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Association between Celiac Disease and Microbiome

Sara Deumić[1]*; Neira Crnčević[1]; Mirsada Hukić[2,3]; Monia Avdić[1,2]

[1]Department of Genetics and Bioengineering, International Burch University, Francuskerevolucije bb, 71210 Ilidža, Bosnia and Herzegovina.

[2]Academy of Sciences and Arts of Bosnia and Herzegovina, Center for Disease Control and Geohealth Studies, Bistrik 7, 71000 Sarajevo, Bosnia and Herzegovina.

[3]Institute for Biomedical Diagnostics and Research Nalaz, Čekaluša 69, 71000 Sarajevo, Bosnia and Herzegovina.

***Corresponding Author(s): Sara Deumić**

Department of Genetics and Bioengineering, International Burch University, Francuskerevolucije bb, 71210 Ilidža, Bosnia and Herzegovina.

Tel: +387-62-917-318; Email: sara.deumic@ibu.edu.ba

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Abstract

Celiac Disease (CD) represents an immune-mediated disorder that involves the body's inability to digest gluten properly. After contact with gluten, patients of all ages might experience symptoms such as bloating, diarrhea, gas, growth issues, and anemia. In the past two decades, its prevalence has drastically increased worldwide, so the need for a better understanding of this disease and novel potential treatment options has never been greater. Today, patients are still advised to follow a completely gluten-free traditional gold standard CD diet. However, lately, the use of probiotics in the diet is sometimes recommended since some studies suggest an association between the gut microbiome and CD. Many factors influence the composition and number of gut microbiota, which can, in turn, potentially influence the onset of CD. This is especially seen in dysbiosis in the organism, the imbalance of harmful and helpful microbes, which can occur due to host genetics, diet changes, exposure to atypical microbes, overuse of antibiotics, breastfeeding, and mode of delivery. The significant findings of studies that analyze the association between CD and gut microbiota indicate some changes in the composition of gut microbiota in CD patients compared to their negative controls. This review paper aims to analyze the potential association between CD and the gut microbiome and to explain the underlining mechanisms that occur during disease development.

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Introduction

Celiac disease (CD) represents a common immune-mediator disorder in the 21st century. This systemic disease is induced by gluten, a protein complex found in barley, wheat, and rye [1]. Between 0.6 and 1.0% of people worldwide suffer from this disease [2,3]. The prevalence of CD also differs in males and females [4]. It is estimated that females are three times more likely to have the disease when compared to men, although men usually have more severe symptoms [5]. When it comes to its prevalence in developing countries, it is mostly prevalent in the Middle East [6] and North Africa. A common factor noticed among the geographic regions is this disease's increased prevalence and incidence. Many believe that this increase is due to changes in the processes of producing and preparing wheat, the westernization of diets, and increased awareness of the disease [7]. In a systemic review and meta-analysis by King et al., in 33 studies, 73% had a significantly increased diagnosis rate over time. These studies measured the incidence at more than one point [8].

In the period up to the 1970s, CD was determined mainly based on the appearance of clinical symptoms such as mal absorption, diarrhea, and weight loss. It was considered very rare, with a global prevalence of 0.03% [1]. Because of this, it is still not completely clear why there is an increased prevalence of this disease over time. This time is too short for the development of any essential changes in the genetic material of humans that could cause drastic changes in digesting gluten. Consequently, some suggest that an environmental influence could be the main factor in the pathogenesis of CD [9].

On the other hand, others believe that these changes in the prevalence of CD are primarily due to the more reliable detection methods available in the modern age [10]. However, in 2007, Lohi et al. noticed that the prevalence of CD in Finland had doubled in the last 20 years. Since the detection methods did not drastically change during this period, this could only be explained by the impact of the environment on disease pathogenesis [11,12].

In recent years, the hypotheses that changes in gut microbiota composition could be linked to many inflammatory diseases have emerged. Potential associations between the microbiome have been recognized in chronic diseases such as diabetes [13], cancer [14], obesity [15], and inflammatory bowel disease [16]. Apart from these diseases, some studies have suggested that there could be a correlation between intestinal dysbiosis and CD [17,18,19]. This review analyzes the potential association between CD and gut microbiome composition.

Clinical manifestations

For a long time, CD was thought to be a rare, mal absorptive condition that mainly affected young children and newborns. Clinical manifestations of this disease differ among age groups. Infants and young children often experience failure to thrive, diarrhea, and abdominal distention. Furthermore, they can sometimes also experience constipation, vomiting, and irritability. On the other hand, adolescents can, apart from the characteristic symptoms like diarrhea and abdominal pain, exhibit manifestations outside the gastrointestinal tract, including anemia, short stature, and even neurologic symptoms [20].

