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EDITED BY
Luca Antonioli,
University of Pisa, Italy

REVIEWED BY
Diana Di Liberto,
University of Palermo, Italy
Agata Mulak,
Wroclaw Medical University, Poland

*CORRESPONDENCE
Kinga Skoracka,
kingskoracka@gmail.com
Szymon Hryhorowicz,
szymon.hryhorowicz@gmail.com

†These authors have contributed equally to this work

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From an understanding of etiopathogenesis to novel therapies—what is new in the treatment of celiac disease?

Kinga Skoracka [1,2†*], Szymon Hryhorowicz [3†*], Francesco Tovoli [4], Alberto Raiteri [4], Anna Maria Rychter [1,5], Ryszard Słomski [3], Agnieszka Dobrowolska [1], Alessandro Granito [4] and Iwona Krela-Kaźmierczak [1,5]

[1]Department of Gastroenterology, Dietetics and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland, [2]Doctoral School, Poznan University of Medical Sciences, Poznan, Poland, [3]Institute of Human Genetics, Polish Academy of Sciences, Poznan, Poland, [4]Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [5]Laboratory of Nutrigenetics, Department of Gastroenterology, Dietetics and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland

Celiac disease, a chronic autoimmune disorder caused by genetic factors and exposure to gluten, is increasingly being recognized and diagnosed in both children and adults. Scientists have been searching for a cure for this disease for many years, but despite the impressive development of knowledge in this field, a gluten-free diet remains the only recommended therapy for all patients. At the same time, the increasing diagnosis of celiac disease in adults, which was considered a childhood disease in the 20th century, has opened a discussion on the etiopathology of the disease, which is proven to be very complex and involves genetic, immunological, nutritional, environmental and gut microbiota-related factors. In this review, we extensively discuss these factors and summarize the knowledge of the proposed state-of-the-art treatments for celiac disease to address the question of whether a better understanding of the etiopathogenesis of celiac disease has opened new directions for therapy.

KEYWORDS

celiac disease, autoimmunity, HLA, novel therapies, gluten-free diet

1 Introduction

Celiac disease (CD) is a chronic, systemic small intestinal enteropathy that develops in genetically predisposed individuals. In human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 positive people, exposure to dietary gluten activates immune response characterized by specific serum autoantibody response in IgA and IgG class—anti-transglutaminase IgA and anti-endomysial antibodies IgA and deamidated gliadin-related peptide IgA and IgG—which results in pathological changes in small intestine such as crypt hyperplasia, lymphocyte infiltration, and villous atrophy (Ludvigsson and Murray, 2019a; Pinto-Sanchez et al., 2021).

The global prevalence of CD is estimated at 0.7%–1.4% of general population (Makharia et al., 2022). In Europe, a higher prevalence has been reported in northern (1.6%) compared

to eastern (0.98%), southern (0.69%), and western (0.60%) countries (Roberts et al., 2021). These data are not dissimilar from those reported in the United States, where Fasano et al. described a 0.8% prevalence in 2003 (Fasano et al., 2003). In India, the estimated prevalence is 1.04% (Makharia et al., 2011) with a geographical gradient from North (where a wheat-based diet is frequent) to South (Ramakrishna et al., 2016). Similar prevalence and gradient have been reported in China (Yuan et al., 2017). Data from the remaining geographical regions are based on the serological prevalence of celiac-specific antibodies rather than biopsy-confirmed CD, but all suggest a prevalence between 0.5% and 2%, with two notable exceptions - in Japan, Fukunaga et al. (Fukunaga et al., 2018) reported a <0.1% prevalence of confirmed CD in a population study involving more than 2,000 subjects. The low prevalence in this country can be attributable to a lower frequency of the HLA-DQ2/DQ8 haplotype (Saito et al., 2000). On the contrary, an African population originally living in Western Sahara, the Saharawi, has been reported to have a particularly high prevalence of CD. In a study involving 989 Saharawi children, the prevalence was 5.6% (Catassi et al., 1999). Possible reasons include a relatively high level of consanguinity, higher frequencies of HLA-DQ2 and -DQ8 genotypes in their general population, and consumption of elevated quantities of gluten (Catassi et al., 1999).

1.1 Genetic and immunological determinants of celiac disease

Genetic determinants are the major contributing player to CD susceptibility. To date, the major histocompatibility complex (MHC) region is the most well-known hereditary component that acts as a prerequisite for CD development, and the strongest effects are attributed to the HLA-DQA1 and HLA-DQB1 genes. Furthermore, almost all patients with CD possess specific variants of human leukocyte antigen (HLA) DQ2 or DQ8 heterodimers – 90%–95% of patients with CD have positive haplotype DQ2 (DQA1*0501/DQB1*0201), while 5%–10% have positive haplotype DQ8 (HLA-DQB1*0302) (Ludvigsson and Murray, 2019a). Even though common HLA-DQ2/DQ8 haplotypes increase the risk of the disease sixfold (Volta and Villanacci, 2011), the HLA-DQ2 and HLA-DQ8 haplotypes are not entirely disease-specific, since a significant percentage of people, most of whom do not have celiac disease, carry these alleles. Thus, it follows that haplotypes DQ2 and DQ8 are necessary but not sufficient for the development of CD (Bevan et al., 1999; Wijmenga and Gutierrez-Achury, 2014; Lindfors et al., 2019).

Currently, the CD is characterized as a polygenic disease with a complex, non-MHC pattern of inheritance, involving MHC and non-MHC genes that together affect the genetic risk of developing the disease. It is well-established that 6 MHC and 43 non-MHC loci, including a higher number of independent genetic variants, are associated with disease risk (Dieli-Crimi et al., 2015).

