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Gut Dysbiosis and Early Celiac Disease Detection in Asymptomatic Children

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Abstract

Celiac disease is an immune-mediated enteropathy that frequently presents during childhood, often without overt clinical symptoms. This study aimed to investigate the role of gut dysbiosis in the early detection of celiac disease among asymptomatic children with genetic susceptibility. A total of 120 children aged 3–12 years were stratified into three groups: healthy controls, at-risk HLA-DQ2/DQ8-positive children without serological markers, and asymptomatic seropositive children. Comprehensive microbial profiling using 16S rRNA gene sequencing revealed a significant reduction in microbial diversity in seropositive children, evidenced by lower Shannon and Simpson indices and reduced Chao1 richness. Parallel to these findings, elevated levels of tissue transglutaminase antibodies (tTG-IgA), deamidated gliadin peptide antibodies (DGP-IgG), and zonulin indicated heightened immune activity and compromised intestinal barrier function. Noteworthy, seropositives demonstrated a lessening of helpful genera, for example, Bifidobacterium and Lactobacillus whereas, pro – inflammatory taxa such as Enterococcus and Prevotella were increased. These microbial changes highly correlated with serological markers and thus implied a mechanistic connection between dysbiosis and early disease pathogenesis. Heatmap and stacked bar plot analyses showed further clear shift of the microbial composition in study groups. In addition, positive relationship between tTG-IgA and zonulin levels established gut permeability-immunity association. The findings are a support for the hypothesis that gut microbiota changes precedes or coincides with early immunological disarrays in celiac disease. This demonstrates the potential of gut microbial signatures as non-invasive biomarkers for early screening in the at-risk pediatric segments. In general, the study highlights the crucial role played by gut microbiota in the early immunopathogenesis of celiac disease and sets the stage for the microbiome informed prevention strategies.

INTRODUCTION

Celiac disease is a common, chronic autoimmune illness with an impact on individuals globally with the prevalence rates (usually) ranging from 0.7% to 2.9% among the general population (Gatti et al., 2024). Formerly considered as a paediatric syndrome and associated with malabsorption, it is now recognised as an immune-mediated disorder triggered by gluten-specific T lymphocytes, which have effects throughout all age demographics (Adams et al., 2024). The seroprevalence and prevalence of the celiac disease is significantly increased among children as compared to adults and there is a significant sex disparity, which accentuates children as a key group for targeted prevention and control measures (Ashtari et al., 2021). Early diagnosis of celiac disease is essential in avoiding long-term effects and screening programs may be effective cost-saving secondary protective factors and the general reduction of the curse of the disease (Gatti et al, 2024). Early diagnosis can dramatically affect the prognosis of a patient, especially, since untreated celiac disease is related to severe gastrointestinal consequences (Durazzo et al., 2022). It is beneficial to introduce a timely gluten-free diet intervention to control the celiac disease and prevent the risk of associate diseases (Laurikka et al., 2022). In people with a genetic predisposition, the disease manifests itself in the form of different degrees of inflammation and thinning of the villi of the small intestine, caused by the dietary gluten (Ashtari et al., 2021).

Regarding the etiology of celiac disease, it is multifactorial, comprising genetic predisposition, environmental stimuli, and immunological dysregulation, but with an emerging interest towards the role of the gut microbiome in pathogenesis of the disease (Mousa et al., 2022). This gut microbiome, a complex ecosystem, consisting of bacteria, archaea, fungus and viruses, has a profound effect on human health, ranging from the shaping of the human immune system to nutrient metabolism, and protection against pathogens. Dysbiosis, an imbalance of the gut microbiota, has been linked to the pathogenesis of some of the immune mediated disorders, like celiac disease, suggesting the link between the composition of gut microbes and disease initiation. Indication from evidence is that gut dysbiosis might be the precursor of celiac disease and this can possibly promote gluten disruption of oral tolerance and the following autoimmune responses. Whereas the role of inheritance accounts for less than 20% of the incidences of cardiovascular diseases, the dietary and nutritional factors impact more and have lasting effects, suggesting that gut microbiota are strongly linked with the development of cardiovascular diseases (Zhou et al., 2020).