The presence of gastrointestinal symptoms is the basis for the clinical classification of CD. 'Typical' and 'atypical' clinical aspects of CD are frequently used to categorize them. However, these terms' definitions vary widely. Even if they could potentially be more frequent than the "usual" symptoms, extra-intestinal manifestations are particularly challenging to categorize. Therefore, a group of professionals supported the other terms of "classical" and "non-classical" CD a few years ago [21]. "Asymptomatic," "atypical," or "silent" CD refers to presentations without gastrointestinal symptoms, while "symptomatic" or "classical" CD refers to presentations with diarrhea, with or without a mal absorption syndrome. Why the phenotypic manifestation of CD varies so much is unknown. Differences in clinical or histologic severity are not explained by the presence of DQ8 as opposed to DQ2 [22].

The prevalence of "typical" CD patients appeared to decline in the 1970s, and at the same time, elderly people with lesser symptoms were discovered. The significant incidence and diverse clinical presentation of CD first became apparent when screening for the condition using sensitive and specific endomysium and transglutaminase antibodies from serum became feasible in the 1980s and 1990s, respectively [23,24].

Distinguishing symptoms from consequences and from disorders that are independently related to CD is a difficulty. With a gluten-free diet, symptoms of CD should improve, but consequences could become chronic and irreversible, especially if treatment is started later than recommended. Type 1 diabetes, autoimmune thyroiditis, and Down's syndrome are a few well-known disorders that have been linked to an elevated risk for CD. It has been questioned if CD could be prevented in some instances by early detection and treatment [25].

Early on, it was understood that untreated CD was linked to gastrointestinal symptoms and signs such as anemia, stunted growth, low bone mineral density, and vitamin deficiencies. Although it was believed that they were exclusively present in combination with malabsorption, it was subsequently realized that they might also be the only symptom. One of the earliest extra-intestinal signs of CD was dermatitis herpetiformis. When, for instance, patients with earlier unexplained neurological and articular complaints were diagnosed, other organ systems were later shown to be impacted [26]. Additionally, due to increased screening, people with CD were frequently diagnosed with symptoms that are typical in the general population, such as headache and fatigue. Remembering the generality and complexity of the symptoms mentioned above is crucial because many other common conditions, including migraine, chronic fatigue syndrome, and Irritable Bowel Syndrome (IBS), can also cause them [27].

Increased surveillance for CD among those with a family history of the condition and those with Down syndrome, Turner's syndrome, or type 1 diabetes-all linked to the condition-has led to the identification of particular instances. Autoimmune disorders are more common in people with CD than in the general population [28].

For unexplained reasons, women are two to three times more likely than males to experience the condition as adults. In general, women are more likely than males to have autoimmune disorders, and iron deficiency and osteoporosis, both of which call for a CD examination, are more frequently detected in women. After age 65, there is a slight decline in the disease's prevalence in women. Adults typically appear with diarrhea, which may be followed by discomfort or pain in the abdomen [29]. Iron deficiency anemia, osteoporosis, and inadvertent detection at endoscopy conducted for other reasons, like symp-

toms of gastric reflux, are other quiet presentations in adults. Abdominal pain, constipation, weight loss, neurological symptoms, dermatitis herpetiformis, hypoproteinemia, hypocalcemia, and high liver enzyme levels are less frequent presentations. A sizable percentage of patients are overweight and have previously been diagnosed with IBS. Before receiving a diagnosis of CD, patients frequently experience severe symptoms for an extended period and require repeated hospital stays and surgeries [30].

The role of gluten in celiac disease pathogenesis

Gluten interacts with immunological, genetic, and environmental variables to cause CD. The human upper gastrointestinal system has difficulty breaking down the gluten protein, which is high in glutamine and proline. The complete wheat protein is referred to as "gluten," and the alcohol-soluble portion called gliadin is where most of the hazardous elements are found. After ingesting gluten, undigested gliadin molecules, such as a 33-amino-acid peptide from a -gliadin fraction, are resistant to being broken down by the digestive system's gastric, pancreatic, and intestinal brush-border membrane proteases and consequently persist in the intestinal lumen. These peptides interact with antigen-presenting cells in the lamina propria after passing past the intestinal epithelial barrier, possibly due to intestinal infections or increased intestinal permeability [31].

Mucosal immune responses in celiac disease

Immune reactions to gliadin fractions in CD patients lead to an inflammatory reaction, primarily in the upper small intestine, characterized by persistent inflammatory cells infiltrating the lamina propria and the villous epithelium atrophy. Both the innate immune system and the adaptive immune system have a role in this reaction. The HLA class II molecules DQ2 or DQ8 on antigen-presenting cells bind to gliadin peptides, which are recognized by gliadin-reactive CD4+ T cells in the lamina propria. The T cells then release pro-inflammatory cytokines, including interferon-γ [32]. The gastrointestinal enzyme tissue transglutaminase deamidates gliadin peptides, enhancing their immunogenicity. Metalloproteinases and other tissue-damaging mediators are released by the subsequent inflammatory cascade, which causes crypt proliferation and villous damage. In addition, gliadin peptides trigger an innate immune response in the intestinal epithelium characterized by increased interleukin-15 production by enterocytes and the activation of intraepithelial lymphocytes that express the natural killer cell marker NK-G2D. Major-histocompatibility-complex class I chain-related A (MHC-A), a cell-surface antigen generated by stress, such as an infection, causes these activated cells to become cytotoxic and kill enterocytes [33].