The MHC region, located on 6p21, carries relevant immune function genes associated with most immune-mediated diseases. The MHC region risk factors we mentioned earlier - HLA-DQA1 and HLA-DQB1 - account for about 22% of the heritability of CD (Gutierrez-Achury et al., 2015). The complex peculiarities in this region, characterized mainly by having numerous genes, high polymorphicity, and linkage disequilibrium, made it very difficult to identify new additional risk variants in this region. A few years ago, precise mapping of the MHC region identified new independent risk variants explaining about 2.5%–3% of disease heritability (Gutierrez-Achury et al., 2015). HLA-DPβ1, HLA-B (classic HLA-B*08 and HLA-B*39:06 alleles), and two SNPs, rs1611710, which shows an effect on HLA-F expression, and rs2301226, which shows an effect on B3GALT4 and HLA-DPB1 expression. Thus, it follows that MHC risk variants account for 25% of the heritability of the disease, leaving a significant portion still unexplained.

In the last years, extensive GWAS studies have shed new light on the risk of CD, identifying independent genetic variants at non-HLA loci that could clarify the complex genetics of this disorder (Smyth et al., 2008; Dubois et al., 2010; Trynka et al., 2011; Coleman et al., 2016). In the case of CD, the first GWAS study resulted in the conclusive identification of the first non-HLA-related CD risk locus, the IL2/IL21 region (van Heel et al., 2007). In the following years, subsequent GWAS studies have shown as many as 14 new regions associated with the development of CD (Hunt et al., 2008; Garner et al., 2009). In 2009, Trynka et al. identified additional susceptibility regions in the *REL, OLIG3,* and *TNFAIP3* (Trynka et al., 2009) increasing the number of non-HLA-related loci identified a year later (Dubois et al., 2010). The same research group, using the Immunochip platform in a study of a large cohort from seven geographic regions, revealed 13 new loci associated with the disease (Trynka et al., 2011). In subsequent years, new GWAS analyses have contributed to adding more risk loci to the "non-HLA risk locus family". There were corresponding studies by Scandinavian groups describing a risk locus involving the *DUSP10* gene after stratification for HLA-DQ risk factors (Östensson et al., 2013) or the Irish group's research—increasing the total number of common non-HLA CD susceptibility loci by two more (*ZNF335* and *NFIA*) (Coleman et al., 2016).

The group of non-HLA genes has greatly expanded where the majority have been reported to be related to other autoimmune diseases, or those related to T and B cell functions such as antigen presentation and cytokine production (Abadie et al., 2011). These genes are involved in the peptide recognition and $CD4^+$ T cell presentation (*HLA-B, HLA-DPB11, HLA-F1HLA-DQA1, HLA-DQB1*) (Gutierrez-Achury et al., 2015) differentiation (*CCR1, CCR2, CCR3, STAT4, PTPN2, RUNX3, THEMIS, ETS1, SH2B3, IL12A, IL18R1, IL18RAP, IL1RL1, IL1RL2, CCR4* (Festen et al., 2011a; Dieli-Crimi et al., 2015), survival (*FASLG, TNFSF18*), migration (*RGS1, ELMO* RGS1, *ITGA4*) (Hunt et al., 2008), activation of T and B cells (*ICOSLG, RGS1, BACH2, POU2AF1, TNFAIP3, ZFP36L1, MAP3K7, IL-21, CCR9, RGS1, CTLA4, ICOS*[3], *CD28,*' *RGS1, PRKCQ, KIAA1109, ADAD1, IL2, IL21, KIAA1109, ADAD1, IL2, IL21, CTLA4, ICOS, CD28, CD80, PTPN 2, IL2, FASLG, CD247, SH2B3, UBASH3A, PRKCQ, TAGAP, ARHGAP31, RGS13 CTLA4, ICOSLG, RGS1, BACH2, POU2AF1, TNFAIP3* and *ZFP36L1*) (Smyth et al., 2008; Dieli-Crimi et al., 2015) or in antigen presentation (*CD80, TNFSF4, CIITA, ELM01, NFIA*) (Abadie et al., 2011; Meresse et al., 2012). It is currently estimated that the identified MHC genetic variants as well as the remaining discovered non-MHC genetic variants explain about 31% of the heritability of celiac disease. It is noteworthy that non-MHC variants have been estimated to account for 6.5% of CD heritability, which means, a much more important role of the classic, known MHC

variants. Thus, it seems that the remaining variants responsible for the largest part of heritability - accounting for practically 70%, are low-effect variants (except for MHC variants) (Dieli-Crimi et al., 2015). Genetic risk variants associated with celiac disease are presented in Supplementary Table S1.

1.2 Nutritional determinants of celiac disease

In the development of CD dietary factors are also crucial. These primarily include exposure to gluten; a person who has never consumed gluten will not develop CD (Ludvigsson and Murray, 2019b). However, it is noteworthy that the diagnosis rate of CD has increased in recent years. This is partly explained by access to better diagnostic tools but there is also much evidence of the contribution of environmental and dietary factors (King et al., 2020).

For many years, breastfeeding and the time of introducing gluten into the diet were considered as factors that could affect the risk of developing CD. Even in the recommendations of the British Society of Gastroenterology from 2014, we can read that children who are breastfed during and after the introduction of gluten to the diet may have a lower risk of developing CD and that large amounts of gluten or exposure to gluten in children not breastfed may increase the risk of developing celiac disease (Ludvigsson et al., 2014). However, in the latest 2019 guidelines, the European Society for the Study of Celiac Disease emphasizes that there is no evidence to support the thesis that the time of breastfeeding or the time of introducing gluten into the infant's diet - at 4 months of age or between 6 and 12 months of age–has an impact on the risk of developing CD (Al-Toma et al., 2019). The results of two studies, PREVENTCD and CELIPREV, are particularly highlighted (Lionetti et al., 2014; Vriezinga et al., 2014).

