

Celiac Disease and Imbalance of Intestinal Flora



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Abstract

Celiac disease is an autoimmune pathology of a genetic nature triggered by the consumption of gluten and characterized by histological changes in the intestine of genetically arranged patients. The characteristic symptoms of CD are diarrhea, constipation, pain and abdominal distension. Allied to this symptomatic set is the imbalance of the human intestinal tract (GI) microbiome, a complex that has in its composition a range of microorganisms that contributes immensely to the metabolism physiology and to maintain the health of the host. Changes in this system leads to a condition known as dysbiosis, where the intestinal microbiota becomes unbalanced and can trigger numerous gastrointestinal complications, including celiac disease.

Keywords: Celiac disease; Microbiome; Intestinal flora

Introduction

Celiac disease (CD) is an autoimmune disease that affects individuals who are consumers of gluten and who are genetically predisposed [1-4]. It is characterized by histological changes in the small intestine, such as atrophy of the intestinal villi and stretching of the crypts, which consequently leads to a reduction in the area of nutrient absorption [5,6]. The CD can be manifested in a classic, non-classic or asymptomatic way, with or without signs and symptoms, which can often be correlated with associated complications [6-11]. The characteristic symptoms of celiac disease are diarrhea, constipation, pain, and abdominal distension [12-14]. In addition to the characteristic intestinal complications, there is the consequent imbalance of the human intestinal tract (GI) microbiome. This biome is complex in its composition and contributes immensely to the physiology of nutrient absorption and maintenance of host health [15]. Changes in this system leads to a condition known as dysbiosis, where the intestinal microbiota becomes unbalanced and can trigger numerous gastrointestinal complications, including celiac disease [16,17]. It is believed that the normal intestinal microbiota is composed of microorganisms of 5-7 of the 52 bacterial phyla currently recognized [18]. Considering the important role of these microorganisms, this article aims to carry out a bibliographic review on the importance of the symbiotic relationship of the microbiota with man.

Literature Review

Celiac disease

The Celiac disease is a permanent intolerance to gluten, characterized by total or subtotal atrophy of the proximal small intestinal mucosa and stretching of the intestinal crypts, resulting in malabsorption of food in genetically susceptible individuals [7,10,19]. It begins as an inflammation in the duodenum (duodenitis, infiltration of cells of the immune system, such as T lymphocytes). The celiac patient has an abnormal immune response to peptides derived from gliadin and glutenin. Sensitive CD4+ T lymphocytes recognize multiple gluten epitopes through presentation through the molecules DQ2 and DQ8. Activated lymphocyte clones proliferate and produce various proinflammatory cytokines responsible for the stimulation of cytotoxic T cells by promoting cell infiltrate and producing metalloproteinases that damage the extracellular matrix [3,6,20-22].

Complications

The only treatment available for CD is the total exclusion of gluten from the diet [19,23,24]. Failure to implement the treatment may lead celiac patients to present, in addition to the classic symptoms, several types of malignant and non-malignant complications that encompass several other

organs and systems and which often do not show significant gastrointestinal symptoms. We highlight as non-malignant complications osteoporosis, infertility, obstetric complications, pulmonary hemosiderosis, neurological and psychiatric disorders, intestinal bleeding and intestinal ulcers, as well as an infinity not yet studied [25-29]. As malignant complications, of a more serious character, we can highlight lymphoma in the small intestine, carcinoma of the esophagus and pharynx, as well as adenocarcinoma of the small intestine whose etiopathogenesis is little elucidated [10,13,30]. In addition to these complications, CD is being correlated with several autoimmune diseases, including type I diabetes, Down syndrome and Turner syndrome [11,31-33]. In case of persistent inadequate diet, symptoms of gluten intolerance persist and lead to disorders that also affect the intestinal flora, which consists of an important set of microorganisms that co-exist with humans and participate in important metabolic functions, in addition to exert an indispensable function of defending the organism against pathogens by preventing external microorganisms or even the microbiota itself from causing infections [34,35]. Severe disorders in this system can trigger various intestinal or extra-intestinal disorders such as intestinal we can highlight the worsening and / or installation of celiac disease, inflammatory bowel disease and irritable bowel syndrome, while extra-intestinal include allergy, asthma, metabolic syndrome, diseases cardiovascular and obesity [15,17,18].

Intestinal flora

The human body is colonized by microorganisms on all surfaces that are topologically attached to the external environment, such as skin, respiratory tract, gastrointestinal tract and genitals. In recent years, there has been an explosion of interest in understanding the structure, function and ecology of the human microbiota to understand the mechanisms of various pathologies [16].

The gastrointestinal tract (GI) is colonized by a dense community of commensal microorganisms referred to as the intestinal flora. It is believed to be composed of a population of 10^{14} bacteria distributed in 160 different species, in addition to viruses, fungi and archaea [36]. The presence and composition of the microbiome is mainly determined by physical factors such as the availability of nutrient sources, temperature or the presence of O_2 , in addition to interactions between microorganisms through antibiotic toxins and intercellular communication. It is therefore not surprising that microbial communities vary dramatically along the length of the gastrointestinal tract and that mucosal adherent microbial communities differ significantly in lumen and faeces [37,38].