Genetic factors of celiac disease

The familial nature of CD suggests a genetic component in its pathophysiology. There is an association between the disease and HLA alleles DQA1*0501/DQB1*0201 [34]. A person cannot acquire CD without alleles that encode the HLA-DQ2 or HLA-DQ8 proteins. These alleles are present in a large number of people, the majority of whom do not have the disease. Therefore, their existence is essential but not sufficient for the disease to manifest. Studies on identical twins and siblings conclude that less than 50% of the genetic basis for CD may be attributed to HLA genes. It has been suggested that several non-HLA genes affect illness susceptibility, although this has not been proven [35].

Previous research has examined the fecal microbial composition of at-risk children to understand the potential role of microbial variables in CD development. Children with a high genetic risk for CD were shown to have a different microbiome than children with low genetic risk, indicating that the high-risk genotype may affect the early gut microbiota composition. Compared to infants at low or intermediate risk for CD, those at high risk for the CD had a greater prevalence of enterotoxigenic *E. coli* [19]. Additionally, in a cohort of 164 babies, individuals at risk for the CD had higher levels of *B. fragilis* and *Staphylococcus* spp. and lower levels of *Bifidobacterium* spp. and *B. longum*. Breastfeeding decreased the differences between *Bacteroides* and *Bifidobacteria*. Recent research revealed that at-risk kids who later acquired CD had a different microbial trajectory correlated with immunological alterations. These alterations in the gut microbiota in kids who later had CD were suggestive of a "premature maturation" of the microbiota. However, the fecal microbiota of children at risk for developing CD was comparable at 9-12 months to that of infants who had not developed the CD by age four. More extensive clinical trials should be conducted to determine whether at-risk individuals who develop the CD have altered duodenal microbial composition or function [36].

Environmental factors of celiac disease

Epidemiological studies have proposed that environmental variables play a significant role in the onset of CD. Breastfeeding's protective qualities and the introduction of gluten in connection with weaning are two examples [37]. The introduction of gluten after 7 months is related to a marginal risk. The first gluten administration before 4 months of age is associated with an elevated risk of disease development. To reduce the incidence of CD, the overlap of gluten introduction and breastfeeding may be a more significant protective factor. The creation of methods for the primary prevention of CD might be made easier with further research into environmental factors [38].

Impact of microbiome on celiac disease pathogenesis

Microbiome in celiac disease

The intestinal barrier and mucosal and systemic immune system development are influenced by microbial colonization, which starts at birth. A disruption of these host-microbe interactions, caused by altered bacterial composition or functions, has been theorized to raise the risk of various autoimmune or inflammatory illnesses, including CD. A potential environmental modulator of CD development is altered microbiota composition in CD patients [39].

In an early investigation, rod-shaped bacteria were found in the duodenal biopsies of Swedish infants with CD who were born during the epidemic but not in control children or those born after the pandemic. *Clostridium* spp., *Prevotella* spp., and *Actinomyces* spp. were later identified as bacteria, and it was proposed that their existence constituted a risk factor for CD that contributed to the rise in disease prevalence in Sweden from 1985 to 1995 [40]. Clinical studies conducted later on in children and people with active CD compared to healthy controls have revealed changes in the microbial composition of the feces and the duodenum. While no unique microbial signature associated with CDhas been identified, numerous studies have noted rising *Bacteroides* and *Proteobacteria* proportions and declining *Lactobacillus* and *Bifidobacterium* proportions. Additionally, it was discovered that CD patients with chronic symptoms have more *Proteobacteria* than patients without

symptoms. These findings indeed point to a link between CD development and altered microbial composition, but studies examining mechanisms and causality are absent. Furthermore, it is still unclear if changes in the microbial makeup are the cause or an effect of minor intestine inflammation [41].

According to recent research, CD patients' microbiota may contain more pathogenic or pro-inflammatory bacteria. The discovery of CD after a *Campylobacter jejuni* infection has been reported, which suggests that bacterial infections might exist before CD development. Comparatively to *Escherichia coli* clones obtained from healthy controls, those from CD patients exhibited more virulent genes. Like *Staphylococcus* spp., isolates of *Bacteroides fragilis* isolated from CD patients have higher levels of virulent genes than strains from healthy controls [42].

In contrast to the research mentioned above, bacterial infections may also prevent the development of CD. While some research has indicated a positive or no link, certain studies demonstrate an inverse relationship between the presence of *Helicobacter pylori* and CD in both adults and children. Inconsistencies among studies may be related to variations in methods used to assess *H. pylori* status or *H. pylori* virulence. The mechanisms behind this link remain unclear. More virulent strains may protect against CD, while less virulent strains may worsen the mucosal response in CD [43].

