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Review

The Combined Effect of Infant and Mother Secretor Status on Infant Susceptibility to Viral Gastroenteritis and Celiac Disease

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Abstract

Celiac disease is a prevalent autoimmune disorder with a rising incidence of 7.5% annually during the second half of the 20th century and the 21st century. Not all genetically susceptible individuals that carry the risk alleles HLA DQ2 and DQ8 go on to develop celiac disease, suggesting that there may be other environmental triggers that contribute to the development of celiac disease in genetically susceptible individuals. Gastroenteritis during infancy has been shown to be associated with increased risk of celiac disease. Secretor status, per the FUT2 genotype, and subsequent alterations in the microbiota, is associated with risk of gastroenteritis in infants. This review investigates the literature from January 2010 to June 2022 to determine the combined effect of secretor status and viral gastroenteritis on the development of celiac disease. Mothers with the secretor phenotype and infants with the non-secretor phenotype provided the most protection against particular strains of gastroenteritis and celiac disease. Both the maternal and infant secretor status, as well as the infant's Lewis status and ABO blood group can influence the infant's susceptibility to different viral strains, which cause gastroenteritis. Gastroenteritis caused by viral infections can

damage intestinal epithelial cells, cause dysbiosis, and affect pro-inflammatory cytokines, which exacerbate celiac disease onset. Understanding the effect of secretor status and gastroenteritis on celiac disease may provide a novel approach to early screening and preventative strategies to reduce risk factors that contribute to the onset of celiac disease.

Keywords
Celiac disease; gastroenteritis; FUT2; secretor status; infant; mother; breastmilk; norovirus; rotavirus; microbiota

1. Introduction

Celiac disease (CeD) is a chronic autoimmune disorder that affects approximately 1.4% of the global population [1], with a significant rise in incidence observed throughout the second half of the 20th century, at an annual rate of about 7.5% [2].

CeD is characterized by an atypical immune response that damages the small intestine following ingestion of gliadin [3], a gluten protein fragment found in grains, barley, wheat, and rye [4]. Upon the exposure of undigested gliadin peptides in the digestive tract, there is an inappropriate activation of the immune system and production of autoantibodies that damage the intestinal villi [4]. With persistent exposure, this can lead to a decrease in nutrient absorption and loss of the intestinal barrier function, which can progress further to chronic intestinal symptoms and nutrient deficiencies [4].

1.1 Celiac Disease Risk Factors

CeD is a complex autoimmune disorder that can be influenced by risk factors including genetic predisposition, environmental exposures, and gastrointestinal infections [5]. CeD is hereditary, modulated by the human leukocyte antigen (HLA) gene and the HLA-DQ2 or HLA-DQ8 genotypes [6]. It has been reported that 30-40% of the population carry these genotypes, with approximately 95% of patients with CeD expressing the HLA-DQ2 genotype and 5% expressing the HLA-DQ8 genotype [7]. Of these genetically susceptible individuals, only 3% manifest CeD [8]. Not all individuals that carry the risk alleles actually go on to develop CeD, and many are still able to ingest gluten without triggering CeD [6]. The risk of developing CeD is increased to 10% in those with a first-degree relative with CeD, such as a parent, child, or sibling [9]. Females are found to be at higher risk of CeD relative to males, with the risk being highest in children [2]. Gene-environment interactions can also trigger the onset of CeD in genetically susceptible individuals [5]. Environmental exposures such as gluten exposure, intestinal infection, changes in the gut microbiome and breastfeeding practices all serve as possible triggers to disease manifestation [10]. Intestinal infections such as gastroenteritis, especially in the first 6-18 months of life, can increase intestinal permeability and exacerbate the risks and symptoms of CeD later in life [11-14]. Gastroenteritis is characterized by the inflammation of the stomach and intestines due to viral, bacterial, or parasitic infections [15]. Viral gastroenteritis, which is caused by viruses such as norovirus and rotavirus, is the most common form of gastroenteritis [16]. Rotavirus is the leading cause of gastroenteritis among children under the age of 5 [17, 18] and norovirus is the leading

cause of viral gastroenteritis among all age groups [19]. The complex interplay between genetic predisposition and environmental factors, such as viral gastroenteritis, leads to varying degrees of celiac disease susceptibility [20].

