead to decreased levels of glutamine resulting in a shortage of the energy supply for intestinal epithelial cells, resulting in increased intestinal permeability."(7) A Fasano (18) references work done by BR Yacyshyn et al, *Dig Dis Sci* 1996 and BR Yacyshyn et al, *Gastroenterology* 1995 which states that "Crohn's disease and ulcerative colitis are inflammatory diseases involving the gastrointestinal tract in which abnormal paracellular permeability defects precede the development of both syndromes and, therefore, appear to play an important role in disease pathogenesis."(18) Recently generated evidence by Fasano is suggesting that zonulin upregulation is detectable in the acute phase of IBD and that its serum levels decrease (but still are higher than normal) once the inflammatory process subsides. (18) As referenced by A Fasano, "while primary defect of the intestinal barrier function (possibly secondary to activation

of the zonulin pathway) may be involved in the early steps of the pathogenesis of IBD, the production of cytokines, including IFN-γ and TNF-α secondary to the inflammatory process serve to perpetuate the increased intestinal permeability by reorganizing tight junction proteins ZO-1, junctional adhesion molecule 1, occluding, claudin-1, and claudin-4." (ref. F Wang et al, *Gastroenterology* (2006) "In this manner, a vicious cycle is created in which barrier dysfunction allows further leakage of luminal contents, thereby triggering an immune response that in turn promotes further leakiness." (18)

GMO's /Environmental toxins / Pollution of the Food Chain by over processing

Another possible environmental trigger leading to increased intestinal permeability and barrier dysfunction is the introduction of genetically modified organisms (GMOs) that have been introduced into the American food supply. "The process of genetic modification involves the transfer of DNA from one species, such as a bacteria, virus, or fish, into that of another, such as corn, soy, or tomatoes." (20) An example of the possible problems caused by the introduction of GMOs involves genetically modified corn. The Bt-toxin produced by genetically modified corn kills insects by punching holes in their digestive tracts. However, its designers maintained that it is not supposed to create holes in human cells. In a study referenced by the review article (R Mesnage et al, *J Appl Toxicol* 2013) researchers "documented that modified Bt-toxins (from GM plants) are not inert on human cells, but can exert toxicity."(20) And so pesticide-producing corn that has been allowed into the American diets producing Bt-toxin does interact with human cells and may be boring small holes in our intestinal walls. This is just one example of the probable environmental pollution taking place in our food chain.

Role of Chiropractic in treatment of a Leaky Gut

The role of chiropractic in the treatment of patients demonstrating symptoms of increased intestinal permeability offers several possibilities. The role can be as the portal of entry healthcare provider, or providing care in conjunction with a patient's primary care physician offering lifestyle and dietary counseling in addition to chiropractic adjustments. According to Dr. Howard F. Loomis, DC, chiropractic is applied basic science evaluating the anatomy (structure) of the body connected to the physiology (function) of the body by way of the neurology. Problems with the anatomy or structure of a body would be considered musculoskeletal dysfunction. Problems with the physiology or function of the body would be considered visceral dysfunction. And problems with the neurology or control of the body would be considered neurological dysfunction. Finally, Dr. Loomis proposes that all symptoms from these dysfunctions are caused by stress. Stress, whether it comes from a mechanical or structural source, or a biochemical or nutritional source, or an emotional or spiritual source, it always evokes an identical response from the body as it attempts to maintain normal function and homeostasis. (21) Dr. Loomis references this idea from work done by Hans Seleye back in the 1960's. "Any stress to a visceral organ or tissue that is too strong, continues too long, or interferes with the ability to maintain normal function will produce symptoms."(21) The symptoms can be associated with muscle contractions. (21) "Visceral dysfunction can be associated with muscle contraction in the muscles that share the same innervation with the organ."(21) Therefore, both vertebral subluxation and visceral dysfunction are always accompanied by muscle contraction. (21) And so, Dr. Loomis poses the question, does the subluxation cause the symptoms, or is the subluxation the effect? To find this answer

> "You must palpate the peripheral tissues related neurologically to the spinal subluxation. Identify the muscle contraction there and then adjust the spine. Re-palpate the peripheral area and determine if the contraction is no longer present. If it is no longer present, the cause is peripheral dysfunction."(21)

Through research and clinical practice, Dr. Loomis has developed protocols designed to identify hidden visceral dysfunctions that are perpetuating muscle contractions, postural asymmetries, reduced joint ranges of motion and chronic structural problems. These protocols involve palpation and identification of peripheral stress points on the body connected to spinal subluxations, interpreting blood chemistries from a basic science point of view and correlating a 24-hour urinalysis to chiropractic methodology. All the information is evaluated and based on the results recommendations are made. Along with chiropractic adjustments, to strengthen and support the body through the healing process, nutritional plant-based enzyme formulas would be recommended based on results of the Loomis protocols. In addition to chiropractic adjustments and nutritional enzyme formulas, dietary and lifestyle recommendations are made to provide a complete program toward improving a patients' health.

When working to restore digestive function there are many ways to heal the gut based on the patients' particular problem. The patient may need to adopt new habits. One such habit is to chew food carefully and completely. (22) In the high stress, fast paced society we live in, we often bolt our food down as quickly as possible and then it's on to the next thing. Saliva in our mouth contains digestive enzymes that begin the process of digesting carbohydrates and fats. The parotid glands under the tongue send messages to the brain and digestive tract preparing the stomach for what is to come. If we don't chew our food thoroughly, then the signals get over run and the body loses the healthful benefits of liberating the enzymes

contained in the foods themselves. It is important to deal with food allergies and sensitivities. It is hard to help someone get better if they are continuing behaviors that fuel the fire of their inflammation such as consuming foods that have become allergenic and so an elimination diet might be recommended. Taking the time to education patients about environmental contaminants, poor food choices, effects of lack of motion and the effects of different medications are all part of the role of chiropractic. As a chiropractor, I feel my role is to partner with a patient, work together to educate and pass on knowledge that I have gained that will help the patient to reduce the effects of stress and regain health through developing healthy habits such as getting adequate movement, enough rest and relaxation, making better dietary choices (less sugar, salt and fat and more fresh vegetables, fruits and lean meats), the list goes on. (23)

Conclusion

A great deal has been learned about the mechanism of intestinal permeability and its regulation. Zonulin has been discovered as an endogenous protein that regulates the paracelluar pathway. It has been learned that the luminal intestinal milieu also effects intestinal permeability and that stress can have an effect as well. Chiropractic has a lot to offer patients suffering from increased intestinal permeability by helping to raise the overall health of the patient. Through chiropractic manipulation, lifestyle coaching, dietary and nutritional enzyme supplement recommendations much relief can be obtained.

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