The first study was a multicenter study conducted by Vriezinga et al. (Vriezinga et al., 2014) on a group of 944 children from 8 countries with HLA-DQ2 or HLA-DQ8 positivity and at least 1 first-degree relative with CD. Children were divided into two random groups–the first group, 475 participants received 100 mg of immunologically active gluten daily between 16 and 24 weeks of age. In the second group, 469 children received a placebo. At 3 years of age, every participant underwent a biopsy to confirm or exclude celiac disease. As compared with a placebo, the introduction of small quantities of gluten at 16–24 weeks of age did not reduce the risk of CD in the group of high-risk children. Also, gluten introduction during breastfeeding did not show any protective effect on CD development. Furthermore, the study revealed that breastfeeding - exclusive as well as any breastfeeding - and duration of breastfeeding did not significantly impact the development of CD (Vriezinga et al., 2014). The second study conducted by Lionetti et al. compared the time of gluten introduction in children born in Italy. Gluten was introduced at 6 months of age in a group of 297 infants or at 12 months of age in a group of 256 infants. All children had a first-degree relative with CD. In this study, the delayed introduction of gluten and breastfeeding did not modify the risk of CD among at-risk infants, although the later introduction of gluten was associated with a delayed onset of disease but without influencing the overall risk (Lionetti et al., 2014).

An interesting issue is also the amount of gluten in a child's diet in the context of the later development of CD. Three studies (Andrén et al., 2019; Lund-Blix et al., 2019; Mårild et al., 2019) were published in the 2019. Two of them were conducted in the at-risk CD population, and one included children independent of HLA. It was observed that higher gluten consumption in the first years of life was associated with a higher risk of being diagnosed with CD or CD autoimmunity. Ludvigsson comments that taking into account the outcomes of these studies, 2 g of gluten per day which responds to one extra slice of bread seems to be linked to a 20%–50% increased risk of CD (Ludvigsson and Lebwohl, 2020).

In conclusion, there is no evidence that breastfeeding, as well as breastfeeding while introducing gluten into the diet, reduces the risk of developing CD. Also, the timing of introducing gluten into a child's diet does not seem to affect the development of the disease–ESPGHAN recommends introducing gluten between 4 and 12 months of age although there is no recommendation regarding the type and the amount of gluten to be used at introduction (Szajewska et al., 2015; ESPGHAN, 2016; Silano et al., 2016). At the same time, ESPGHAN suggests avoiding large amounts of gluten during the first month after gluten introduction (ESPGHAN, 2016).

It is also worth noting that our diet and lifestyle have changed significantly over the last few decades. Several links could be made between a Western-style diet (WD) and CD development but this area has yet not been fully investigated. Nevertheless, WD can be characterized as a high-caloric diet, rich in refined grains and sugar, salt, saturated fats, and animal protein, and low in fiber, vitamins, and trace elements (García-Montero et al., 2021). Such a composition of diet could increase the risk of CD contributing to gut dysbiosis and changes in intestinal barrier function. This can increase intestinal permeability, further leading to mucosal inflammation, leakage of toxic bacterial metabolites into the circulation, and finally systemic endotoxemia and chronic inflammation (García-Montero et al., 2021). Since WD is based on processed foods, and low in fresh fruits and vegetables, its anti-inflammatory and antioxidant status is low which also can predispose to low-grade chronic inflammation (Malesza et al., 2021).

Furthermore, Malesza et al. (Malesza et al., 2021) state that changes in microbiota induced by a high-fat diet that is common for Western dietary patterns can also disrupt the expression of inflammation- and metabolism-related genes, reduce short-chain fatty acids (SCFA) production, increase lipopolysaccharide (LPS) production and the activity endocannabinoid system. Authors summarize that a high-fat diet enhances oxidative stress by increasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, stimulating closely related ER stress, downregulating gut peptide signaling pathways, and reducing their secretion by enteroendocrine cells (Malesza et al., 2021). A summary of dietary factors associated with CD is presented in Table 1.

1.3 Gut microbiota and celiac disease

In normal conditions, the gut microbiota includes at least six bacterial phyla: *Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria,* and *Verrucomicrobia*

TABLE 1 Diet-related factors associated with celiac disease.

Factor	Impact	References
Exposure to gluten	Exposure to gluten may activate cell-mediated and humoral immune responses leading to crypt hyperplasia, lymphocyte infiltration, and villous atrophy in the small intestine in genetically predisposed individuals	Ludvigsson and Murray (2019b)
Time of gluten introduction to the diet	The timing of introducing gluten into a child's diet does not seem to affect the development of the disease	Lionetti et al. (2014), Vriezinga et al. (2014)
Breastfeeding	Exclusive/any breastfeeding, and breastfeeding at the time of gluten introduction, does not reduce the risk of developing CD during childhood	Lionetti et al. (2014), Vriezinga et al. (2014)
Amount of gluten	Higher gluten consumption in the first years of life is associated with a higher risk of CD development	Andrén et al. (2019), Lund-Blix et al. (2019), Mårild et al. (2019)
Western and high-fat diet	Western-style diet possibly could predispose to CD development	García-Montero et al. (2021), Malesza et al. (2021)
	1. Western and high-fat diets impact gut microbiota, driving gut dysbiosis	
	2. Gut dysbiosis results in a reduction of SCFA production, further increasing LPS production and the activity endocannabinoid system, and decreasing antimicrobial Paneth cell peptides	
	3. WD and high-fat diets increase ROS and RNS production, stimulating closely related ER stress, further downregulating gut peptide signaling pathways, and reducing their secretion by enteroendocrine cells	
	4. Reduction in tight junction expression, increased intestinal permeability, leakage of toxic bacterial metabolites into the circulation, systemic endotoxemia, and chronic inflammation	
	5. Dysbiosis and high-fat diet drive activation of TLR4 by LPS and SFA, NF-κB stimulation and production of IL-6 and TNF-alfa, and activation of neutrophils and macrophages. Increased secretion of bile acids can impair gut barrier function and have pro-inflammatory effects	