1.2 Secretor Status and Gastroenteritis

It is hypothesized that the maternal non-secretor phenotype, which is determined by the FUT2 gene (rs601338) AA genotype, can increase risk of viral gastroenteritis and therefore risk of CeD in an infant [21, 22]**.** A reason for this could be because the maternal non-secretor phenotype influences the development of the neonatal microbiome and subsequent risk of gastrointestinal infections [21]. The neonatal microbiome is first established through various contacts with the mother, one of which is through breast milk [23]. Breast milk fed infants from mothers with a non-secretor phenotype show delays in microbial establishment, and increased vulnerability to infections, including gastroenteritis during infancy and later in life [18, 21, 24]. The secretor status of the infant can also influence risk of developing gastroenteritis by determining the presence of the protective carbohydrates that help prevent the attachment of the viruses [25]. Human milk oligosaccharide (HMO) content is partially determined by the expression of the secretor gene, FUT2, and the Lewis gene, FUT3 [26]. The FUT2 gene is responsible for fucosylation of the HMOs, adding fucose sugars branches, which provide food for neonatal gastrointestinal bacteria and support the establishment of the microbiome [26]. Alterations in the gut microbiome have been shown to affect immune development and susceptibility to infections [27]. Thus, the secretor status of both the mother and infant has been shown to influence the risk of viral infection in the infant.

1.3 Secretor Status and Genes

The secretor status of an individual refers to the presence of blood-group antigens in an individual's bodily fluids [25]. There are a number of genes that determine the presence of blood-group antigens, including the FUT2, FUT3 and ABO genes [25]. The FUT2 gene encodes an enzyme, α-1, 2-fucosyltransferase, which regulates the expression of ABO histo- (ABH) blood group antigens in the gastrointestinal mucosa and other bodily secretions [25]. This expression of ABH blood group antigens determines whether an individual has a 'secretor' or 'non-secretor' phenotype [21]. Individuals with one or more copies of the functional allele of the FUT2 gene have the secretor phenotype (produces the H antigen) whereas individuals with two copies of the loss-of-function mutation for the FUT2 gene have the non-secretor phenotype [21]. The ABO gene further determines the ABO blood group of an antigen [28]. Individuals with the A, B, and AB alleles were found to express glycosyltransferase, which converts the H antigen into the A or B antigen [28]. Individuals with O phenotype were not able to convert the H antigen [28]. ABH was also found to act as a ligand for viruses [29]. The FUT3 gene encodes an enzyme called α-3/4-fucosyltransferase 6, which adds additional fucose to the H antigen after it has been modified by FUT2 [30]. Both the FUT2 and FUT3 genes regulate the Lewis antigen system, which is another blood group system [31]. These Lewis glycans are also used as ligands by various viruses and determines susceptibility to infection by specific strains [29]. Thus, all three genes play a role in secretor status by influencing antigen production.

An individual's risk for viral gastroenteritis, a risk factor of CeD, is influenced by both their own, and their mothers secretor statuses [25]. The aim of this literature review is to determine the combined effect of secretor status and viral gastroenteritis on the development of CeD.

2. Methods

2.1 Search Strategy

PUBMED was searched using the MeSH terms and keywords: "celiac disease" + "non-secretor" + "FUT2" + "gastroenteritis" + "breastfeeding" + "microbiome" + "mother", which resulted in 194 papers. Publications were searched from January 2010 to June 2022. Inclusion criteria included publications in English, published in peer-reviewed journals, and publications pertinent to the relationship between CeD, viral gastroenteritis, or secretor status. Exclusion criteria included any papers before 2010, and studies which looked at gastroenteritis caused by bacterial, fungal, or parasitic infections, and review papers. 26 primary papers were selected after the inclusion and exclusion criteria were applied and duplicates were removed.

2.2 Data Extraction and Quality Assessment

Data extracted from the studies included the author's names, publication date, sample size, sample demographic, method of CeD diagnosis (sero-prevalence and biopsy), consideration of controls, type of statistical analysis, and key findings.

