Considering Intestinal Hyperpermeability and Immune-Inflammatory Metabolism in the Treatment of Food Allergy

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ABSTRACT

Food Allergy is a chronic systemic immuno-inflammatory condition that depends on several factors, but, above all, the gastrointestinal epithelial barrier. The rupture of this intestinal barrier results in a deleterious increase in intestinal permeability allowing the paracellular permeation of molecules greater than 150 Da into the bloodstream, producing an equivalent immune response, decreasing the immune tolerance. Intestinal Hyperpermeability has been linked not only to food allergy but also to Metabolic Syndrome and Non-Alcoholic Fat Liver Disease. Here we review the factors that contribute to producing Intestinal Hyperpermeability, as well the factors that contribute to the restoration of the epithelial barrier, improving the clinical outcome of food-allergic patients. The main factors that increase the Intestinal Hyperpermeability are A) Immune-Inflammatory (food allergy itself and autoimmune conditions); B) Iatrogenic (steroids, non-steroidal anti-inflammatories, antacids, antibiotics, and gastric-bypass surgeries); C) Infectious (rotavirus, HIV, SARS-CO2, *Helicobacter pylori*, *Candida albicans*, etc.); and D) Lifestyle-related (alcoholic beverages, food addiction, food overconsumption, consumption of industrialized food with high-fructose content and emulsifiers). The main factors that restore the intestinal barrier and immune tolerances are the intestinal microbiota and functional nutrients such as Vitamin A and vegetal fibers. Mucoprotectants agents, such as gelatin tannate and xyloglucan, are in study to become part of the medical arsenal to treat Intestinal Hyperpermeability conditions.

Keywords: COVID-19, diet therapy, fatty acids, food allergy, hypersensitivity, intestinal absorption, intestinal hyperpermeability, leaky gut syndrome, metabolic syndrome, mucoprotectants, precipitins, probiotics, short-chain vitamin A.

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I. INTRODUCTION

Food Allergy is a chronic systemic immuno-inflammatory condition that can manifest in a multitude of specific and nonspecific clinical presentations, most of them related to an abnormal increase in intestinal permeability [1]. The three main functions of the gastrointestinal tract are: A) Digest the ingested food to produce elemental nutrients; B) Absorb these elemental nutrients; and C) Block the permeation of microorganisms and undigested meal components, leading to their elimination [2], [3]. Digestion is the result of the sequential activity of salivary, gastric, pancreatic, and intestinal enzymes that break down nutritional macromolecules into elemental nutrients capable of being metabolized [4]. Transcellular physiologic uptake of basic nutritional molecules is mediated by carriers, transporters, and channels located at the lumen membrane of polarized epithelial cells [5]. Intestinal P-Glycoprotein and the Organic Anion-Transporting Peptides (OATPs) are membrane transport proteins that facilitate the absorption of anion compounds and drugs into the epithelial cell [6]. The pharmacologic activity of some natural foods may interfere in the treatment of allergies by reducing the bioavailability of some anti-allergic medications (as quantified by the area under the time-plasma concentration curve) [7]. Several studies showed that co-administration of apple juice, grapefruit juice, and/or orange juices reduces the intestinal absorption of the co-administered fexofenadine and montelukast, in a dose-dependent manner, by inhibiting the OATPs transmembrane activity [8]-[11]. These food-drug interactions must be considered by the prescribers and by the allergic patients using these medications.

The broad concept of the intestinal barrier includes the gastrointestinal mucus, the luminal epithelial cell layer, the subepithelial cell layer, the mucosal immune system (represented by immunocytes and by the production of the secreted IgA, which orchestrates the phenomena of immune exclusion), and the lumen components, such as the

