The Celiac and Microbiome

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Abstract
The celiac disease is a lifelong problem where many intestinal and extra intestinal symptoms are manifested. The causes and evolution of the microbial flora of the celiac is discussed with the vision of future approach.

Keywords: CD; Dysbiosis; Diversity; Cytokines; Bacteria; Microbial Flora; Microbiome

Introduction
Celiac disease is a lifelong immune-mediated, multisystem disorder that may develop in genetically predisposed individuals when exposed to dietary gluten. It occurs in individuals carrying the HLA class II haplotype DQ2 or DQ8 [1]. It is characterized by elevated titers of celiac-specific autoantibodies, and inflammatory enteropathy with a wide range of gastrointestinal and extra-intestinal manifestations [2]. There is dysbiosis of the microbial flora with villus atrophy and lymphocytes in the villous architecture [3]. The dictionary definition of celiac disease (CD) is: a disease in which the small intestine is hypersensitive to gluten, leading to difficulty in digesting food, caused by gluten or its family.

Gluten is a heterogeneous compound protein, composed of glutenin (alcohol-insoluble fraction), and gliadin (alcohol-soluble fraction) found in cereals such as wheat, barley, and rye which causes dough elasticity. As little as 50 mg of gluten (1/100th a slice of bread) can trigger disease in susceptible people [4]. Gluten is almost everywhere, found in any wheat product or related to gliadin.

The pathogenesis of the disease is a combination of three main factors: genetic, environmental and immunological. The combination of all plays a crucial role in the evolution of the disease [5]. Host genetic background (HLA-DQ2 or DQ8 and other non-HLA genes); which includes, higher incidence in 1st degree relatives [6], external trigger (gluten), and environmental cofactors (such as intestinal pathogens, infant-feeding practices, immune-modulatory drugs and antibiotics) alter gut microbiota composition mainly in the neonatal period leading to microbial imbalance and dysbiosis [7,8]. The glutamine-rich proteins cannot be completely digested by the endogenous peptidases; hence, residual peptides initiate a cascade damage in the small intestine within the lamina propria with villus atrophy and cell infiltration (lymphocytes) in various degrees [9].

The microbiome consist of all the microbes within us and living in our body, they out number our cells of the body by 10 times, this means that their genomes exceed more than our genes by 100 times [10].

Lately, the microbiome is considered as an organ by itself like any other organ of our body, it has immunological and bioreactor and enzymatic capabilitie

The commensal microbiome of the intestine (Microbial flora) provides the body with nutritional benefits, produces essential amino acids and vitamins of metabolic benefits, degrades complex polysaccharides from dietary fibers, and helps in the formation of short fatty acid. It has an immunologic effect in shaping the host immune system and protective effect in fighting against pathogenic microorganisms [11]. Normal gut microbiome in healthy subject is in symbiosis and hemostasis.
Changes in the microbial flora or microbiota composition may have a role in the pathogenesis of celiac disease and could be one of the factors in its evolution. Its effect could be more than the diet-genetic interaction [2,12].

For the celiac disease to develop we need the genes, the wrong food (gliadin) to eat and the microbiome dysbiosis in order to complete the picture of the evolution of CD with its inflammatory cascade. Microbiome dysbiosis or microbial flora alteration is now considered as a risk factor mainly if it happens during the first year of life, depending on type of feeding, “breast or bottle”, time and amount of gluten introduction “the earlier the higher”, and if it is associated with recurrent intestinal infections [13,14].

The changes in the composition of the intestinal flora have been detected in children and adults with active celiac disease. There is decreases in the abundance of Firmicutes spp, Bifidobacterium the anti-inflammatory bacteria and increases in Proteobacteria spp, these bacteria alter the metabolic function by decreasing the concentration of protective short-chain fatty acids of the microbiota [15-17].

Children born by cesarean section have unbalanced microbiome where Bacteroides and Clostridia are increased, they are more likely to encounter and develop celiac disease if other factors are present too [18].

The unbalanced microbiome in children with CD included greater or lesser prevalence of certain bacterial species and reduction in species diversity as mentioned before.

There is distinct atypical microbiome even in children who are genetically predisposed and not developed the disease yet, they differ from their health sibling [19,20].

Due to the decreased number of symbiotic bacteria which is protective, the growth of pathobiont increases in the small intestine (pathobiont are dormant pathogenic bacteria become active when there is dysbiosis).