3. Results

3.1 Host Secretor Status, Gastroenteritis, and CeD

3.1.1 Secretor Status and Gastroenteritis

The secretor status of an individual, as imparted by the FUT2, FUT3, and ABO genes, was found to influence susceptibility to viral infection due to their influence on histo-blood group antigen family (HBGA), which act as host receptors for viral attachment [32-35]. Loureiro Tonini et al. [32] found that the FUT3 gene is important for the production of Lewis antigens (Le^a and Le^b), which determines the presence of soluble A, B and H antigens (HBGA) in bodily fluids, and is subsequently associated with the susceptibility to viral infections. They determined that the common culprits of viral gastroenteritis, rotavirus and norovirus, were more prevalent in children with the secretor phenotype as compared to children with the non-secretor phenotype [32]. Similar results were also observed by Payne et al. [34], which found that in a study of 189 patients infected with rotavirus, 0.5% had the non–secretor phenotype and 99.5% had the secretor phenotype. Payne et al. [34] additionally found that non-secretor status could act as a protective mechanism against severe rotavirus gastroenteritis. Consistent with this, patients with the secretor phenotype were shown to be associated with a greater risk of infection transmission and disease severity, including prolonged diarrhea and frequent vomiting [36].

Loureiro Tonini et al. found that viruses can use Lewis HBGA as attachment factors or ligands [32]. Pérez-Ortín et al. [35] found that the specific Lewis antigen that is present in an individual, either the Le^a or Le^b antigens, confers different susceptibilities to infection from particular strains of viruses,

including rotavirus and norovirus. In addition to the proclivity of rotavirus to infect individuals with the secretor phenotype, Pérez-Ortín et al. [35] also found that children that were Le^b positive were found to be more likely to be infected by rotavirus.

Differences between the influence of secretor status between the two different types of viruses were also reported by Rossouw et al. [33]. Rossouw et al. [33] who suggested that although both viruses preferentially infect individuals with the secretor phenotype, the association between rotavirus and individuals with the secretor phenotype is stronger (91% of patients with the secretor phenotype versus 9% of patients with the non-secretor phenotype infected by rotavirus) than the association between norovirus and individuals with the secretor phenotype (78% of patients with the secretor phenotype versus 22% of patients with the non-secretor phenotype infected by norovirus).

3.1.2 Risk of Infection by Specific Strains of Rotavirus

The preferential infection of norovirus and rotavirus in individuals with the secretor phenotype may not be consistent across all strains of the two viruses. Different strains of rotavirus were found to infect secretors versus non-secretor phenotypes differently according to histo-blood group phenotypes [37].

Patients with the secretor phenotype were found to be more susceptible to the P[4], P[8]-1, P[8]-2, P[8]-3 strains of rotavirus with the effect of secretor status most strongly associated with the P[4] strain, which was found to exclusively effect patients with the secretor phenotype, and most weakly associated with the P[8]-3 strain that also affected many patients with the non-secretor phenotype [37]. Patients with the non-secretor phenotype were found to be exclusively susceptible to the P[8]-4 strain of rotavirus [37].

Studies have also shown that the Lewis antigens, which can act as a receptor for viruses and is also influenced by secretor status, may also play a significant role in host susceptibility to rotavirus infections [32, 38, 39]. Lee et al. [38] found that the rotavirus P[6] strain was found to be weakly associated with infants who are negative or weakly positive for the Le^b antigen. Another population-based case-control study found a strong relationship between Lewis-positive secretor status and higher risk of rotavirus infection, when looking at the strains G3 (63.4% of cases), G1 (17.4%), G9 (8.9%), P[8] (85.1%), P[6] (only two cases), and P[4] (only one case) [39].

ABO blood group antigens, in addition to Lewis antigens, may also influence a host's susceptibility to rotavirus infection [35, 40]. Pérez-Ortín et al. [35] found that children with blood groups A and AB were more susceptible to infection by the P[8] strain of rotavirus as compared to children with blood group O. The rotavirus P[10] VP8 protein on the other hand was shown to be able to bind to HBGAs in patients of all ABO groups, regardless of whether they have the secretor or non-secretor phenotype [40].

3.1.3 Risk of Infection by Specific Strains of Norovirus

Similar to rotavirus, different strains of norovirus confer different risks of viral infections among individuals with different secretor statuses [41]. The GII.10 strain was found to infect patients of all ABO groups and all secretor and non-secretor phenotypes [41]. The GII.3, GII.1, and GII.7 strains of norovirus were found to infect individuals who were Lewis positive with the non-secretor phenotype, however, no binding was observed in HBGA expressed in the saliva of individuals with

the non-secretor phenotype [42]. Ayouni et al. [42] hypothesized that non-HBGA ligands or precursors could act as an alternative attachment pathway for noroviruses during infancy. Ayouni et al. [42] also suggested that norovirus recognition by intestinal cells in patients with the non-secretor phenotype may also be mediated by the Lewis antigen. Furthermore, Loureiro Tonini et al. [32] suggested that in a population with primarily the P[8] strain of rotavirus and noroviruses in genogroup II (GII), the number of children who were found to be Lewis-negative may be higher among those with norovirus infections as compared to rotavirus infections. No significant association was made between norovirus infection and ABO blood group system [32].