TABLE 2 Gut microbiota changes associated with celiac disease.

Observation ⬆	Reference
⬆ *Bifidobacteria* and an *Bacteroides*	Valitutti et al. (2019)
number of *Bacterioides fragilis* and *Staphylococcus spp*.	Palma et al. (2012)
⬇ number of *Bifidobacteria* and *B. Longum*	
⬆ *Firmicutes* and *Proteobacteria*,	Sellitto et al. (2012)
⬇ *Actinobacteria* and *Bacteroidetes* were significantly restricted in children with a genetic predisposition to CD	
⬆ number of enterotoxigenic *E. coli* (ETEC) in infants with a high genetic risk versus those of intermediate risk on formula feeding	Olivares et al. (2018)
microbial species and strains linked to autoimmune and inflammatory conditions (e.g., *Dialister invisus, Parabacteroides sp., Lachnospiraceae*) and relative lack of species with anti-inflammatory effects (e.g., *Streptococcus thermophilus, Faecalibacterium prausnitzii,* and *Clostridium clostridioforme*) before the diagnosis of CD in infants	Leonard et al. (2021)

(Arumugam et al., 2011). Changes in the composition and function of gut microbiota have been linked to many gastrointestinal diseases, including CD. Both cross-sectional and cohort-prospective studies investigated the role of the intestinal microbiome in CD.

Cross-sectional studies provided highly heterogeneous results. Limitations of these studies included highly individual-specific microbial profiles, small sample sizes, and spurious "healthy controls" (actually including patients who underwent upper digestive endoscopy for symptoms) (Valitutti et al., 2019). Despite these limitations, a decrease in *Bifidobacteria* and an increase in *Bacteroides* (both on feces and mucosal biopsies) were commonly reported (Valitutti et al., 2019). More reliable information about the dynamic changes in the gut microbiome of CD patients came from prospective studies. In the PROFICEL study, De Palma et al. (Palma et al., 2012) reported modification of the gut microbiota before the actual development of CD. In detail, infants with genetic susceptibility to CD had feces characterized by a higher number of *Bacteroides fragilis* and *Staphylococcus spp*. and a lower number of *Bifidobacteria* and *B. Longum* vs. healthy controls (Palma et al., 2012). The same study group published two additional studies. In the most extensive longitudinal analysis of gut microbiota, Sellitto et al. (Sellitto et al., 2012) examined stool samples at several time points (7 days, 30 days, 6 months, 8 months, 10 months, 12 months, 18 months, and 24 months) in infants. The results of this study suggested relevant differences

TABLE 3 Environment-related factors associated with celiac disease.

Factor	Impact	References
Viral infections	The cumulative effect of gliadin and viruses	Stene et al. (2006), Bouziat et al. (2017), Lindfors et al. (2020), Barone and Auricchio (2021), Oikarinen et al. (2021), Tapia et al. (2021)
	Viral infections are involved in immune activation and the breakdown of tolerance against gluten in genetically predisposed individuals	
	In infants, viruses could affect the maturation and development of the mucosal immune system and cause long-term changes in the gut microbiota	
	Viral ligands delay vesicular trafficking, and activate innate immunity, and inflammatory markers, e.g., NFkB and MAPK, activate TLRs	
Bacterial infections	Mixed results	Riddle et al. (2013), Dore et al. (2018), Amlashi et al. (2021)
	Possible mechanism	
	Molecule mimicking; T cell receptor cross-reactivity between gliadin and bacterial peptides	
Smoking	Significantly decreased risk of celiac disease compared with non-smokers	Wijarnpreecha et al. (2018)
Persistent organic pollutant	Higher odds of CD associated with specific persistent organic pollutant	Gaylord et al. (2020)
Type of delivery	Type of delivery is not an independent factor of celiac disease	Koletzko et al. (2018)