Functional variations in the microbiota may also impact metabolic procedures crucial to CD etiology. There are many bacteria in the GI tract that, in vitro, contribute to the metabolism of gluten, and these bacteria may differ between healthy people and people with CD. It is challenging to ascertain whether functional changes exist before the disease's onset because most investigations have compared the microbial composition of active or treated CD to healthy controls [44].

Dysbiosis in celiac disease patients

Dysbiosis, an imbalance of harmful and helpful microbes in the organism, can occur due to host genetics, diet changes, exposure to atypical microbes, and overuse of antibiotics [45]. This imbalance is associated with CD. It was found that patients who had CD had more rod-shaped bacteria in their small bowel environment compared to their healthy negative controls. These results were obtained after biopsies of the small bowel [39].

Intestinal microbiota plays an essential part in the pathogenesis, clinical manifestation, and outcome of CD. For instance, it can regulate and change the immune system responses through the expression of cytokines and pro-inflammatory and anti-inflammatory peptides. Apart from this, it can also promote mucosal epithelium maturation[46]. Many factors can affect the gut microbiota composition, especially in newborns. Breastfeeding is one of them. The maternal oligosaccharides aid the growth and survival of a stable and healthy gut microbiome. Some studies suggest that gluten introduction during the period of breastfeeding and the duration of the breastfeeding period can delay or reduce the onset of CD. However, this is still controversial, and more data needs to be obtained[47].

The main bacterial phyla in the gastrointestinal microbiome include *Bacteroides*, *Firmicutes*, and *Actinobacteria*[48]. Moreover, according to duodenal biopsies and stool cultures, patients with CD also contain an increased abundance of gram-negative bacteria, *Clostridium*, *E. coli*, and *Bacteroides*, compared to their negative controls [49,50,51]. Table 1 shows the composition of the gut microbiome and the significant symptoms among different age groups of CD patients.

In a study on a group of children with and without CD, fecal microbiota composition was examine dusing a method involving Fluorescent In Situ Hybridization (FISH) and Flow Cytometry (FCM). The results indicated that children with CD contained a significantly reduced ratio of Gram-positive to Gram-negative bacteria compared to their negative controls. Interestingly, these results were seen in both treated and untreated children. In untreated CD patients, there was a higher abundance of the *Bacteroides–Prevotella* group than their negative controls. On the other hand, this group possessed a smaller abundance of the *Bifidobacterium* genus [50].

Figure 1: Symptoms and microbiome composition among different age groups of Celiac disease patients. Data from [20, 50,52,53,54,55].

Celiac disease characteristics in different age groups			
Patients	**Most common symptoms**	**Major bacterial phylum in the GI tract**	**Reduced bacterium phylum in the GI tract**
Infants	failure to thrive, diarrhea, abdominal distention, constipation, vomiting, and irritability [20]	*Proteobacteria* [52]	*Bifidobacterium* [52]
Children	diarrhea, abdominal pain, and constipation [53]	*Proteobacteria*, *Bacteroidetes*, *Actinobacteria* [54,50]	*Bifidobacterium* [55]
Adults	diarrhea, abdominal pain, constipation [53], anemia, short stature, and neurologic symptoms [20]	*Firmicutes, Bacteroidetes*, *Actinobacteria*, *Clostridium* [54,50]	*Bifidobacterium* [50]

Association between mode of delivery and Celiac disease

Since the rates of cesarean section, more commonly called c-section, have increased in recent years, the idea of studying the long-term- and short-term- effects on these infants has sparked an interest in the science community [56].

During childbirth, vaginally delivered infants' nasal cavities, skin and oral cavities, and other parts of the bodies are exposed to a more significant number of beneficial microbiota when compared to c-section infants. The microbiome composition of newborns who experienced a natural mode of delivery is similar to the mother's vaginal microbiome. On the other hand, c-section infants have a microbiome that resembles the mother's skin microbiome [57]. This is because the direct contact between the newborn and the mother's vaginal flora does not occur in the c-section mode of delivery [58].

The uterus environment throughout fetal development is sterile. During birth, the infant's skin first comes in contact with an environment rich in microbes and microbial substances. Additionally, the natural mode of delivery allows the child to be exposed to the mother's skin, intestinal, and vaginal flora. This results in colonizing the child's skin and the gastrointestinal microbiome. Usually, the first intestinal bacteria that can be detected in newborns include *Lactobacilli*, *Streptococci*, as well as *Enterobacteriaceae*[59,60,61].

The short-term effects of c-section delivery can include the development of allergies, asthma, altered immunity, and reduced diversity of the gut microbiota. The persistence of these conditions during the child's life is still not understood completely, and more research needs to be done to confirm it [62].

A few observational studies suggest that elective cesarean delivery is associated with an increased risk of CD at a young age. This is due to the dysbios is due to the lack of beneficial microbiota. In these studies, the increased risk of CD during pediatric age is linked to fewer *Bifidobacterium* species and overall reduced microbiome diversity [63,64]. However, the hypothesis that cesarean section increases the risk of autoimmune diseases remains one of the most controversial topics about newborns. Other studies suggest no association between the mode of delivery and the development of CD, so more research needs to be done on this topic.