3.1.4 Mechanism for Strain Specific Infection Risk

Gozalbo-Rovira et al. found that viruses often interact with host cell surface glycans, such as HBGA in order to infect the host [43]. Rotaviruses were found to rely on HBGA as a ligand to bind and enter host cells [40]. FUT2 and secretor status determine HBGA expression, specifically, the fucosylation of HBGA [43]. Individuals who have the secretor phenotype express a functional FUT2 enzyme, which leads to HBGA expression [43]. Gozalbo-Rovira et al. [43] reported that since individuals who have the non-secretor phenotype do not have the functional FUT2 enzyme, there is no fucosylation of the HBGA precursor, Gal-β1,3-GlcNAc. Gozalbo-Rovira et al. [43] found that the L-fucose moiety (Gal-β1,3-GlcNAc), associated with the fucosylated HBGA H type-1 antigen, causes a conformational change that leads to an indirect contact with the VP8 domain of the P[8] strain. The VP8 domain is part of the rotavirus spike protein that facilitates viral attachment and entry [43]. On the other hand, the non-fucosylated HBGA precursor associated with individuals with the non-secretor phenotype have increased ligand affinity for VP8, which is associated with inhibition of rotavirus infection [43].

3.1.5 Dysbiosis and CeD

Different compositions of the gut microbiota have been associated with various disease states, including CeD [44, 45]. Alterations in the abundance of *Bifidobacterium* [46]*, B. bacteriovorus* [44], *Bacteroidetes* and *Firmicutes Firmicutes* [47] has been associated with an increased prevalence of CeD. Mårild et al. [45] also found that intestinal dysbiosis may influence CeD onset.

Wacklin et al. [48] found that the diversity and composition of the microbiota, specifically bifidobacteria, was significantly associated with secretor status. Individuals with the non-secretor phenotype had significantly reduced bifidobacterial diversity, richness, and abundance, especially variants related to B. bifidum, B. adolescentis and B. catenulatum/ pseudocatenulatum [48]. Parmar et al. [24] also suggested that individuals with the non-secretor phenotype are associated with an increased risk of CeD due to its role in gut immune homeostasis.

Xu et al. [46] reported a causal relationship between higher relative abundance of *Bifidobacterium* and CeD onset. Iebba et al. [44] reported reduced levels of mucosa-associated *B. bacteriovorus* in patients with CeD. Iebba et al. also reported that the abundance of *B. bacteriovorus* differs based on location in the small intestine, with a high abundance in the duodenum and a gradual decrease towards the rectum, even in healthy patients [44]. Reduced levels of *Bacteroidetes* and *Firmicutes*, were linked to an increased risk of intestinal inflammatory diseases, such as CeD [47]. Distressed tissue was found to elevate the levels of the pro-inflammatory cytokine, interleukin-

15 (IL-15) [47]. IL-15 was found to alter the composition of the microbiota and was associated with shifts in the abundance of Bacteroidetes and Firmicutes [47].

3.2 Maternal Secretor Status, Gastroenteritis, and CeD

3.2.1 Secretor Status, CeD, and Antibodies in Breastmilk

Khodayar-Pardo et al. [49] found that the breast milk of mothers who had the secretor phenotype contains IgA antibodies that offer protection from infection and may have differing protective effects according to secretor status. Breast milk contains anti-norovirus IgA antibodies that can inhibit norovirus GII.4 binding to receptors in the salivary cells [49]. Khodayar-Pardo et al. [49] analyzed the GII.4-2006b variant and found that it was able to infect individuals with both the secretor and non-secretor phenotype, however in this study, breast milk antibodies were shown to have a stronger inhibitory effect against norovirus infection in individuals with the non-secretor phenotype. Additionally, Olivares et al. [50] found lower levels of secretory immunoglobulin A in the breast milk of mothers with CeD.