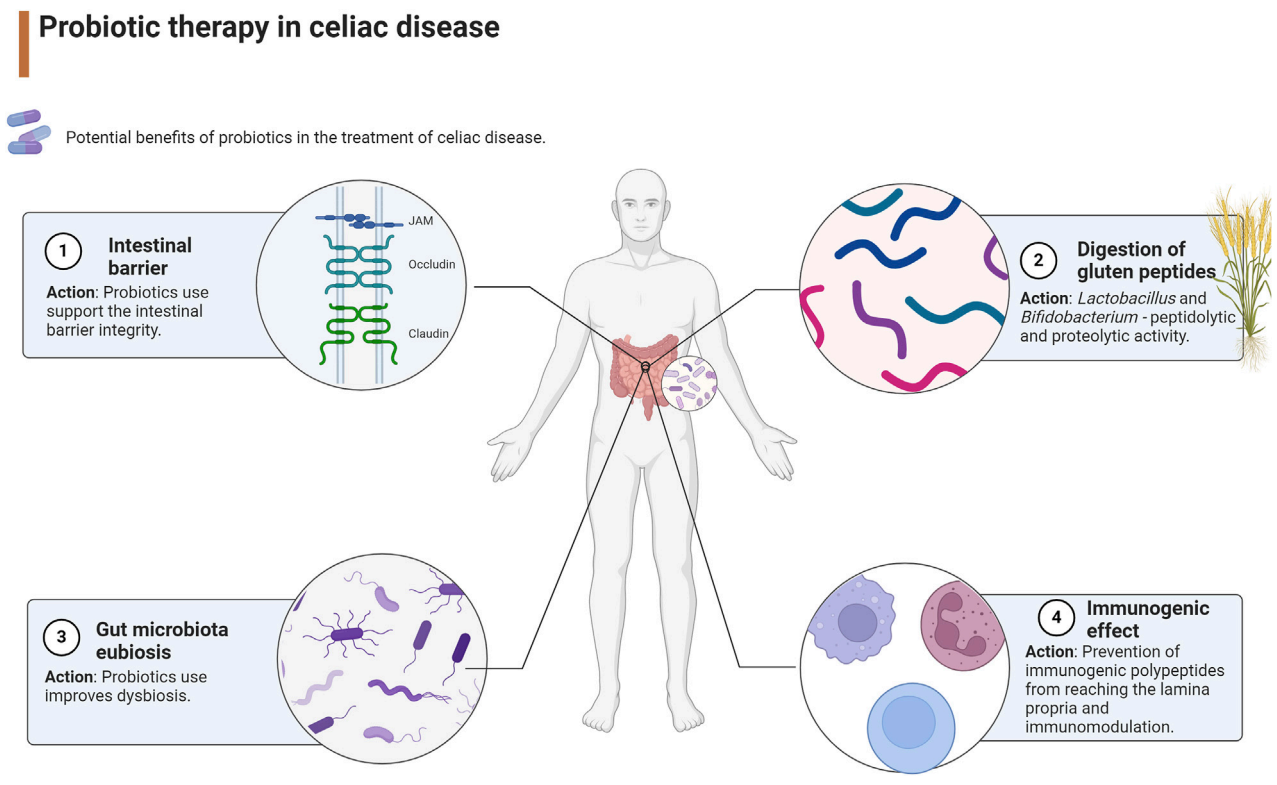

FIGURE 1
Probiotic therapy in celiac disease (Kõiv and Tenson, 2021).

between the evolving microbiota of infants with a genetic predisposition for CD compared to those from infants with a non-selected genetic background. In detail, children with a genetic predisposition to CD had increased *Firmicutes* and *Proteobacteria*, while *Actinobacteria* and *Bacteroidetes* were significantly restricted. Additionally, they also found that stool microbiota in these infants did not stabilize, nor was it similar to adult microbiota at 1 year of age (Sellitto et al., 2012). In another study examining stool samples from infants at genetic risk within the first week of life, and at 4 months and 6 months of age, a higher

TABLE 4 Completed and ongoing clinical trials concerning celiac disease novel treatment. Based on Alhassan E et al. Cell Mol Gastroenterol Hepatol. 2019; 8 (3):335–345. doi:10.1016/j.jcmgh. 2019.04.017 and Varma et al. Drugs. 2022 October; 82 (15):1515–1526. doi: 10.1007/s40265-022-01784–2. Epub 2022 October 17. PMID: 36251239.

Status	Drug	Therapeutic approach	Clinical trial number (trial phase)	Outcomes summary
Completed	1) IMGX003 (Latiglutenase)	1) Degradation of gluten peptides; peptidase therapy	1) NCT00859391 (0)	1) Reduction of gluten-induced intestinal mucosal damage and symptom severity (NCT03585478)
	2) AN-PEP	Reduction of immunogenic potential of gluten	NCT00959114 (2a)	2) No effect in preventing mucosal damage after consumption of 7 g of gluten per day for 2 weeks
	3) BL-7010	2) Endopeptidase derived from the fungus Aspergillus niger	NCT00669825 (I)	3) Not available
	4) STAN-1	3) Prevention of gliadin breakdown into immunogenic peptides	NCT01255696 (IIa)	4) No significant difference in tTG-IgA concentration between groups: STAN-1 vs. placebo for 12 weeks + gluten 1 g/day
	5) KAN-101	4) Gluten degradation before absorption	NCT01917630 (Iib)	5) Not available
	6) Necator americanus inoculation	5) Antigen-specific immune tolerance, tolerogenic immunotherapy	NCT03585478 (II)	6) Symptom improvement, no changes in intraepithelial lymphocyte counts and Marsh scores, reduction in intestinal T cells expressing IFN-γ after hookworm infection with an increase in CD4 (+) Foxp3 (+) regulatory T cells
	7) Nexvax2	6) Gluten tolerization	2) NCT00810654 (I/II)	7) Well tolerated, discontinued — not significant improvement
	8) TIMP-GLIA (CNP-101)	7) Gluten vaccine and tolerization	NCT02060864 (I)	8) Well-tolerated, prevention of gluten-induced activation
	9) AMG 714	8) Immune gluten tolerization	NCT01335503 (I)	9) Not available
	10) Larazotide acetate (or AT-1001	9) Anti-IL-15 monoclonal antibody	3) NCT01990885 (I/II)	10) Symptom improvement, lack on data on histologic improvement
	11) TAK062	10) Tigh junction modulator, prevention of gliadin-induced permeability, reduction of small intestinal inflammation	4) NCT00962182 (I/II)	11) Safe and well-tolerated
	12) RO5459072	11) Gluten degradation	5) NCT04248855 (I)	12) Not available
	13) Hu-Mik-Beta-1	12) Inhibition of cathepsin S	6) NCT00671138 (I/II)	13) Not available
		13) Cytokine receptor antibodies	NCT00671138 (II)	
			NCT02754609 (I)	
			7) NCT02528799 (I)	
			NCT03644069 (II)	
			NCT03543540 (I)	
			NCT00879749 (I)	
			8) NCT03738475 (Iia), NCT03486990	
			9) NCT02637141/ NCT02633020/NCT03439475	
			10) NCT01396213 (Iib)	
			NCT00386165 (I)	
			NCT00492960 (II)	
			NCT00362856 (II)	
			NCT00386490 (I)	
			NCT00889473 (II)	