The alteration of the intestinal microflora may cause massive damage to the duodenal mucosa in the small intestine since its pathogens will release massive inflammatory cytokines. The proinflammatory marker and other cells -derived factor of the colonization of harmful gram-negative bacteria are the result of the major component of the dysbiotic microflora. This will lead to loss of tolerance against prolamins.

Moreover, some of these bacterium species show as biological marker and indicate the severity of the disease [21].

When the celiac disease is active there is decrease in certain microbes as Firmicutes spp. With an increase in Proteobacteria the more of this dysbiosis the more the disease is active. More over the decrease in the good bacteria as Bifidobacterium, which have anti-inflammatory properties and the increase in the proportion of Bacteroides and Escherichia coli which have inflammatory cytokines, could be a cause and a result of the severity of the disease.

This altered changes in composition and diversity has an effect on metabolic function since it is the cause of the decrease of protective short chain fatty acid of gut the microbial flora [15,16].

The reduction of the Bifidobacterium with or without the Lactobacillus species compared to the gram-negative bacteria which produce inflammatory cytokine when the gliadin is ingested in celiac patient cause increase in interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and interleukin 12 (IL-12) which are inflammatory by nature [22].

Some strains of Bifidobacterium genus protect against the inflammatory response and mucosal damage caused by gliadin peptides by decreasing inflammatory cascade [23], exert immunoregulatory effects and reduce the release of the inflammatory cytokines IFN-γ and TNF-α and increasing interleukin 10 (IL-10) in peripheral blood mononuclear cells.

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*Bifidobacterium lactis* which is a probiotic provides mucosal protection by inhibiting the toxic effect of gliadin when ingested on the intestinal mucosa of the small intestine (on cell and villi) [24]. This prevents (intraepithelial lymphocytes) and atrophy of jejunal mucosa.

Adenovirus, hepatitis C virus, rotavirus and bacterial infections are capable of triggering and initiating or augmenting gut mucosal responses to gluten and may play a role in the pathogenic mechanism of this disease [25].

The active celiac patient has higher harmful bacteria as Gram-negative bacteria: (*Bacteroides, Prevotella, Escherichia coli*) and lower helpful bacteria as Gram-positive bacteria including the protective *Lactobacilli* and *Bifidobacterium* [26,27].

There is a difference in the bacterial composition in the duodenum with those who are treated by free gluten and those who are not [28].

This seen also with infants who are breast fed, because of the protective bacteria in breast fed are higher than those bottle fed infants with and without carrying HLA-DQ-2 haplotypes. Moreover, breast-feeding reduces the genotype-related differences in microbiota composition which may explain the protective role of breast milk in many disorders including CD [29].

To sum up, the main changes in the microbiome composition found in patients with CD compared to controls are the increase of *Bacteroides, Proteobacteria, Prevotella, Haemophilus, Serratia, E. coli, Enterobacteriaceae, Staphylococcaceae, Klebsiella, Bacteroidetes, Clostridium* and the decrease of *Lactobacilli, Bifidobacteria, Streptococcaceae, Firmicutes* [21]. What is interesting is that this dysbiosis was only partially normalized after gluten free diet introduced [27,28]. There are significant differences between the duodenal bacterial composition of patients with newly diagnosed CD and that of treated patients maintained on gluten free diet. (The only effective treatment of CD) which contributes partially to the restoration of the intestinal microbiome to normal healthy state because of the prevalence of small intestine bacterial overgrowth which is considered as a potential cause for non-responsive CD [28,30].

**Conclusion**

Celiac disease (gluten-sensitive enteropathy), is an immune intestinal reaction to gluten, a protein found in wheat, barley and rye. It is associated with the overgrowth of pathobionts and reduction of symbionts, thus leading to dysbiosis and passage of gliadin to Lumina propria via tight junction and initiating inflammatory cascade. The consequence is the release of pro-inflammatory cytokines and other cell-derived factors, resulting in destruction of the duodenal mucosa with mucosal villus atrophy.

CD promotes the colonization of harmful Gram negative and other bacteria and induces the known manifestation of the disease. The severity of CD disease is associated with the diversity and composition of the microbiome and the presence of some bacterium species that may be a biological marker of disease activity.

The manipulation of the microbial flora in CD patient may contribute the its evolution and etiopathogenesis as it could counter effect the inflammatory cascade of the disease (e.g. via regulation of the cytokine network of pro-inflammatory and anti-inflammatory factors) [31]. The hypothesis is the ability to prevent celiac disease by manipulating the microbiome to "bring it back to the right course".

Could this be a possibility by "Probiotic or Fecal transplant?" [12].

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**Bibliography**