Using probiotics as a potential treatment for Celiac disease

Until now, the most accepted treatment for CD is a strict gluten-free diet that includes the complete avoidance of gluten in food and any gluten contaminations. When it comes to cereals, gluten can be found in durum wheat, Khorasan wheat, barley, rye, bread wheat, and others. The nutritional value of gluten is low, but it improves the palatability of food. There are alternative grains that can be used instead, as well as other sources of starch that can offer flours for cooking and baking, even though wheat, rye, and barley should be avoided [65].

Although the gluten-free food industry has started to develop more in recent years, it is still challenging to have a lifestyle without any contact with gluten. This is primarily because of the possibility of cross-contamination that can occur during the preparation of gluten-free food at home, in the food industry, and in restaurants. Also, since CD patients cannot have a completely balanced diet, many patients often have nutrient deficiencies. Gluten-free food can sometimes lack important fibers and vitamins, such as vitamin D, folate, and vitamin B12, as well as minerals like magnesium, calcium, zinc, and iron [66,67]. Vitamin deficits could arise as a result of the alternative flours' lack of B vitamin fortification; these deficiencies have been found in patients who have been on a diet for a long time (more than 10 years). Vitamin supplementation is therefore suggested. Because they are inherently gluten-free, meats, dairy products, fruits, and vegetables contribute to a healthier and more varied diet [65].

Numerous studies have compared the gut microbiome in CD patients with different diets. It was found that CD patients that followed a gluten-free diet for at least two years could not completely restore the microbiota in their duodenum. Moreover, their microbiome was less abundant compared to their negative controls. Their ratio of harmful to beneficial bacteria was still abnormal. Even though the number of *Staphylococci* and *E. coli* was restored after the patients followed a gluten-free diet, their fecal samples showed that the number of *Bifidobacteria* was still lower than in their negative controls [49].

A diet containing a low content of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has a specific beneficial effect on CD patients. In a study conducted by Roncoroni et al., this diet was shown to reduce the typical CD symptoms and the psychological health of these patients more than the usual gluten-free diet [68]. Since abnormalities in the gut microbiota carry on even after a gluten-free diet, new therapeutic approaches are needed. It is of crucial importance that the novel approaches target the microbiome directly. Because of this, the idea of introducing probiotics into the diet of CD patients has recently emerged. Some probiotic strains can induce an immune response without causing additional host inflammation. Bacteria such as *Lactobacilli*-made *Bacteriocins* can make pores in the cell membranes of pathogens. This leads to cell lysis and improves the overall gut microbiome homeostasis [69].

The microbiome in the colon environment is involved in the metabolism of gluten and its peptides. The bacteria that may be involved in these processes include *Bifidobacterium spp*. and *Lactobacillispp*[70,71]. In 2016, Caminero et al. analyzed how core gut commensals and pathogens exhibit unique gluten breakdown patterns with different immunogenicity and can influence the risk of developing an autoimmune disorder. After partial digestion by human proteases, gliadin peptides can be detoxified by *Lactobacilli*. Proteases of *Pseudomonas aeruginosa* produce immunogenic peptides. *Lactobacilli* can also help in the degradation of these peptides. When this happens, the peptides become less immunogenic. These findings indicate that probiotics can potentially be used as an additional therapy for CD patients [44].

Many studies suggest that the diet of CD patients should be supplemented with *Bifidobacterium longum* and *Bifidobacterium breve*. These bacteria can modulate responses in the peripheral immune system. They can reduce the levels of TNF-alpha pro-inflammatory cytokines and increase the production of anti-inflammatory cytokines such as IL-10. Moreover, these bacteria can prevent inflammation of the intestinal mucosa. This is especially important for CD patients [72,73].

Conclusion

While CD symptoms should improve with a gluten-free diet, complications could worsen and become chronic and irreversible, significantly if treatment is delayed longer than is ideal. A stringent gluten-free diet that avoids any traces of gluten in food and other sources of contamination has been the most widely used treatment for CD up to this point. Numerous studies recommend adding *Bifidobacterium longum* and *Bifidobacterium breve* to the diets of people with CD. These microbes can alter how the peripheral immune system reacts. They can boost the production of anti-inflammatory cytokines like IL-10 and decrease the levels of pro-inflammatory cytokines like TNF-alpha.

Further in-depth clinical investigations should be carried out to ascertain whether at-risk people who develop the CD have changed duodenal microbial composition or function. The intricacy of separating the effects of genetics and environment influencing the microbiota is highlighted by the fact that diet and environment both affect the composition of the gut microbiota. To better understand the role of gene-microbe interactions in the development of CD, more extensive clinical trials are required where the microbiota's composition and function are examined in at-risk individuals throughout time. With more study into environmental factors, developing CD primary prevention strategies might be more straightforward.