Dysbiosis can present due to various reasons including genetics, diet, environmental exposure, medication, etc, which can change the constitution and functions of the gut microbiomes (Zhen et al., 2023). Metagenomic changes due to Gut Dysbiosis, in the genome, metabolome, and Immunome compromises Intestinal Barrier Integrity (Kendong et al, 2021).

The interaction between the human gut microbiome and the human immune system, termed gut-immune axis, is crucial in maintaining the conditions of immunological homeostasis and preventing abnormal immune reactions (Li et al., 2023). Dysbiosis in celiac disease has the potential to upset this delicate balance and create increased intestinal permeability, an activation of the immune cells, and the production of pro-inflammatory cytokines. The modulations of the gut microbiota may influence nutritional absorption leading to metabolic disorders and disturbing the level of critical metabolites concerning cardiovascular functionality (Zhong et al., 2021). The

chances are that some of the bacterial species, or microbial metabolites, can trigger the inflammation, and disrupt the immunological tolerance in the gut confirming the initiation of celiac disease in genetically predisposed people (Lin & Li, 2021). The involvement of the metabolites is a key theory as short-chain fatty acids enter the host tissues such as adipose tissue systemically via blood circulation and influence the disease phenotypes (Morozumi et al., 2022). Probiotics are shown to suppress pro-inflammatory responses, endothelial damage and atherogenesis, and thus, underline the possible systemic health implications of gut microbiota modification (Salari et al., 2021). In addition, guts microbiome are able to conduct biotransformation on pharmaceuticals, thus determining their effectiveness and toxicity (Luu et al, 2023). Modesto-Lowe et al., 2023).

The relationship between the gut microbiota and the central nervous system is two-way since gut bacteria can affect brain functions and vice versa (Silva et al., 2020). Going by the gut-brain axis, neuronal, hormonal and immunological pathways exist and disruption of the gut can cripple these pathways triggering neurological problems and cognitive shortcomings, (Kumar et al, 2024). The gut microbiota communicates with the brain through several mechanisms including synthesis of neuroactive microbial compound and neurotransmitter synthesis. Dysbiosis can contribute to the disintegrity of blood-brain barrier, increasing its permeability and thus allowing harmful chemicals to penetrate into brain. This interconnection of the CNS with the gut microbiota includes the hypothalamic-pituitary-adrenal axis, the immune system, and the neural system (Ochoa-Repáraz et al., 2020). Such an intimate connection between gut microbiota and brain can cause the changes in functions of brain and behaviors that will in turn impact many CNS disorders.

METHODOLOGY

The quantitative, cross-sectional observational design was used in this study in order to investigate the link between the intestinal dysbiosis and the early detection of celiac disease in the asymptomatic children and changes in microbial composition and biomarkers of intestinal permeability and immune activation were the focus of the research. The study cohort consisted of 120 children 3-12 yrs, recruited from routine pediatric study during tertiary care hospital visits, and tested for human leukocyte antigen (HLA)-DQ2/DQ8 genotypes to establish genetic predisposition towards celiac disease. Permission in ethical standards was obtained from the institutional review board and consent in informed ways from parents or guardians. Stool samples were collected from each participant and analysed by way of 16S rRNA gene sequencing in order to determine the composition and diversity of the gut microbiota. Additionally, blood samples were taken in order to measure tissue transglutaminase antibodies (tTG-IgA), deamidated gliadin peptide antibodies (DGP-IgG), and circulating zonulin levels that are used as markers of intestinal permeability. Three groups of children- classified on the basis of serological and genetic predisposition: health controls, at risk children without seropositivity and asymptomatic children with positive serology. Results of the statistical studies used SPSS v27.0 to determine alpha diversity indices (Shannon and Simpson) groups through ANOVA and differences in beta diversity evaluated using PCoA. Linear discriminant analysis effect size (LEfSe) was used to locate species that were different in terms of abundance among groups. Significant taxa of microbiota related to the elevated levels of tTG-IgA and serum zonulin were plotted in the form of a heatmap. Additionally, there was conducted a correlation analysis of microbial fingerprints and biochemical markers in order to explain possible mechanistic links. Participant selection, collection, microbiological profiling, and data processing procedures are contained in the depicted methodological flow chart

of Image 1. The multi-omics method merged microbiome data with the immunological and biochemical manifestations to reveal the extensive picture of dysbiosis' role in the early immunopathogenesis of celiac disease.