3.2.2 Secretor Status and Human Milk Oligosaccharides (HMOs)

HMOs are a complex group of carbohydrates that was found to be present in breastmilk and play a role in an infant's immune health [43, 50-53]. Azad et al. [51] found that the abundance of HMOs can affect the growth of commensal bacteria. A critical modification of HMO's, fucosylation, which is the addition of adding a fucose sugar to a molecule was found to be closely linked to maternal secretor status, FUT2, and FUT3 [51]. Mothers with the secretor phenotype were more likely to have fucosylated HMOs in their breast milk, while mothers with the non-secretor phenotype had significantly reduced levels of fucosylated HMOs in their breast milk [54]. Bai et al. [52] found that the differences in abundance of total and fucosylated HMOs between individuals with the secretor versus non-secretor phenotype are more prominent in early lactation.

HMOs were found to play a role in preventing viral attachment by acting as anti-adhesion molecules [43, 53]. Viruses were found to interact with HMOs as a substitute for their normal receptors [43, 53]. Abundant HMOs can inhibit binding of noroviruses and rotaviruses by acting as a competitive substitute for viral binding to HBGAs [43, 53]. A study by Gozalbo-Rovira et al. [43] found that rotaviruses could interact with a building block of HMOs, lacto-*N*-biose. Another study by Koromyslova et al. [53] found that the G1.1 and GII.17 noroviruses interact with an HMO, 2'-fucosyllactose.

3.2.3 Secretor Status, CeD, and Microbiome

Paganini et al. [55] suggested that infants born to and breastfed by mothers with the secretor phenotype are more likely to have an established microbiome. It was observed that the levels of fucosylated HMOs, which provide prebiotics for inoculated and acquired bacteria from birth and during the neonatal period, increased in the breast milk of mothers with the secretor phenotype throughout the course of lactation [55]. Lewis et al. [56] found that during the neonatal period, maternal HMOs provide the initial food and species of bifidobacteria for the establishment of the infant's microbiome while the infant develops their own mechanisms to sustain microbial growth. Smith-brown et al. [54] found that children breastfed exclusively for at least 4 months by mothers

with the secretor phenotype had higher levels of bifidobacteria in their gut microbiome compared to those fed by mothers with the non-secretor phenotype. The establishment of a bifidobacteria-rich microbiota is delayed in infants from mothers with the non-secretor phenotype [56].

Maternal secretor status and already existing CeD alter HMO fucosylation and were shown to be associated with microbial shifts, which contributes to CeD susceptibility in the infant [50]. Olivares et al. [50]. found that a higher concentration of fucosylated HMOs in breastmilk was found to promote early establishment of bifidobacteria. Mothers with CeD were found to have an overall lower concentration of *Bifidobacterium spp.*, and *Bacteroides fragilis* in their breastmilk as compared to mothers without CeD [50].

4. Discussion

In this literature review, we examined the effect of both maternal and infant secretor status on the risk of gastroenteritis and CeD to gain a better understanding of CeD etiology. 26 papers were included in this literature review: seven investigated the association between secretor status and risk of gastroenteritis [32-34, 36, 37, 39, 42]; six studied the genetic role of secretor status on gastroenteritis [32-34, 36, 39, 42]; two investigated the role of Lewis status on gastroenteritis [35, 38]; one looked at the genetic role of secretor status on celiac disease [24]; seven focused on the influence of microbiota changes due to infections and subsequent effect on celiac disease [44-47, 52, 54, 56]; and six studied the effect of secretor status on breast milk [49-52, 54, 56].

Overall, findings suggest that both the maternal and infant secretor phenotypes play a role in the risk of gastroenteritis and CeD (see Figure 1). An individual's secretor status, in conjunction with Lewis status, and ABO blood group, determines its susceptibility to different strains of rotavirus and norovirus [32-35, 37, 40-42]. The individual's secretor status can also alter the gut microbiota, leading to greater susceptibility to gastroenteritis [57] or CeD [24]. Maternal secretor status also influences an individual's immune system during infancy through concentrations of fucosylated HMOs [43, 50-53], and antibodies [49, 50] in breastmilk. Maternal secretor status also influences the species of microbiota passed onto the infant [54, 58].