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TABLE 4 (*Continued*) Completed and ongoing clinical trials concerning celiac disease novel treatment. Based on Alhassan E et al. Cell Mol Gastroenterol Hepatol. 2019; 8 (3):335–345. doi:10.1016/j.jcmgh. 2019.04.017 and Varma et al. Drugs. 2022 October; 82 (15):1515–1526. doi: 10.1007/s40265-022-01784–2. Epub 2022 October 17. PMID: 36251239.

Status	Drug	Therapeutic approach	Clinical trial number (trial phase)	Outcomes summary
			NCT00620451 (II)	
			11) NCT03701555 (I)	
			12) NCT02679014	
			13) NCT01893775 (I)	
Ongoing	1) TAK062	1) Gluten degradation	1)NCT05353985(II)	
	2) KAN-101	2) Tolerogenic immunotherapy	2) NCT05574010 (1/2)	
	3) AN-PEP	3) Endopeptidase	2) NCT05574010	
	4) Latiglutenase	4) Peptidase therapy	3) NCT04788797	
	5) TAK-101	5) Gluten degradation	(IV)	
	6) Teriflunomide	6) Adaptive T cell activation	4) NCT04839575 (II)/ NCT04243551 (II)/	
	7) Deamidation and sequestration	7) Gluten sequestration	5) NCT04530123 (II)	
	AGY	8) Anti-IL-23 monoclonal	6) NCT04806737	
	8) Immune targets	Antibody	7) NCT03707730 (II)	
	Guselkumab	9) Anti-IL-15 monoclonal	8) NCT04704843 (Ib)	
	9) PRV-015 Anti-IL-15 monoclonal antibody	Antibody	9) NCT04424927	
	10) PTG-100	10) A4b7 integrin antagonist	(IIb)	
			10) NCT04524221 (Ib)	

number of enterotoxigenic *E. coli* (ETEC) was identified in infants with a high genetic risk versus those of intermediate risk on formula feeding (Olivares et al., 2018). The Celiac Disease Genomic, Environmental, Microbiome, and Metabolomic (CD-GEMM) was another multicenter prospective study investigating blood and stool biomarkers in infants at risk for CD (Leonard et al., 2015). The first paper was published in 2021, reporting longitudinal analyses of gut microbiota, functional pathways, and metabolites, starting from 18 months before CD onset in 10 infants who developed CD and 10 matched nonaffected infants (Leonard et al., 2021). The authors found that the evolving microbiome of CD infants was characterized by an abundance of microbial species and strains that had previously been linked to autoimmune and inflammatory conditions (e.g., *Dialister invisus, Parabacteroides* sp., *Lachnospiraceae*). On the other hand, a relative lack of other species known to have anti-inflammatory effects (e.g., *Streptococcus thermophilus, Faecalibacterium prausnitzii,* and *Clostridium clostridioforme*) occurred before the diagnosis of CD (Leonard et al., 2021). Gut microbiota changes associated with CD are presented in Table 2.

1.4 Environmental determinants of celiac disease

Environmental factors appear to significantly influence the development of CD. Common gastroenterological infections have been shown to increase the risk of developing CD (Kagnoff et al., 1984; Beyerlein et al., 2017; Kemppainen et al., 2017; Mårild et al., 2019).

Studies indicate that enteral viruses in particular are associated with the development of CD. Lindofrs et al. conducted a prospective metagenomics screening of the stool virome in 83 CD genetically predisposed children and 83 controls. They observed that frequent exposure to enterovirus between 1 and 2 years of age was associated with an increased risk of CD autoimmunity. Moreover, they revealed that enteroviruses and higher amounts of gluten in the diet have a cumulative effect on CD development (Lindfors et al., 2020). Similarly, Khar et al. found that a higher frequency of enterovirus, but not adenovirus infections, during early childhood was associated with later CD in a cohort of 220 Norwegian children (Kahrs et al., 2019). Oikarinen et al. confirmed the association observed in two previous studies between enterovirus infections and the later development of CD (Oikarinen et al., 2021). It is also indicated that early-life parechovirus and rotavirus infections are associated with subsequent CD in genetically at-risk children and that also reovirus infection may trigger CD (Stene et al., 2006; Bouziat et al., 2017; Tapia et al., 2021).