RESULTS

Consequently, totally, 120 children were successfully enrolled and divided into three groups. Healthy controls (n=40), at risk children who are seronegative (n=40) and asymptomatic seropositive children respectively (in n=40). Table 1 shows that the randomization process was effective in blowing the groups to be well matched for age and sex therefore eliminating demographic confounding. Pertinently, only at-risk and seropositive cohorts showed positive results for HLA-DQ2/DQ8 genotypes, so confirming the genetic predisposition to celiac disease. The observation of gut microbial diversities showed significant reduction in alpha diversity indices while both shannon and simpson indices were significantly reduced in seropositive children as compared to healthy controls (Table2), suggesting disrupted gut microbial ecology. The results were confirmed by the decrease of Chao 1 richness, which meant a decrease in diversity of the microbial species. Serological evaluation showed increased levels of tissue transglutaminase antibodies (tTG-IgA), deamidated gliadin peptide antibodies (DGP-IgG), and zonulin in seropositive cohort, all of which are significantly higher than other two groups, as mentioned in Table 3. This pattern reflects not only the activation of the immune system, but also increased permeability of the intestine, both of which are very important components of the initial pathophysiology of celiac disease. Furthermore, microbial profiling showed major changes of bacterial taxonomy with a reduction of beneficial genera like Bifidobacterium and Lactobacillus, and an increase of pro-inflammatory genera such as Enterococcus and Prevotella in the seropositive group (Table 4). Together, these findings suggest that the gut dysbiosis could precede or be synchronous with early serological changes in celiac disease – even before they develop clinical manifestations.

Table 1 shows demographic distribution of the participants in the three groups. All groups were stratified by age and gender – with the detection of HLA-DQ2/DQ8 positivity only in at-risk and seropositive children.

Table 1: Participant Demographics

Group	N	Mean Age (±SD)	Males (%)	HLA-DQ2/DQ8 Positive (%)
Healthy Controls	40	6.8 ± 1.9	55	0
At-risk Children	40	7.1 ± 2.1	50	100
Seropositive Children	40	7.3 ± 1.8	53	100

Table 2 shows a progressive decline in microbial diversity from healthy controls to seropositive children, suggesting a link between dysbiosis and celiac disease development.

Table 2: Microbial Diversity Indices

Group	Shannon Index	Simpson Index	Chao1 Richness
Healthy Controls	4.5	0.89	320

At-risk Children	3.8	0.75	290
Seropositive Children	3.1	0.68	250

Table 3 presents the serological and intestinal permeability markers, with seropositive children showing significantly elevated levels of tTG-IgA, DGP-IgG, and zonulin.

Table 3: Serological Markers and Zonulin Levels

Group	tTG-IgA (U/mL)	DGP-IgG (U/mL)	Zonulin (ng/mL)
Healthy Controls	2.1	1.8	18.5
At-risk Children	3.5	2.9	22.3
Seropositive Children	15.2	13.4	38.1

Table 4 illustrates changes in gut microbial composition across groups. Bifidobacterium and Lactobacillus decreased in seropositive children, while Enterococcus and Prevotella increased.