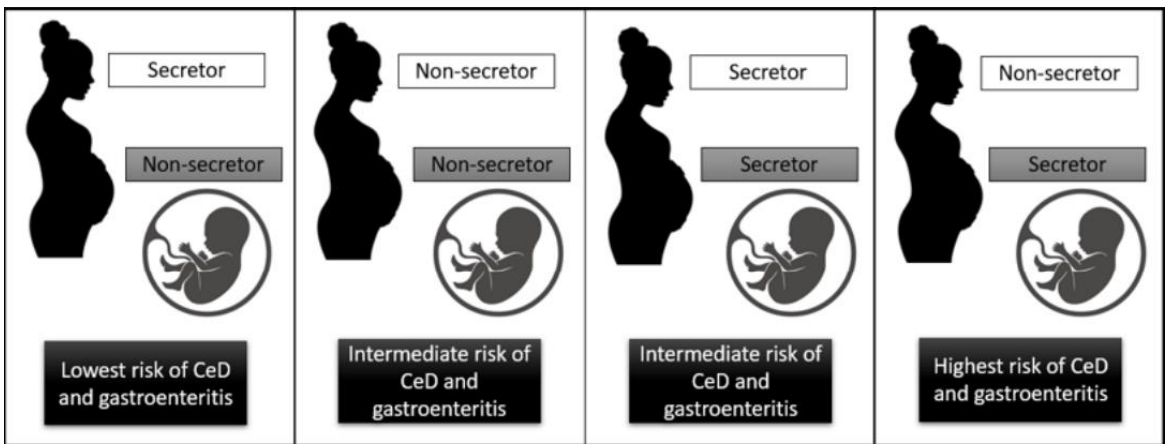

Figure 1 Combined effect of infant and mother secretor status on risk of CeD and gastroenteritis.

4.1 Host's Susceptibility to Gastroenteritis

Understanding the roles that the FUT2, FUT3, and ABO genes play on the risk of gastroenteritis and CeD may help to elucidate why some genetically susceptible infants, who have the HLA-DQ2 and HLA-DQ8 genotypes, develop CeD, while others do not.

The host's genetics determine susceptibility to different viral strains [32-35, 37, 40-43]. Patients with the secretor phenotype were found to be at greater risk of the P[4], P[8]-1, P[8]-2, and P[8]-3 strain of rotavirus, and patients with the non-secretor phenotype were found to be at risk of the P[8]-4 strain of rotavirus [37]. Patients with the secretor phenotype were found to be susceptible to norovirus infections in general, and patients with the non-secretor phenotype were found to be susceptible to the GII.1, GII.3, and GII.7 strains of norovirus [42]. Children who were found to be Le^b positive were found to be at greater risk of rotavirus [35]. Individuals with blood groups A and AB were found to be more susceptible to the P[8] strain of rotavirus [35].

The host's FUT2, FUT3, and ABO genes also influence the microbiota composition since they play a role in fucosylated HMO production, which is a prebiotic for microbiota. An imbalanced gut microbiome may affect intestinal permeability and immune response, which are involved in the pathogenesis of CeD [59]. Reduced butyrate producing bacteria, *Bacteroidetes* and *Firmicutes*, may facilitate CeD development as well [60].

4.2 Maternal Effect on Host's Susceptibility to Gastroenteritis and CeD

The mother's genetics and secretor status influence the HMOs [43, 50-53], antibodies [49, 50], and bacterial species that are passed down to the infant [54, 58]. The primary establishment of a host's immune system during infancy is largely affected by the mother's breastmilk composition, which is affected by secretor status [50].

Infants breastfed for at least 4 months by mothers with the secretor phenotype were found to have greater populations of *Bifidobacterium* in their gut microbiome compared to infants of mothers with the non-secretor phenotype [54]. A possible theory is that as the infant microbiome is exposed to different bacteria rich environments, it takes on new bifidobacteria species over time [56]. The bifidobacteria-rich microbiota will only be established once a species that is able to digest the mother's HMO is introduced to the infant's microbiome [56].

The abundance of HMOs has been shown to influence risk of both gastroenteritis and CeD, by modifying viral adhesion [43, 53] and establishment of the microbiome [50], which contribute to immune development. HMOs promote growth of commensal bacteria such as *Bifidobacterium*, which has been previously linked to CeD risk [46].

4.3 Gastroenteritis and CeD Susceptibility

Frequent rotavirus infections during childhood may elevate the risk of developing CeD [61, 62]. Gastroenteritis can cause an increase in gut permeability, which allows for enhanced gluten penetration into the bloodstream, and could lead to an increased risk of developing CeD [12, 63]. Silvester & Leffer suggest that this effect could be a possible consequence of gastrointestinal infection related side effects such as heightened turnover of epithelial cells, villous atrophy similar to CeD, and apoptosis of mature enterocytes [62]. Gastroenteritis also leads to elevated levels of

the pro-inflammatory cytokine, IL-15, which causes increased intestinal permeability and alters antigen presentation [47, 62].