The intestinal microbiota co-evolved with man and plays an important role in physiological processes related to immunity and metabolism acting positively to maintain host health [36,39,40]. In immunogenic processes, we highlight its role in protecting intestinal lumen epithelium by competing with microorganisms

that may cause opportunistic infections, production and secretion of bacteriocins, stimulation of antimicrobial peptide production by epithelial cells, IgA synthesis and the promotion of good functioning of the cellular junctions, which reduces the possible invasion of the tissue by pathogenic bacteria [36,41]. In metabolism, the microorganisms of the intestinal microbiota participate in the biotransformation of nutrients such as lipids, carbohydrates and unabsorbed proteins in the upper digestive tract, causing a certain ease in the absorption of the intestinal villi [42,43]. In addition, they benefit from having the same bioavailable nutrients for the host as energy source.

The occurrence of some imbalance in the microorganisms of the microbiome may lead to a state known as dysbiosis, where the altered intestinal microbiota may cause the development of various gastrointestinal diseases including inflammatory bowel disease, colon cancer, celiac disease, and irritable bowel syndrome, As well as extra intestinal diseases such as obesity and autism [36,39,44]. There is a growing body of evidence to suggest that multiple intrinsic and extrinsic factors such as genetic variation, diet, stress, and medication can dramatically affect the balance of the intestinal microbiota [16,17].

Influence of intestinal flora in DC

Recently, many studies have addressed the importance of intestinal flora in the development / evolution of celiac disease, showing the relationship between the change in the structure of intestinal cells, such as increased permeability and its detachment, influences the aggravation and development of the main symptoms of celiac disease [45,46]. In the equilibrium of the intestinal microenvironment, each bacterium presents its function, but when a disturbance occurs in this environment, mainly through the reduction of certain bacterial groups considered probiotic, other bacteria can multiply and gain access to the cells of the endothelium of free form, this ends for causing a number of problems [47,48]. In the composition of the intestinal flora of healthy people it is common to find bacteria belonging to the genus *Lactobacillus* spp. And *Bifidobacterium* spp. [49]. These bacteria are responsible for the degradation of gluten polypeptides, protecting the cells of the intestinal epithelium, which leads to less irritation and inflammation of the intestine, as well as compete in the environment against pathogenic bacteria, thus preventing them from freely propagating through the intestine of the host [50,51]. Studies have shown that the intestinal microbiota of individuals with celiac disease, when compared to healthy individuals, present a lower number of *Lactobacillus* spp. and *Bifidobacterium* spp., and an increase in the number of bacteria that can cause intestinal diseases [15,52,53].

The bacteria that make up the genus *Lactobacillus* spp. are Gram-positive, microaerophilic and have as final product of the metabolism carbon and lactate [54]. The *Lactobacillus* may present a new guideline in the treatment of DC, thanks to its enzymes that have the ability to degrade gluten. Biotechnology

tests have selected species of this genus, which are efficient and low in toxicity, for use in breads and pasta, and in some cases even in wheat flour composition, causing the gluten proteins to arrive degraded in the intestine of the consumer, which reduces the incidence of inflammation of intestinal epithelial cells [55-57].

The genus *Bifidobacterium* spp. Deserves special attention among probiotics that help maintain and function the intestinal flora. This genus is formed by Gram-positive and anaerobic bacteria, which have the capacity to produce antibacterial compounds such as organic acids and bacteriocins [58]. From the metabolic point of view, they are able to produce lactic acid and acetic acid without the production of CO₂, which leads to reduced production of intestinal gases [59]. The *Bifidobacterium* species, which colonize humans, have the ability to utilize glucose, galactose, lactose and fructose as carbon sources. Thanks to these characteristics of their metabolism, they are great inhibitors of pathogenic bacteria, both Gram-positive and negative [47]. Analyzing the context of the importance of these two bacterial genera, in maintaining the normal functions of the intestine, it is possible to infer that an increase in their quantity would probably lead to a control of the celiac disease, mainly the inflammation of the intestinal epithelium, and a consequent improvement in the patients' lives [60].

The presence of Gram-negative bacteria, such as enterobacterias, is normal, being commonly located in the intestinal tract of humans, and although they are mainly pathogenic, do not cause problems in their host, but when they are in a larger number can cause problems [61]. Among the major bacteria in this group are *Escherichia coli*, *Salmonella* sp., *Shigella* sp., which are known to cause health problems due to their toxins. Their excessive presence in the intestines of people with celiac disease can lead to an even greater decrease in gluten tolerance due to the fact that this group of cells produce toxins and lodge in enterocytes, causing more irritation to the cells and reducing the amount of bacteria which aid in the degradation of gluten [62,63]. Another bacterial genus that stands out, in relation to the increase of its quantity present in the intestinal flora of coeliacs, is *Clostridium* spp. Bacteria of this genus are known to produce toxins that cause a range of problems in humans [64]. The main bacterium in this group colonizing the intestine is *Clostridium difficile*, responsible for the production of two toxins of high pathological effect, known as Toxin A and Toxin B [65,66]. Both are enterotoxins, which exhibit a high degree of cytotoxicity, and have the ability to affect intestinal epithelial cells, disrupting their functioning and causing tissue damage [67]. An intact intestinal epithelium prevents the action of pathogenic bacteria normally found in the intestinal flora of humans Human beings, so the action of these toxins leads to a worse perspective in the evolution of the disease [2,68].

Understanding how microbial flora is composed and what type of influence the major bacteria exert on the human body can be an important factor in improving the quality and efficacy

of treatments in patients suffering from some intestinal disease, such as celiac disease, As well as improving the quality of life of these individuals [69,70].

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