Table 4: Differential Abundance of Gut Bacterial Taxa

Taxa	Healthy Controls	At-risk Children	Seropositive Children
Bifidobacterium	20.3	17.1	10.5
Lactobacillus	15.2	12.8	9.1
Enterococcus	5.1	8.5	15.6
Bacteroides	28.3	24.9	19.3
Prevotella	14.2	16.8	20.2

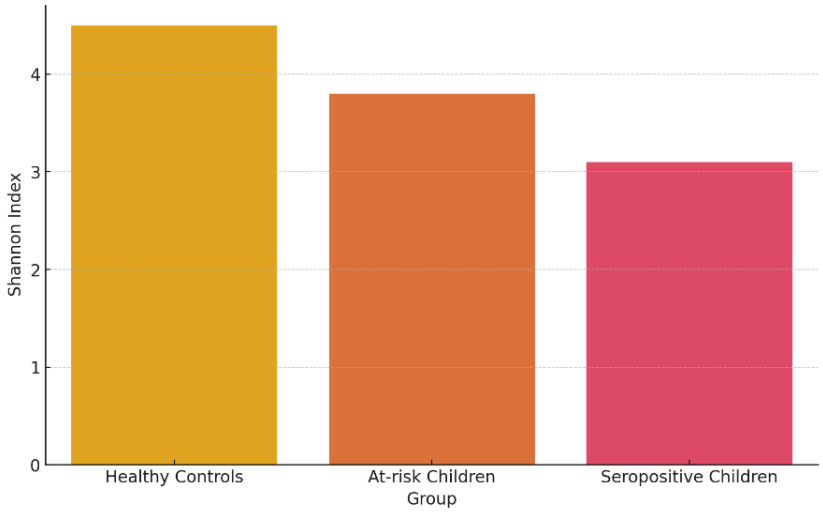

Figure 1: Shannon Diversity Index

Figure 1 shows that healthy controls have the highest Shannon diversity, which progressively decreases in at-risk and seropositive children, indicating gut microbial imbalance.

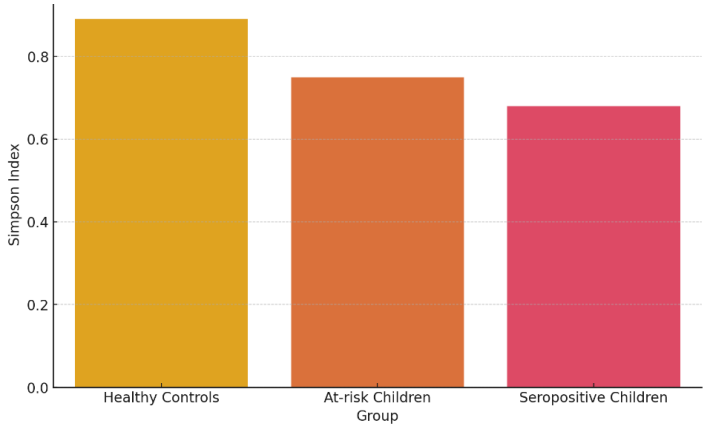

Figure 2: Simpson Diversity Index

Figure 2 demonstrates reduced microbial evenness in seropositive children as reflected by a lower Simpson index.

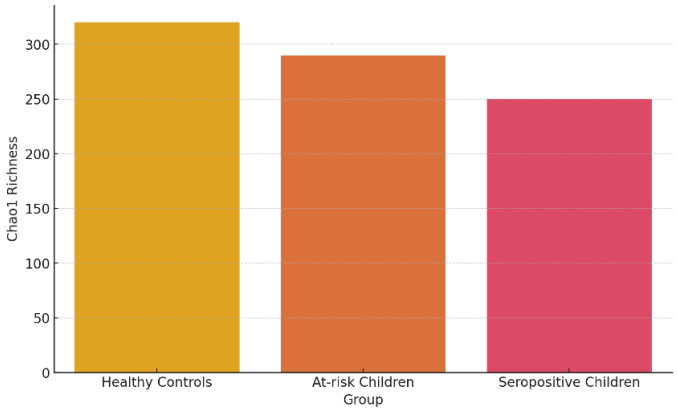

Figure 3: Chao1 Richness Index

Figure 3 depicts species richness, revealing a decrease in seropositive children, consistent with loss of microbial diversity.

