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REVIEW ARTICLE

Does Gut Microbiota Modulation Offer a Pathway to Manage Celiac Disease?

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ABSTRACT: Celiac disease is a significant life-long health condition with an estimated prevalence of 0.5 to 1 percent globally. Celiac disease is caused by an autoimmune abnormal response of the body to ingestion of gluten. Individuals experiencing Celiac Disease experience varying degrees of quality of life depending on their circumstances. Strict dietary restrictions and/or regular use of probiotics can be challenging due to issues in availability and cost. The main treatment strategy for Celiac Disease is a gluten-free diet which has limited compliance. Several proxy strategies have been tested over the years including prebiotics, probiotics, and post-biotics providing various types of alterations in gut microbiome designed to modulate the autoimmune response to gluten and its components. The current paper focuses on the therapeutic manipulation of gut microbiome to facilitate the management of Celiac Disease. It also discusses the known mechanisms by which gut microbiota influence various other body systems and the factors that influence these complex interactions. The limitations of the papers reviewed have consistently shown the need for further research to fully elucidate the molecular underpinning and understanding of the long-term impact of the use of probiotics and intestinal microbes on the human body.

KEYWORDS: Celiac Disease, Gut Microbiota, Probiotics, Autoimmune Disorders.

Introduction

Celiac disease (CD) is not a life-threatening autoimmune disorder, but it affects the quality of life of affected individuals as it requires considerable lifelong changes in daily diet. It has an estimated global prevalence of about 1%.[1] The intake of gluten (a protein found in commonly used grains such as wheat, barley, and rye) triggers CD.[2] Ingesting gluten in people having CD causes severe damage to enterocytes in the small intestine and leads to villi atrophy.[3] If left completely untreated, patients with CD often experience total villous atrophy with flat mucosa in the small intestine.[4] Villous atrophy has severe effects such as the risk of lymphoproliferative disorders.[5] It also causes malabsorption of nutrients from the small intestine leading to malnutrition disorders such as anemia.[6,7] Due to this mucosal damage caused by undiagnosed/ untreated CD, the most common treatment is a lifelong gluten-free diet. However, such changes do not always lead to complete relief from gastric symptoms as CD causes irreversible damage to the small intestine.[8] When fully developed clinically, the typical features of the small intestine are chronic inflammation and villi atrophy.[9] Figure 1 below shows normal villi compared with the villi in CD.

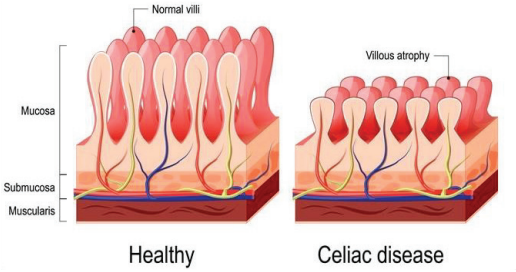

Figure 1: Villous Atrophy in Celiac Disease. (Image Credit: Shutterstock standard license)

Epidemiological data over the last decade suggests that gluten intolerance may occur at the time of its introduction into the diet or at a later time point and manifests itself through various intestinal and extra-intestinal symptoms.[10,11] Moreover, certain environmental factors that influence the composition of the human gut microbiota, such as gestational age at birth, type of delivery, intestinal infections in infancy and early childhood, and antibiotic exposure, have also been associated with the risk of developing CD.[12,13] Gut microbiota plays a significant role in mediating immune function by maintaining epithelial integrity.[14] Clinical research data appear to suggest a link between chronic inflammatory diseases and the gut microbiome composition and function. Given the villous atrophy in CD, the link may hold for this condition as well.[15]

This review paper aims to explore the hypothesis that manipulation of the intestinal microbiota may have the potential to treat CD. In addition, this paper reviews current clinical research on alteration to gut microbiota to treat and/or manage the symptoms of other gastrointestinal disorders, such as irritable bowel syndrome and some forms of colorectal cancer.

Review Methodology

The focus of this paper lent itself to the search of one major database, PubMed. The major component of this database is often referred to as MEDLINE, which is the biomedical database provided and managed by the National Library of Medicine (NLM) in the United States. The database Medline was searched twice first by using Medical Subject Headings (MeSH) terms to identify key publications; and secondly by using the Title/Abstract Screening method. These searches yielded forty publications for the period between 2010 - 2024.

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Additional filters were applied that limited the literature search to only publications in the English language, and a cut-off of 2010. The use of English language search was to enable the author to read and fully understand the major findings without having to use the somewhat imprecise Google Translate platform. The search was limited to publications since 2010 to use more recent evidence. Furthermore, a preliminary search indicated clustering of research outputs from 2015 onwards. The extension to 2010 was to ensure no major output between 2010 and 2014 was missed.