References

1. Green PH, Cellier C. Celiac disease. N Engl J Med. 2007; 357: 1731-1743.

2. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the

United States: a large multicenter study. Arch Intern Med. 2003; 163: 286-292.

3. Biagi F, Klersy C, Balduzzi D, Corazza GR. Are we not over-estimating the prevalence of coeliac disease in the general population?. Ann Med. 2010; 42: 557-561.

4. Green PH, Stavropoulos SN, Panagi SG, Goldstein SL, McMahon DJ, et al. Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol. 2001; 96: 126-131.

5. Bai D, Brar P, Holleran S, Ramakrishnan R, Green PH. Effect of gender on the manifestations of celiac disease: evidence for greater malabsorption in men. Scand J Gastroenterol. 2005; 40: 183-187.

6. Dalgic B, Sari S, Basturk B, Ensari A, Egritas O, et al. Turkish Celiac Study Group. Prevalence of celiac disease in healthy Turkish school children. Am J Gastroenterol. 2011; 106: 1512-1517.

7. Alarida K, Harown J, Ahmaida A, Marinelli L, Venturini C, et al. Coeliac disease in Libyan children: a screening study based on the rapid determination of anti-transglutaminase antibodies. Dig Liver Dis. 2011; 43: 688-691.

8. King JA, Jeong J, Underwood FE, Quan J, Panaccione N, et al. Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. Am J Gastroenterol. 2020; 115: 507-525.

9. Kondrashova A, Mustalahti K, Kaukinen K, Viskari H, Volodicheva V, et al. Epivir Study Group. Lower economic status and inferior hygienic environment may protect against celiac disease. Ann Med. 2008; 40: 223-231.

10. Murray JA, Van Dyke C, Plevak MF, Dierkhising RA, Zinsmeister AR, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950-2001. Clin Gastroenterol Hepatol. 2003; 1: 19-27.

11. Lohi S, Mustalahti K, Kaukinen K, Laurila K, Collin P, et al. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther. 2007; 26: 1217-1225.

12. Cummins AG, Roberts-Thomson IC. Prevalence of celiac disease in the Asia-Pacific region. J Gastroenterol Hepatol. 2009; 24: 1347-1351.

13. Knip M, Honkanen J. Modulation of type 1 diabetes risk by the intestinal microbiome. Curr Diab Rep. 2017; 17: 1-8.

14. Kareva I. Metabolism and gut microbiota in cancer immunoediting, CD8/Treg ratios, immune cell homeostasis, and cancer (immuno) therapy: concise review. Stem Cells. 2019; 37: 1273-1280.

15. Maruvada P, Leone V, Kaplan LM, Chang EB. The human microbiome and obesity: moving beyond associations. Cell Host Microbe. 2017; 22: 589-599.

16. Akobeng AK, Singh P, Kumar M, Al Khodor S. Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications. Eur J Nutr. 2020; 59: 3369-3390.

17. Sollid LM. Molecular basis of celiac disease. Annu Rev Immunol. 2000; 18: 53-81.

18. Chibbar R, Dieleman LA. The gut microbiota in celiac disease and probiotics. Nutrients. 2019; 11: 2375.

19. Olivares M, Benítez-Páez A, de Palma G, Capilla A, Nova E, et al. Increased prevalence of pathogenic bacteria in the gut microbiota of infants at risk of developing celiac disease: The PROFICEL study. Gut Microbes. 2018; 9: 551-558.

20. D'Amico MA, Holmes J, Stavropoulos SN, Frederick M, Levy J, et al. Presentation of pediatric celiac disease in the United States: prominent effect of breastfeeding. Clin Pediatr (Phila). 2005; 44: 249-258.

21. Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, et al. The Oslo definitions for coeliac disease and related terms. Gut. 2013; 62: 43-52.

22. Johnson TC, Diamond B, Memeo L, Negulescu H, Hovhanissyan Z, et al. Relationship of HLA-DQ8 and severity of celiac disease: comparison of New York and Parisian cohorts. Clin Gastroenterol Hepatol. 2004; 2: 888-894.

23. Kivelä L, Kaukinen K, Lähdeaho ML, Huhtala H, Ashorn M, et al. Presentation of celiac disease in Finnish children is no longer changing: a 50-year perspective. J Pediatr. 2015; 167: 1109-1115.

24. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. Pediatrics. 2009; 124: 1572-1578.

25. Elli L, Bonura A, Garavaglia D, Rulli E, Floriani I, et al. Immunological comorbity in coeliac disease: associations, risk factors and clinical implications. J Clin Immunol. 2012; 32: 984-990.

26. Rajalahti T, Repo M, Kivelä L, Huhtala H, Mäki M, et al. Anemia in pediatric celiac disease: association with clinical and histological features and response to gluten-free diet. J Pediatr Gastroenterol Nutr. 2017; 64: e1-6.