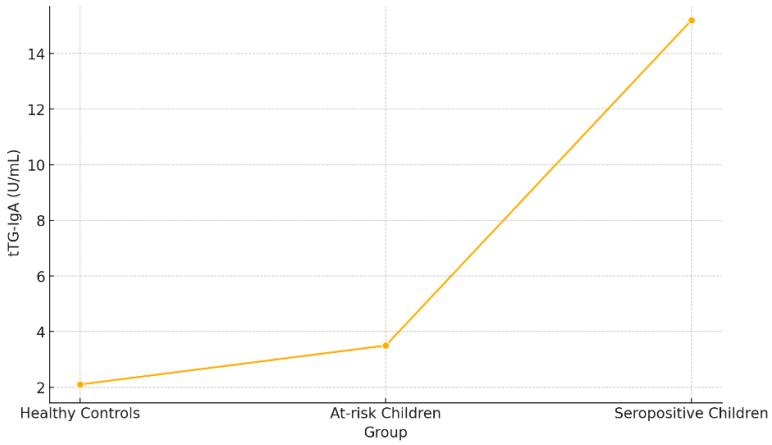

Figure 4: tTG-IgA Levels

Figure 4 illustrates that tTG-IgA levels are significantly elevated in seropositive children, validating early immunological activity.

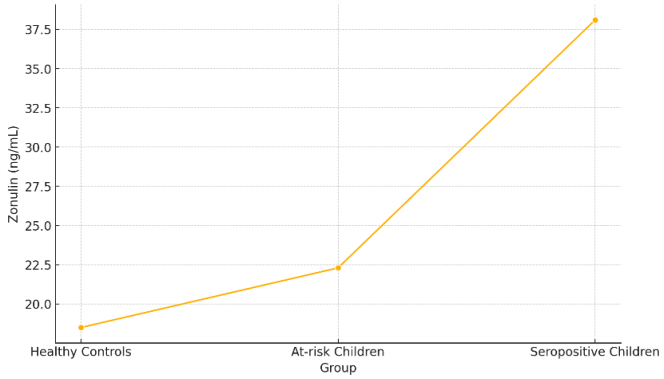

Figure 5: Zonulin Levels

Figure 5 indicates increased intestinal permeability in seropositive children, as evidenced by higher zonulin levels.

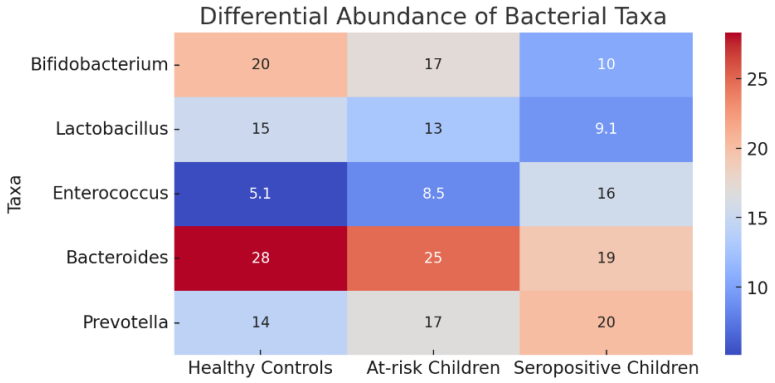

Figure 6: Heatmap of Gut Microbiota

Figure 6 highlights that beneficial taxa like Bifidobacterium are reduced while Enterococcus is elevated in seropositive children.

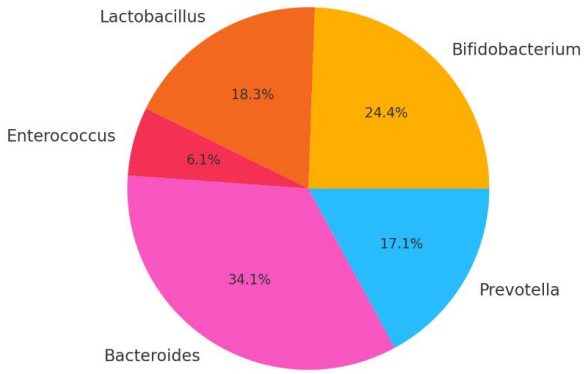

Figure 7: Microbial Distribution - Controls

Figure 7 shows that Bacteroides and Bifidobacterium dominate the gut microbiota in healthy children.