microbiota and the indigestible fibers that adsorb and block the permeation of undesirable substances [12]-[19]. The mucus layer is also a protective and immunomodulatory component of the intestinal barrier [20]. Intestinal mucus enhances immune tolerance by providing immunoregulatory signals that prevent inflammation and sensitization to food allergens [21]. The epithelial barriers surround the internal environment (*milieau interior*) to act at a stage opposite to the external environment, as conceptualized by the creator of the definition of "homeostasis", the French physician *Docteur* Claude Bernard in the mid-19th century [22]. The rupture of the intestinal epithelial barrier results in a deleterious increase in intestinal permeability allowing the paracellular permeation of molecules greater than 150 Da into the bloodstream, producing hyperosmolar stress, homeostasis imbalance, and a (physiologic or deleterious) immune response [23]. The entry into the internal environment of macromolecules, mainly undigested proteins, peptides, and bacterial endotoxins, overloads the immune system, which is mobilized to identify, neutralize, and eliminate these foreign antigens, whose nutritional fate is, from then on, completely lost [24]. When undigested food proteins gain access to the circulatory system, they trigger an immune response that usually results in the mobilization of immune cells and production of antibodies, a condition medically known as "Intestinal Hyperpermeability" or "Leaky Gut Syndrome" [25], [26]. When digestion is compromised, for instance, after the use of antacids that inactivate gastric pepsin, large amounts of undigested proteins and peptides gain access to the intestinal lumen, increasing their risk of permeating between a leaky layer of damaged epithelial cells, producing local and systemic inflammation [27]. Under physiologic circumstances, antigen-antibody immune complexes travel free or adsorbed by the membranes of red blood cells until they are cleared from the circulation by the reticuloendothelial system, primarily in the spleen and liver [28], [29]. Up to a certain limit, this situation does not produce any disturbance, however, in greater quantities, these circulating immune complexes can be deposited in organic tissues and produce inflammatory diseases mediated by the activation of the Complement System [30]. The search for these food-specific antibodies through precipitation tests has been one of the cornerstones of both Microbial Immunology and Allergology as medical sciences [31]-[35]. Intestinal hyperpermeability has recently been linked not only to food allergy but also to Metabolic Syndrome and Non-Alcoholic Fat Liver Disease, two interrelated inflammatory diseases that have emerged from the industrialized diet [36], [37]. The immune alterations seen in metabolic syndrome follow a similar pattern to the metabolic alterations produced by the activation of the immune cells in allergic individuals [38]. The "Warburg effect", first described in cancer cells, consists of a metabolic shift from oxidative phosphorylation to anaerobic glycolysis, a common feature of metabolic syndrome, obesity, allergy, cancer, and excessive fructose intake [39], [40]. Here we review the factors contributing to the abnormal increase in intestinal permeability and can potentially amplify the effect of dietary food allergens that participate in allergic and inflammatory reactions (Table I), as well the factors that contribute to the restoration of the epithelial barrier, improving the clinical outcome of food-allergic patients (Table II).

II. Factors that Increase the Intestinal Hyperpermeability

A. Immune-Inflammatory Non-Infectious Causes

Inflammation is the immune response designed to repair tissues under metabolic stress. The optimal inflammatory response must be limited and regulated to prevent further tissue damage, otherwise, when sustained, inflammation can induce adverse consequences for metabolic homeostasis, what is now known as "metaflammation", a chronic condition developed as a metabolic response to excessive ingestion of nutrients [41], [42]. The main cause of Intestinal Hyperpermeability in the food-allergic patient is the food allergy itself. The intestinal epithelium of the food-allergic individual is recruited by a large number of mast cells. Triggered by the food allergens, the mast cells degranulate several inflammatory mediators that further increase Intestinal Hyperpermeability by damaging the intercellular Tight Junctions, perpetuating the inflammatory condition [43]. Some food allergens may also possess intrinsic proteolytic activity against the epithelial Tight Junctions proteins, disrupting the barrier integrity, such as the kiwifruit's cysteinyl proteases [44]. Auto-immune conditions that produce intestinal inflammation, such as Celiac Disease and Crohn's Disease, present a similar effect [45]. The increase in Intestinal Hyperpermeability can be interpreted as a consequence as well as a cause of intestinal inflammation, as has been suggested by studies carried out with patients with Crohn's disease and their relatives, who also had increased intestinal permeability without any intestinal inflammation [46]. Even low-grade inflammatory conditions, such as the Irritable Bowel Syndrome, are associated with Intestinal Hyperpermeability [47].