The introduction of a virus, bacteria, or parasite during gastroenteritis can lead to dysbiosis in an individual [64]. Mårild et al. [45] suggested that dysbiosis can trigger CeD. Another major source of dysbiosis is the erroneous use of antibiotics to treat viral gastroenteritis [45]. Intestinal dysbiosis has been associated with CeD [65]. As per the study by Meisel et al. [47], dysbiosis could also influence IL-15 response, which could further influence microbiota composition leading to greater risk of intestinal inflammatory diseases such as CeD.

4.4 Limitations

This review is meant to draw connections between secretor status, gastroenteritis, and CeD to provide further insight into the etiology of CeD and potential preventative treatment methods. Considering that CeD does not currently have a curative treatment option, preventative measures is the most impactful strategy to reduce the incidence of CeD. Due to the broad nature of this review, a literature review was conducted in lieu of a systematic review with the aim to elucidate a connection between multiple conditions. Non-English publications were omitted from this review, which may be a source of bias. Only PubMed was searched for publications thus, publications not indexed by PubMed may have been missed. Furthermore, statistical analyses were not carried out for this study due to the wide range of study types. Therefore, any trends observed in this review is a descriptive summary of the findings.

4.5 Clinical Implications and Future Directions

Screening for infants susceptible to viral infections and CeD based on their and their mother's FUT2, FUT3, and ABO genotypes can allow us to identify at-risk individuals and take preventative measures to reduce the risk of disease development.

Since we are able to observe the differences in cytokine levels in the breast milk of mothers with secretor versus non-secretor phenotypes [50], a possible treatment method that aims to normalize cytokines may help reduce the symptoms of CeD. A possible method would be to use prebiotic and probiotic supplementation to modify the microbiome and thus, modify cytokine production. Future research could investigate appropriate prebiotic and probiotic supplementation, which could reduce the proliferation of the pro-inflammatory cytokines associated with CeD pathogenesis.

Infants of mothers with the non-secretor phenotype show a delay in bifidobacteria establishment, which would normally provide protection from pathogens and contribute to the development of the neonatal immune system [56]. Therefore, a reasonable treatment could be the use of strain specific probiotics and specific prebiotics to encourage early establishment. Probiotic mixtures used in premature infants, including *B. breve* and *B. longum* subsp. *infantis*, has been shown to be effective at promoting high levels of bifidobacteria, and may be an option for infants breastfed by mothers with the non-secretor phenotype to enhance immune maturation and balance the immune system to suppress inflammation [66, 67]. Although this is a promising option, more research is needed on the specific strains, their impact on the infant's microbiome, and the expected impact on immune development, infection, and onset of CeD.

Vaccinating individuals genetically predisposed to CeD against rotavirus and norovirus during infancy could also eliminate possible risk of gastroenteritis exacerbating the development of CeD [62].

5. Conclusion

The increasing prevalence of CeD in recent years has garnered an interest into this area of research. The consensus from the current literature is that the secretor status of both the mother and the infant confers risk of viral gastroenteritis and CeD in the infant, with an increased risk of later-life CeD among infants with viral infections due to damage to the intestinal epithelium and dysbiosis. In particular, infants who have the secretor phenotype, A or AB blood types, present the Le^b antigen, and have mothers with the non-secretor phenotype and/or CeD are at greatest risk of viral gastroenteritis and CeD.

The only known treatment for CeD is a gluten-free diet. However, knowing the risk level of the individual based on their and their mother's genetic profile can allow for early screening and preventative measures to reduce the onset and severity of CeD. Analyzing the specific strains of viruses in the environment and screening for the infant's FUT2, FUT3, and ABO genotypes may allow for precautionary measures to be taken for infants at risk of viral infections.

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Author Contributions

ID: was involved in literature search, literature review, data extraction, assessment of quality, and writing the manuscript. RM: was involved in literature search, literature review, data extraction, assessment of quality, and critically reviewing the manuscript. AG: was involved in literature search, literature review, data extraction, assessment of quality, and critically reviewing the manuscript.

Competing Interests

Authors are affiliated with a genetic testing company, DNALabs. DNALabs offers various genetic testing services, including the analysis of HLA, FUT2 and several other genes that are related to inflammation, nutrition, and lifestyle. There are no other conflicts of interest for this manuscript.

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