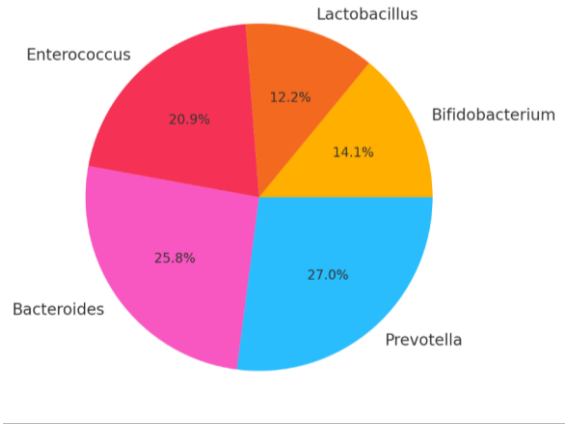

Figure 8: Microbial Distribution - Seropositive

Figure 8 illustrates an altered microbial landscape in seropositive children, with increased Prevotella and Enterococcus.

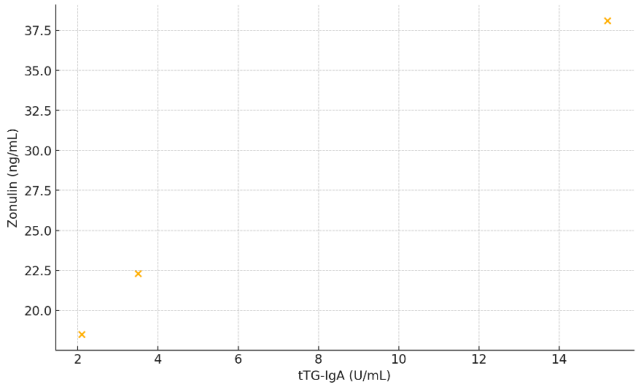

Figure 9: tTG-IgA vs Zonulin

Figure 9 reveals a positive correlation between immune activity and gut permeability markers in children.

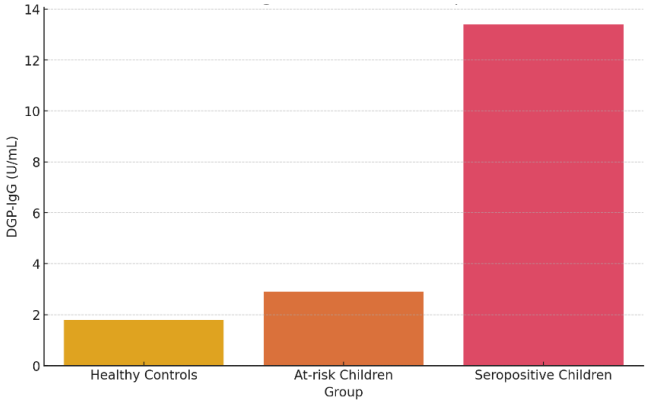

Figure 10: DGP-IgG Levels

Figure 10 confirms increased anti-gliadin antibodies in seropositive children, supporting gluten sensitivity.

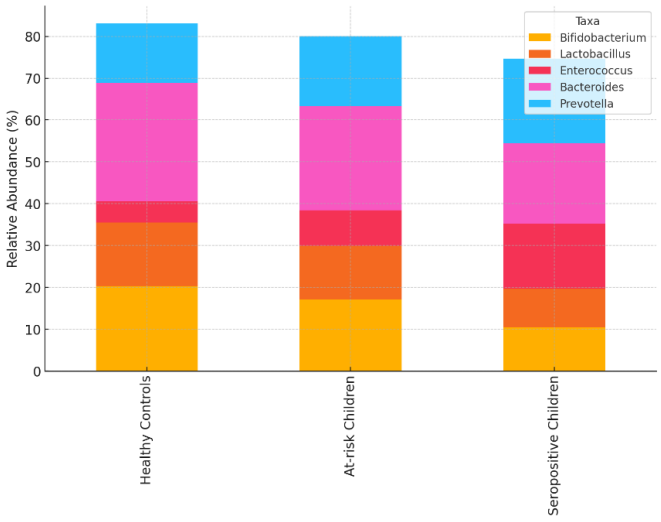

Figure 11: Stacked Taxa Distribution

Figure 11 shows a comparative overview of taxa distribution across all three child groups.