B. Iatrogenic

One of the main pharmacological causes of increased intestinal permeability is the use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs). Despite their systemic anti-inflammatory action, NSAIDs produce inflammation at mucosal sites, disrupting the epithelial barrier [48]. In addition to this action, NSAIDs also increase the availability of substrate (arachidonic acid) for the lipoxygenase pathways, blocking the cyclooxygenases and inducing lipoxygenase-dependent food allergy reactions with lower thresholds [49]-[51]. Simultaneous use of NSAIDs with ingestion of known food allergens is not recommended for food-allergic patients [52]. Antacids, by increasing the presence of undigested proteins in the lumen near the injured epithelium, also contribute to the development of food allergies [53]-[56]. High doses of corticosteroids are also associated with gastric and intestinal epithelial damage [57]. Abusive use of antibiotics may also be implicated in the appearance of food allergies, by disturbing the intestinal microbiota which produces short-chain fatty acids such as butyrate that stimulate the mucus production by intestinal goblet cells [58], [59]. Gastric-enteric bypass surgeries are also a common cause of disruption of enzymatic digestion,

and the development of food allergies and celiac disease [60], [61].

C. *Immune-Inflammatory Infectious Causes*

Viral infections such as rotavirus, HIV, and, more recently, the COVID-19 produced by the SARS-CoV2, also increase intestinal permeability, allowing not only food proteins to enter, but also microbial translocation from the lumen into the bloodstream [62]-[64]. Helicobacter pylori is a bacteria positively associated with epithelial hyperpermeability and food allergy [65], [66]. Bacterial endotoxins may increase intestinal permeability by apoptosis [67]. Fungal opportunistic infections, such as Candida albicans, may also be associated with increased intestinal permeability in immunocompromised hosts [68].

D. *Lifestyle Causes*

The industrialized lifestyle has aggreged food components to the human diet that, by increasing Intestinal Hyperpermeability, have a dual deleterious effect on the development of food allergies and Metabolic Syndrome. When associated with food addiction and overconsumption, industrialized food has tolled a heavy burden, not only on adults but also on children and adolescents [69]-[71]. One of the best-studied dietary components implicated in Intestinal Hyperpermeability is fructose [72]. Fructose is a naturally occurring monosaccharide found in most fruits [73]. The excessive consumption of industrialized high-fructose food products, provided by the ingestion of concentrated corn syrups and soft drinks, is believed to induce dysfunction in Tight Junction proteins, increasing absorption of undigested proteins, plasma endotoxin concentration, and fat deposition in liver cells [74]. This phenomenon is blocked by metformin, not only because of its effect on insulin signaling but also because of its effect on decreasing Intestinal Hyperpermeability [75]. Synthetic additives from the food industry used as emulsifiers (also known as surfactants or detergents) have a mucolytic activity or inhibit the P-glycoprotein, increasing intestinal permeability by dissolving the mucus layer [76]. The main food additives associated with this activity are carboxymethylcellulose, polysorbate, and fatty acid esters (E471, E473, and E475) [77]. They have been implicated in disrupting the protective mucus layer, increasing the microbiota encroachment, and leading to an inflammatory state [78]. The use of alcoholic beverages is an established factor to increase intestinal permeability [79], [80]. Gluten is a complex mixture of cereal storage proteins [81]. Gluten proteins are poorly digested by humans. Its undigested peptides are highly immunogenic and implicated in several hypersensitivity diseases [82]. Gluten administration to mice subjected to chemical-induced colitis, impaired epithelial damage, and increased intestinal permeability by inducing weakness and disorganization of desmosomes and adhesion junctions [83]. Some gluten-derived peptides induce the production of IL-15 by innate immunocytes activating cytotoxic lymphocytes and lowering their sensibility to the regulatory effect of Treg cytokines [84].