It seems that viral infections are involved in immune activation and the breakdown of tolerance against gluten in genetically predisposed individuals. Moreover, viral infections in infants could affect the maturation and development of the mucosal immune system and cause long-term changes in the gut

microbiota (Kiliccalan, 2021). An interesting study was conducted by Kemppanien et al. to investigate the relationship between reported infections, rotavirus vaccination status, time to the first introduction of gluten, breastfeeding, and risk of celiac disease autoimmunity in the group of 6327 genetically predisposed children aged 1–4 years from The Environmental Determinants for Diabetes in the Young (TEDDY) study. They observed that gastrointestinal infections increase the risk of CD autoimmunity within the following 3 months by 33% and that the risk is modified by HLA genotype, infant gluten consumption, breastfeeding, and rotavirus vaccination. The risk of developing CD autoimmunity was additionally higher in winter-born infants to whom gluten was introduced before the age of 6 months, and 10 times higher in children without the HLA-DQ2 allele (carrying the HLA-DQ8/8 or HLA-DQ4/8 genotypes) and breastfed for less than 4 months. In contrast, the risk was reduced in children vaccinated against rotavirus who had introduced gluten into their diet before the age of 6 months (Kemppainen et al., 2017). This study shows the cumulative effect of risk factors (Barone and Auricchio, 2021).

Interesting results are also given by studies on bacterial infections pointing to an inverse association between *H. pylori* infection and CD development (Amlashi et al., 2021), although Dore et al. did not find any relationship between *H. pylori* and CD risk (Dore et al., 2018). In turn, Riddle et al. observed an increased risk of CD following Campylobacteriosis (Riddle et al., 2013).

Among environmental factors, the relationship between smoking and the development of CD, as well as the type of delivery, was also examined. It was observed that smokers have a significantly decreased risk of CD compared with non-smokers (Wijarnpreecha et al., 2018). In turn, the mode of delivery was not an independent risk factor for the development of CD autoimmunity or CD in children in TEDDY cohort (Koletzko et al., 2018).

Gaylord et al. (Gaylord et al., 2020) conducted a study to identify whether persistent organic pollutants (POPs) which are endocrine disruptors could be potential risk factors for CD. Authors found higher odds of CD associated with specific POPs, in particular with p,p'-DDE (p,p'-dichlorodiphenyldichloroethylene). This study is the first to highlight the potential role of endocrine disruptors in the development of CD. However, further research is needed in this area.

Environment-related factors associated with celiac disease are presented in Table 3.

2 Celiac disease novel therapies

Currently, the only effective form of treatment for CD is a strict gluten-free diet. So far no drugs for celiac disease treatment have been approved by the Food and Drug Administration. However, given the numerous limitations of a gluten-free diet, including cost, reduced quality of life, or lack of response to treatment with a gluten-free diet in up to 7%–30% of patients, new treatment strategies are being sought (Varma and Krishnareddy, 2022).

Refractory CD (RCD) is diagnosed when relapsing symptoms persist despite a strict gluten-free diet (GFD) for more than 12 months and in the absence of other diseases, including overt lymphoma. Treatment of RCD involves a combination of nutritional support and immunosuppressive therapy - steroid therapy, thiopurines infliximab, and mesalamine. However, this treatment is often not effective (Al-Toma et al., 2019). Some patients diagnosed with RCD may respond to trace amounts of gluten in the diet, even below - considered safe for the vast majority of CD patients - 20 ppm. Hollon et al. conducted an interesting study on a group of patients who were non-responsive to GFD treatment. The study involved 17 patients who remained symptomatic despite adhering to a strict gluten-free diet, six of whom were diagnosed with RCD before entering the study. They were then placed on a 3–6 months special diet consisting of unprocessed, whole gluten-free products known as the Gluten Contamination Elimination Diet (GCED). Out of the 17 patients, 14 (82%) responded positively to the GCED. After undergoing GCED, all five previously diagnosed RCD patients became asymptomatic and no longer met the criteria for RCD. Out of the 14 patients who responded to the GCED, 11 (79%) were able to successfully return to a traditional GFD without experiencing a recurrence of symptoms (Hollon et al., 2013).

However, new approaches are being sought to treat CD more effectively and move beyond a strict GFD. One proposed strategy aims to reduce immunogenic gluten peptides through intraluminal digestion. This involves the oral administration of exogenous endopeptidases that digest gluten in the intestinal lumen. This prevents gluten from reaching the lamina propria and stimulating the immune system (Varma and Krishnareddy, 2022). Other proposed strategies aim at blocking immune response to gluten peptides by:

- transglutaminase transglutaminase 2 (TG2) blockers preventing deamidation of gluten peptides and their efficient presentation to $CD4^+$ T cells (Paolella et al., 2022);
- inhibiting epithelial damage driven by IL-15 with anti-IL15 antibodies or opposing the outgrowth of malignant IELs in type II refractory CD;
- immunotherapy to restore gluten tolerance through stimulation-induced death of small intestinal epithelial cells and immune activation through the production of regulatory T cells (Cerf-Bensussan and Schuppan, 2021; Varma and Krishnareddy, 2022).

A promising new therapeutic approach is the first TG2 inhibitor in clinical trials, ZED1227, which is an oral selective inhibitor of TG2 (Büchold et al., 2022). In phase 1 clinical studies consumption of 500 mg ZED1227 for up to 8 days turned out to be safe. In phase 2, authors checked in remised patients with CD who were challenged with daily gluten intake - 3 mg of gluten - for 6 weeks, if exposure to ZED1227 prevents symptoms from recurring. The trial was a randomized, double-blind, placebo-controlled, dose-finding study. Authors found that the ZED1227 effectively attenuated gluten-induced intestinal mucosal injury (Schuppan et al., 2021).