27. Jericho H, Sansotta N, Guandalini S. Extraintestinal manifestations of celiac disease: effectiveness of the gluten-free diet. J Pediatr Gastroenterol Nutr. 2017; 65: 75-79.

28. Goh C, Banerjee K. Prevalence of coeliac disease in children and adolescents with type 1 diabetes mellitus in a clinic based population. Postgrad Med J. 2007; 83: 132-136.

29. Rampertab SD, Pooran N, Brar P, Singh P, Green PH. Trends in the presentation of celiac disease. Am J Med. 2006; 119: 355-e9.

30. Dickey W, Kearney N. Overweight in celiac disease: prevalence, clinical characteristics, and effect of a gluten-free diet. Am J Gastroenterol. 2006; 101: 2356-2359.

31. Shan L, Molberg Ø, Parrot I, Hausch F, Filiz F, et al. Structural basis for gluten intolerance in celiac sprue. Science. 2002; 297: 2275-2279.

32. Nilsen EM, Jahnsen FL, Lundin KE, Johansen FE, Fausa O, et al. Gluten induces an intestinal cytokine response strongly dominated by interferon gamma in patients with celiac disease. Gastroenterology. 1998; 115: 551-563.

33. Hüe S, Mention JJ, Monteiro RC, Zhang S, Cellier C, et al. A direct role for NKG2D/MICA interaction in villous atrophy during celiac disease. Immunity. 2004; 21: 367-377.

34. Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology. 1993; 105: 910-922.

35. Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. Clin Gastroenterol Hepatol. 2005; 3: 843-851.

36. Rintala A, Riikonen I, Toivonen A, Pietilä S, Munukka E, et al. Early fecal microbiota composition in children who later develop celiac disease and associated autoimmunity. Scand J Gastroenterol. 2018; 53: 403-409.

37. Carlsson A, Agardh D, Borulf S, Grodzinsky E, Axelsson I, et al. Prevalence of celiac disease: before and after a national change in feeding recommendations. Scand J Gastroenterol 2006; 41:

553-558

38. Stene LC, Honeyman MC, Hoffenberg EJ, Haas JE, Sokol RJ, et al. Rotavirus infection frequency and risk of celiac disease autoimmunity in early childhood: a longitudinal study. Am J Gastroenterol. 2006; 101: 2333-2340.

39. Forsberg G, Fahlgren A, Hörstedt P, Hammarström S, Hernell O, et al. Presence of bacteria and innate immunity of intestinal epithelium in childhood celiac disease. Am J Gastroenterol. 2004; 99: 894-904.

40. Ou G, Hedberg M, Hörstedt P, Baranov V, Forsberg G, et al. Proximal small intestinal microbiota and identification of rod-shaped bacteria associated with childhood celiac disease. Am J Gastroenterol. 2009; 104: 3058-3067.

41. Wacklin P, Laurikka P, Lindfors K, Collin P, Salmi T, et al. Altered duodenal microbiota composition in celiac disease patients suffering from persistent symptoms on a long-term gluten-free diet. Am J Gastroenterol. 2014; 109: 1933-1941.

42. D'argenio V, Casaburi G, Precone V, Pagliuca C, Colicchio R, et al. Metagenomics reveals dysbiosis and a potentially pathogenic N. flavescens strain in duodenum of adult celiac patients. Am J Gastroenterol. 2016; 111: 879.

43. Dore MP, Salis R, Loria MF, Villanacci V, Bassotti G, et al. Helicobacter pylori infection and occurrence of celiac disease in subjects HLA-DQ 2/DQ 8 positive: A prospective study. Helicobacter. 2018; 23: e12465.

44. Caminero A, Galipeau HJ, McCarville JL, Johnston CW, Bernier SP, et al. Duodenal bacteria from patients with celiac disease and healthy subjects distinctly affect gluten breakdown and immunogenicity. Gastroenterology. 2016; 151: 670-683.

45. Krishnareddy S. The microbiome in celiac disease. Gastroenterol Clin North Am. 2019; 48: 115-126.

46. Cenit MC, Olivares M, Codoñer-Franch P, Sanz Y. Intestinal microbiota and celiac disease: cause, consequence or co-evolution?. Nutrients. 2015; 7: 6900-6923.

47. Akobeng AK, Ramanan AV, Buchan I, Heller RF. Effect of breast feeding on risk of coeliac disease: a systematic review and meta-analysis of observational studies. Arch Dis Child. 2006; 91: 39-43.

48. Tap J, Mondot S, Levenez F, Pelletier E, Caron C, et al. Towards the human intestinal microbiota phylogenetic core. Environ Microbiol. 2009; 11: 2574-2584.

49. Collado MC, Donat E, Ribes-Koninckx C, CalabuigM, Sanz Y. Specific duodenal and faecal bacterial groups associated with paediatric coeliac disease. J Clin Pathol. 2009; 62: 264-269.

50. De Palma G, Nadal I, Medina M, Donat E, Ribes-Koninckx C, et al. Intestinal dysbiosis and reduced immunoglobulin-coated bacteria associated with coeliac disease in children. BMC Microbiol. 2010; 10: 1-7.