III. FACTORS THAT RESTORE THE INTESTINAL BARRIER

A. *Microbiota*

The intestinal microbiota is essential for the maintenance of the intestinal mucosa [85]. It produces antimicrobial peptides that inhibit the multiplication of pathobionts. It also produces, from fermentable dietary fibers, short-chain fatty acids such as butyrate, propionate, and acetate, which are essential nutrients for the intestinal epithelium [86]. The supplementation of probiotics from the genera Clostridium was able to prevent food allergies in mice [87]. However, there are not yet equivalent studies in humans, since the meta-analyses show controversial and ambiguous results with no robust evidence to prescribe probiotics for the treatment of allergies. [88], [89]. Until 2021 there was no recommendation from the scientific societies to employ probiotics for the prevention or treatment of food allergies [90].

B. *Dietary Factors*

Some food-derived and breastfeeding oligosaccharides (non-digestible carbohydrates) are known for their prebiotic effect, stimulating the growth of protective bacteria species, improving the immune response of newborns, and reducing allergic manifestations [91]. Glutamine is a non-essential amino acid that plays a key role in intestinal physiology [92]. Short-term glutamine in critically ill patients seems to improve the intestinal barrier [93]. Its supplementation in the formula for malnourished children improved the intestinal barrier function as compared with the unsupplemented formula [94]. However, the long-term oral supplementation with glutamine did not improve the increased intestinal permeability of patients with Crohn's disease [95]. Glutamine is abundantly found in most food nutrients and its deficiency only occurs in hypercatabolic states and severe malnutrition states; therefore its supplementation is not recommended to treat or prevent food allergy in well-nourished patients. [96] The active metabolite of Vitamin A, retinoic acid binds to nuclear receptors, regulating the transcription of several genes. Its main immune function is to modulate Th2 hypersensitivity reactions and the immune homeostasis of mucosal surfaces. Vitamin A is acquired from dietary plants such as carotenoids (carrots, cantaloupe, mangoes, oranges, broccoli, bell peppers, spinach), and animal food sources (milk, cheese, eggs, oily fish) as retinol [97]. The bacterial fermentation of dietary fibers results in the production of the Short-Chain Fatty Acids, that by diverse vitamin A-dependent mechanisms, increase immune tolerance to foods [98]. Until now, the best dietary intervention to restore intestinal barrier integrity is to avoid the consumption of alcoholic beverages and industrialized food, as well as to increase the consumption of natural fibers and foods naturally rich in vitamin A.

C. *Medicines*

There is nowadays an effort to study mucoprotectants to treat Intestinal Hyperpermeability. Gelatin tannate and xyloglucan are the most promising agents and have been approved to be used therapeutically in some European countries [99].

TABLE I: FACTORS THAT PRODUCE AND INCREASE INTESTINAL HYPERPERMEABILITY

NON-INFECTIOUS INFLAMMATION
Food allergy
Autoimmune conditions

INFECTIOUS INFLAMMATION
Viral infections: rotavirus, HIV, SARS-CoV2
Bacterial infections: *Helicobacter pylori*, bacterial gastroenteritis
Fungal opportunistic infections: *Candida albicans*

IATROGENIC
Steroids
Non-steroidal anti-inflammatories
Antacids
Antibiotics
Gastric-bypass surgeries

LIFESTYLE
Alcoholic beverages
Food addiction
Food overconsumption
Industrialized high-fructose food overconsumption
Food-industry emulsifiers overconsumption

TABLE III: FACTORS DESCRIBED TO DECREASE THE INTESTINAL HYPERPERMEABILITY

PREBIOTICS
Fermentable dietary fibers
Breastfeeding oligosaccharides

PROBIOTICS
Clostridium sp (experimental evidence only)

NUTRIENTS
Short-chain fatty acids
Glutamine
Vitamin A

MUCOPROTECTANTS
Gelatin tannate
Xyloglucan

IV. CONCLUSION

The study of the epithelial barrier integrity is a challenge to most physicians that do not have easy tools to evaluate the participation of this condition in their patients. However, the Intestinal Hyperpermeability must be considered when advising patients with Food Allergy and several chronic inflammatory diseases, since the epithelial barrier hypothesis provides a comprehensive understanding of these conditions [100].

CONFLICT OF INTEREST

The author declares that he does not have any conflict of interest.

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