Results

Gut Microbiota Modulation: A recent narrative review by Saviano *et al.*[8] published in 2023 discusses the major role that the intestinal microbes play in the pathogenesis of CD. Several factors are implicated in modulating gut microbiota in CD including diet, prebiotics, probiotics, and postbiotics. It is clear from this review and previous works, that a balanced bacterial population in the gut can be very beneficial in ameliorating the symptoms and supporting the management of CD. Additionally, the review outlines the role of ingestible enzymes which have been identified recently. These enzymes can help in digesting a major proportion (up to 97 percent) of gluten and its components such as gliadin (a sub-component protein peptide of gluten). These enzymes can be taken with gluten-containing foods. However, it must be understood that at this point, the use of enzymes cannot be taken as a gold-standard management guideline for CD. This is because these interventions are still not sufficient to replace a Gluten Free Diet which is the predominantly prevalent management of CD. It is not entirely understood yet how the molecular interaction between the intestinal bacteria and the immune system response to gluten exactly takes place. Therefore, this is an area for future molecular and immune research.

An important study in this regard was undertaken by Afzaal *et al.*[10] which reviewed the evidence regarding the role of human gut microbiota in influencing the immunological, neural, hormonal, and endocrine systems of the human body. It was found that the microbes also act as a defense against invasion of pathogenic bacteria. This disturbance of healthy symbiosis between non-pathogenic and pathogenic bacteria can lead to diseases such as inflammatory bowel disease, anxiety, depression obesity, diabetes, and cancer. However, the review could not find sufficient evidence base to clearly explain how the microbial system influences the development of these chronic diseases and the responsible signaling mechanisms involved in these complex interactions. Therefore, the authors recommend further research to investigate the basis of these novel influences on remote body systems by the gut microbiota.

Role of Probiotics: Evidence for the efficacy of probiotics in the management of CD comes from a quasi-randomized controlled trial to evaluate the efficacy of probiotics as an additional treatment for celiac disease, i.e., in addition to a gluten-free diet.[9] The sample population of 170 patients, was divided equally into the intervention group which was given a gluten-free diet and probiotics, and a comparison group, which received only a gluten-free diet but no probiotics. The results of the study showed a statistically significant difference in the reduction of gastrointestinal irritation in the intervention group (i.e., those who received probiotics) manifested by lower stool frequency compared to the comparison group. The study authors conclude that probiotics are highly effective in modulating the symptoms and improving the quality of life in children with CD.

Similarly, another narrative review by Pecora *et al.*[11] published in 2020 covers studies published over a 10-year period from 2009-2019, which looked at the role of probiotics in preventing and treating CD. The findings indicate that there is promising data that shows a positive role of probiotics in the treatment of CD; but that there is a lack of robust evidence on the role of probiotics in 'preventing the onset of CD.' The main role of probiotics was to ameliorate the symptoms of CD, in conjunction with a gluten-free diet. Further research including more human trials on this subject is required to establish the type and duration of probiotics to be used for CD.

To conclude the key results, it is important to circumscribe the findings on the role of probiotics in modulating the gut microbiota in the management of CD. This is because most of the available evidence pertains to this aspect of CD rather than its prevention or elimination. The paper by Chibar & Dieleman[12] demonstrates how gut microbiota can cause intestinal inflammation in several chronic diseases. Compared to healthy individuals, intestinal dysbiosis has been reported in patients diagnosed with CD – even among those who are on a gluten-free diet. The authors identify several studies that show differential bacterial population proportions in patients with CD compared to healthy (non-CD) subjects. However, it is still not clear if the imbalance of microbial species due to the loss of diversity of certain microbiomes is the cause or effect of CD. In this context, using probiotics remains the preferred strategy to modulate the gut microbiome to mitigate the anti-inflammatory reaction in CD. Nonetheless, as indicated earlier, this does not obviate the need for further longitudinal studies to support their use in the treatment of CD. More research is needed with therapeutic microbial formulations on the use of probiotics to restore the gut microbiome to an anti-inflammatory state. It also needs to be investigated if this can lead to a longer-term cure strategy to drastically reduce the symptoms of CD and restore the quality of life.

Though the relationship between alterations in gut microbiota and symptoms of CD is not fully understood, there are several hypotheses trying to explain the link. Infections, types of foods and prevailing dietary patterns, use of antibiotics, etc., and the link between genetic susceptibility to CD and the role of environmental factors in making the symptomatology become apparent earlier and their role in aggravating CD. Regarding the latter, its role in the alteration of the gut microbiota by enhancing the production of inflammatory responses by activating an immune response through immunogenic gluten peptides; epitopes that mimic gliadin; the stimulation of proinflammatory immune systems that release damaging cytokines for gut barrier integrity, and contribution to pathogenesis and active phase of CD is an area of ongoing

research.[16,17] At present, rebalancing of intestinal microbiota through using probiotics is considered to be the only viable strategy in the treatment of CD in addition to the elimination of dietary gluten.[8,12]

The main mechanism through which probiotics appear to improve the intestinal microbiota is through the production of short-chain fatty acids such as butyrate that can help in reducing inflammation in the colonic gut through their action on colonic epithelia.[18] Clinical data has established a potential role for probiotics in modulating the gut microbiota that in turn is instrumental in managing the immune response in patients with CD.[19] Analysing the benefits from use of probiotics to explore if these can potentially translate into finding a cure for CD remains an area of considerable interest for international research. Exploring this potential therapeutic role may also involve the development of probiotic supplements that provide superior mitigation or even elimination of symptoms caused by gluten ingestion thus making a significant contribution to improving the quality of life for celiac disease patients.