51. Nadal I, Donant E, Ribes-Koninckx C, Calabuig M, Sanz Y. Imbalance in the composition of the duodenal microbiota of children with coeliac disease. J Med Microbiol. 2007; 56: 1669-1674.

52. Olivares M, Neef A, Castillejo G, De Palma G, Varea V, et al. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut. 2015; 64: 406-417.

53. Vriezinga SL, Schweizer JJ, Koning F, Mearin ML. Coeliac disease and gluten-related disorders in childhood. Nat Rev Gastroenterol Hepatol. 2015; 12: 527-536.

54. Verdu EF, Galipeau HJ, Jabri B. Novel players in coeliac disease pathogenesis: role of the gut microbiota. Nat Rev Gastroenterol Hepatol. 2015; 12: 497-506.

55. Collado MC, Donat E, Ribes-Koninckx C, Calabuig M, Sanz Y. Imbalances in faecal and duodenal Bifidobacterium species composition in active and non-active coeliac disease. BMC Microbiol. 2008; 8: 1-9.

56. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. Biol Rev Camb Philos Soc. 2012; 87: 229-243.

57. Goedert JJ. Intestinal microbiota and health of adults who were born by cesarean delivery. JAMA Pediatr. 2016; 170: 1027.

58. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. J Nutr. 2008; 138: 1796S-800S.

59. Lotz M, Gütle D, Walther S, Ménard S, Bogdan C, et al. Postnatal acquisition of endotoxin tolerance in intestinal epithelial cells. J Exp Med. 2006; 203: 973-984.

60. Adlerberth I. Factors influencing the establishment of the intestinal microbiota in infancy. Nestle Nutr Workshop Ser Pediatr Program. 2008; 62: 13-33.

61. Chassin C, Kocur M, Pott J, Duerr CU, Gütle D, et al. miR-146a mediates protective innate immune tolerance in the neonate intestine. Cell Host Microbe. 2010; 8: 358-368.

62. Tita AT, Landon MB, Spong CY, Lai Y, Leveno KJ, et al. Timing of elective repeat cesarean delivery at term and neonatal outcomes. N Engl J Med. 2009; 360: 111-120.

63. Jakobsson HE, Abrahamsson TR, Jenmalm MC, Harris K, Quince C, et al. Decreased gut microbiota diversity, delayed Bacteroidetescolonisation and reduced Th1 responses in infants delivered by caesarean section. Gut. 2014; 63: 559-566.

64. Rutayisire E, Huang K, Liu Y, Tao F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. BMC Gastroenterol. 2016; 16: 1-2.

65. Hallert C, Grant C, Grehn S, Grännö C, Hultén S, et al. Evidence of poor vitamin status in coeliac patients on a gluten-free diet for 10 years. Aliment Pharmacol Ther. 2002; 16: 1333-1339.

66. Korponay-Szabó IR, Kovács JB, Lörincz M, Gorácz G, Szabados K, et al. Prospective significance of antiendomysium antibody positivity in subsequently verified celiac disease. J Pediatr Gastroenterol Nutr. 1997; 25: 56-63.

67. Ciacci C, Ciclitira P, Hadjivassiliou M, Kaukinen K, Ludvigsson JF, et al. The gluten-free diet and its current application in coeliac disease and dermatitis herpetiformis. United European Gastroenterol J. 2015; 3: 121-135.

68. Roncoroni L, Bascuñán KA, Doneda L, Scricciolo A, Lombardo V, et al. A low FODMAP gluten-free diet improves functional gastrointestinal disorders and overall mental health of celiac disease patients: A randomized controlled trial. Nutrients. 2018; 10: 1023.

69. Vanderpool C, Yan F, Polk BD. Mechanisms of probiotic action: implications for therapeutic applications in inflammatory bowel diseases. Inflamm Bowel Dis. 2008; 14: 1585-1596.

70. Caminero A, Herrán AR, Nistal E, Pérez-Andrés J, Vaquero L, et al. Diversity of the cultivable human gut microbiome involved in gluten metabolism: isolation of microorganisms with potential interest for coeliac disease. FEMS Microbiol Ecol. 2014; 88: 309-319.

71. Olivares M, Laparra M, Sanz Y. Influence of Bifidobacterium longum CECT 7347 and gliadin peptides on intestinal epithelial cell proteome. J Agric Food Chem. 2011; 59: 7666-7671.

72. Melchiorre MG, Chiatti C, Lamura G, Torres-Gonzales F, Stankunas M, et al. Social support, socio-economic status, health and abuse among older people in seven European countries. PloS one. 2013; 8: e54856.

73. Francavilla R, De Angelis M, Rizzello CG, Cavallo N, Dal Bello F, et al. Selected probiotic lactobacilli have the capacity to hydrolyze gluten peptides during simulated gastrointestinal digestion. Appl Environ Microbiol. 2017; 83: e00376-17.