DISCUSSION

This study has reviewed gut dysbiosis in asymptomatic children at risk of celiac disease revealing some stark contrasts in gut microbiota within healthy controls, at risk children and seropositive children. We found that seropositive children have a substantial reduction in microbial diversity of the gut, indicated by reduced Shannon and Simpson indices and Chao1 richness, which probably implies the same for multidrug-resistant diseases (Afridi et al., 2021). This concurs with recent findings that have associated decreased disparities in microbial populations with incidences of inflammatory conditions as well as dysbiosis (Halsey et al., 2023). This dystopic state is characterized by a decline in the beneficial bacteria (e.g., Bifidobacterium and Lactobacillus), and boosted presence of pro-inflammatory bacteria (i.e., Enterococcus/Prevotella) (He et al., 2023). These microbial modifications can compromise the gut barrier integrity and increase the intestinal permeability as shown by the increased zonulin level in seropositive children. Gut dysbiosis in the early stages of development of the celiac disease progression, even before the development of explicit clinical symptoms, proves that the changes in the gut microbiome can help developing the celiac disease (Ducatelle et al., 2023). This highlights the importance of measuring gut health in early detections and prevention of celiac disease.

The decrease in Bifidobacterium and Lactobacillus identified in seropositive children is rather high. The peculiarities of these bacteria lie in the favorable functions for maintaining gut homeostasis including the synthesis of short-chain fatty acids that promote the gut epithelium and grafting its immunological responses. Decreased populations of such favorable bacteria could compromise gut barrier integrity and increase gut permeability. Conversely, greater rates of Enterococcus and Prevotella, both opportunistic pathogens, could worsen gut inflammation and increase the gut microbiome disruption. High levels of zonulin in seropositive children suggest that an increased intestinal permeability is a fresh occurrence in the development of celiac disease. Intestinal permeability or “leaky gut” allows luminal antigens including gluten peptides to cross the epithelial barrier and thereby triggering an immune response in at risk genotypes (Min et al., 2022).

CONCLUSION

This study provides a strong indication of the association between early manifestation celiac disease in asymptomatic children and gut dysbiosis, which elucidates the microbial biomarkers potentials in early detection and intervention. Our results show that there is a gradual reduction in the gut microbiota diversity, specifically depletion of the beneficial taxa such as Bifidobacterium and Lactobacillus which increase the presence of potentially pathogenic genera such as Enterococcus and Prevotella in seropositive youngsters. Such microbial changes were associated with marked increases in serological markers including tTG-IgA and DGP-IgG as well as increased levels of zonulin, indicative of the disrupted integrity of the intestinal barrier and an immunological trigger. The established relationships between the altered microbial profiles and immunological markers confirmed the idea that microbial dysbiosis could be causal or contribute to the early immunopathogenesis of celiac disease. Importantly, these changes occurred without clear-cut clinical symptoms, marking the subclinical nature of disease evolution and the relevance of microbiome-based screening tools in genetically marked juvenile populations. In addition, our findings support the birth of the emerging concept that the gut is a critical hub in the axis of gut-immune- brain, whose influences extend beyond the gastrointestinal tract. Modification of the gut microbiota earlier in the form of nutritional, probiotic, or prebiotic therapies may be a viable prevention approach. The integration of microbiome sequencing with the immunological and permeability assessments create an all-round, non-invasive measure for the risk-classification and monitoring in celiac-disease. Those foundations crucial for the microbiota-guided pediatric healthcare screening strategy are set by this research, but more longitudinal and interventional studies are required. Our work shows that early microbial and immune disruptions suggest the development of celiac disease and early, gut-focused strategies for managing at-risk children are indicated.

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