Discussion

The development of CD in an individual appears to be due to a combination of several genetic and environmental factors. Ingestion of gluten by individuals who may be genetically predisposed can trigger an autoimmune response that can cause inflammation in the gut.[17] The gut microbiome is a group of bacteria and other microorganisms in our digestive system, that affects our health directly as well as by influencing the diet we take.[20] Human gastrointestinal tracts consist of 100 trillion microorganisms, the majority of which are bacteria but also include fungi, viruses, and protozoa.[21] A substantial body of research exists that documents the links between microbiome composition and various diseases such as irritable bowel syndrome, inflammatory bowel disease, and broader systemic conditions such as obesity, type 2 diabetes, and allergies.[21,22]

It is well established that gut microbiota plays a role in intestinal immune response and maintenance of intestinal homeostasis.[23] Clinical studies have shown altered gut microbiota composition or function in celiac disease patients compared to healthy controls but it could be different in various immune-related disorders.[24, 25] For example, the microbiota in patients of CD is different than in patients with dermatitis herpetiformis, which is suggestive that the microbiota has a role in disease manifestation.[26] Gut microbiota composition is shaped very early in life and can be influenced by not only gestational age but also the type of delivery, method of milk feeding, the type of diet and lifestyle as well as other factors.[27] It is reasonable to assume that changing the composition of gut microbiota could potentially alter the intestinal barrier and increase epithelial permeability.[28]

Probiotics are living bacteria that provide a health benefit when administered orally, by interacting with the host gut environment.[29,30] Whilst the focus of this paper has been primarily on CD, it has also been shown that similar pathophysiological mechanisms could be associated with other gut disorders such as irritable bowel syndrome with underlying inflammatory pathology) to more serious chronic health conditions such as type 2 diabetes [30], autoimmune disorders such as multiple sclerosis[32] and cancers.[33] Table 1 below shows the most studied probiotics.

Table 1: Most Studied and Recommended Probiotics.

The Lactobacillus genus	The Bifidobacterium genus
• L. acidophilus • L. rhamnosus • L. casei • L. plantarum	• Bifidobacterium longum • Bifidobacterium breve
Foods naturally containing less concentrated quantities of Probiotics. • Yogurt and kefir • Cottage cheese • Miso soup • Kombucha • Sauerkraut or kimchi • Pickles and pickle juice	

https://my.clevelandclinic.org/health/treatments/14598-probiotics; last accessed on January 10, 2025

There is also limited evidence to suggest the role of fecal microbiota transplantation (FMT) which transplants feces from a healthy donor to a patient of CD to restore gut microbiota. However, more case reports are needed to fully evaluate the potential of this therapy. [34]

From a healthy lifestyle perspective, adding foods in your diet that naturally contain probiotics is recommended for improved gut health and very likely to reduce inflammatory symptoms. The Figure 2 below highlights some common benefits of probiotics on health.[35] Parents can encourage use of these foods from an early age to promote healthy eating habits in children.

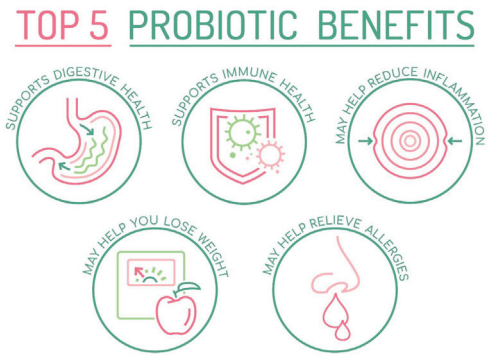

Figure 2: Health Benefits of Probiotics. (Image Credit: Shutterstock standard license)

Conclusion

This review paper summarizes the previously existing evidence found in the literature supporting the hypothesis that alterations in gut microbiota through the use of probiotics could potentially lead to finding better therapeutic options for the management of Celiac Disease. In addition, the role of probiotics and gut eubiosis (well-balanced gut flora) in

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preventing many diseases carrying a high morbidity and mortality burden such as obesity, Type 2 Diabetes, hypertension, autoimmune disorders, and cancers is outlined. It appears justifiable to recommend the use of probiotics as part of a balanced diet, especially for patients of CD, as the evidence clearly shows its positive effect on gut health as well as anti-inflammatory benefits. The limitations of the papers reviewed have consistently shown the need for further research to fully elucidate the molecular underpinning and understanding of the long-term impact of the use of probiotics and intestinal microbiome on the human body. These molecular pathways are recommended as an important area of research focus for future clinical research studies The link between molecular changes and environmental factors (epigenetics) requires investment in longitudinal studies that start either *in utero* or very early in life as the current evidence shows that gestational age at birth, mode of delivery, type of milk feeding, and many similar factors are also implicated in the development of CD.

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