TAK-101, a gliadin encapsulation in negatively charged poly (DL-lactide-glycolic acid) nanoparticles, is another promising approach. In a phase 2 study, 33 patients with CD underwent a 14-day gluten challenge to assess whether TAK-101 induces gluten-specific tolerance. The study found that the drug resulted in an 88% reduction in interferon-γ spot-forming units compared to the placebo (2.01 vs. 17.58, $p = .006$). Additionally, TAK-101 reduced changes in circulating $\alpha4\beta7+CD4^+$ (0.26 vs. 1.05, $p = .032$),

αEβ7+CD8$^+$ (0.69 vs. 3.64, $p = .003$), and γδ (0.15 vs. 1.59, $p = .010$) effector memory T cells. TAK-101 was well tolerated and prevented gluten-induced immune activation, so this immunotherapy shows potential for CD treatment and requires further clinical development (Kelly et al., 2021).

In addition, researchers focus on investigating modulators of tight junctions, known as zonula occludens, regulating intestinal permeability which is increased in CD patients resulting in the activation of immune response to indigestible gluten peptides. This process is mediated by a key tight junction modulator–zonulin. Production of zonulin is induced–mainly–by bacteria overgrowth and gluten that binds to receptor CXCR3 in erythrocytes (Fasano, 2020; Machado, 2023). On the other hand, zonuline activates tight junction relaxation, causing the delivery of gliadin peptides to lamina propria. The therapeutic approach targeting zonulin seems to be promising since intestinal permeability is theorized to be an initial promoting event in the etiologic of CD (Hoilat et al., 2022).

One of the zonulin inhibitors, that blocks its receptor and acts as an anti-zonulin receptor inhibitor, is larazotide acetate also known as AT-1001 - a novel, eight-amino acids peptide (Hoilat et al., 2022). Larazotide acetate rebuilds the disturbed tight junction complex, preventing the intestinal permeation of gliadin (Slifer et al., 2021).

Larazotide acetate in phase I and II studies was shown to be safe, well tolerated and to prevent worsening of gluten-induced symptom severity and to suppress serological markers. However, a placebo-controlled phase III study was terminated (Varma and Krishnareddy, 2022).

A meta-analysis of four trials, including a total of 626 patients, indicates that larazotide acetate is safe and more effective than placebo in alleviating gastrointestinal symptoms in patients with celiac disease who are challenged with gluten. However, it is considered more of a supplement to a gluten-free diet rather than a replacement for it (Hoilat et al., 2022).

Moreover, an important role in the degradation of intestinal villi in CD patients appears to be IL-15, which is an inflammation-stimulating cytokine. A study using the first anti-IL-15 monoclonal antibodies - AMG 714 - was conducted by Lähdeaho et al. on a group of 64 patients with CD (Lähdeaho et al., 2019). In a randomized, double-blind, placebo-controlled, parallel-group study, 150 mg and 300 mg of AMG 714 compared with placebo in adults with CD after controlled gluten provocation, there was no statistically significant difference in change in villous height to crypt depth ratio from baseline after 12 weeks of treatment. However, at the 300 mg dose, authors observed alleviation of some symptoms in response to gluten ingestion assessed by lower - than at the 150 mg and placebo dose - intraepithelial lymphocyte density, patient-reported outcomes, and diarrhea. The authors indicate that the study suggests that the inhibition of IL-15 is a viable strategy in the treatment of CD and point to the need for further studies on non-responsive to gluten-free diet CD (Lähdeaho et al., 2019).

Trials have been also conducted on antigen-specific immunotherapy. Nexvax2 is a therapeutic vaccine that contains three gluten peptides derived from wheat, barley, and rye, including HLA-DQ2-restricted epitopes commonly recognized by gluten-specific T-cells. However, studies have shown that the vaccine did not achieve the desired effect of reducing symptoms caused by gluten consumption and did not increase tolerance to gluten peptides (Goel et al., 2017).

Moreover, novel therapies include probiotic therapy that potentially may improve gut microbiota composition and maintain gut microbiota homeostasis, digest gluten peptides into small polypeptides, and limit the availability of immunogenic polypeptides to lamina propria (Krishnareddy, 2019; Varma and Krishnareddy, 2022). The potential benefits of probiotics in the treatment of celiac disease are presented in Figure 1.

Reviews of studies indicate that probiotics may improve gastrointestinal symptoms in patients with CD, moderate the immune response, and improve dysbiosis in patients with CD and autoimmune CD. However, high-quality clinical trials are needed to increase the certainty of the evidence (Seiler et al., 2020; Mozafarybazargany et al., 2023). The positive impact of probiotics on CD is primarily attributed to their ability to improve the tightness of the intestinal barrier. Moreover, studies have shown that bacteria from the *Lactiplantibacillus* and *Bifidobacterium* genera, which possess extensive peptidolytic and proteolytic activity, are particularly effective in breaking down gluten compared to other intestinal bacteria (Moawad et al., 2023).

In 2023 Khorzoghi et al. observed that 12-week treatment with a probiotic combination containing *Bifidobacterium and Lactiplantobacillus* species *and S. thermophilus* resulted in a reduction in the intensity of CD clinical symptoms - fatigue, muscle discomfort, bloating, and a gassy feeling - compared to placebo (Soheilian Khorzoghi et al., 2023).

However, it seems that probiotics are not seen as a promise for a quick cure, but rather as a supplement to alleviate the severity and symptoms (Kõiv and Tenson, 2021).

Moreover, endopeptidases of several *Lactobacillus* species–*L. ruminus, L. john donne, L. amylovorus, L. salivarius, L. alimentaris, L. brevis, L. sanfranciscenis and L. hilgardi*–can degrade gluten peptides when added to the starter culture for wheat bread production. This presents promising opportunities for the practical application of these strains in gluten-free food production.

In Table 4 we present ongoing and completed clinical trials concerning pharmaceutical treatment of CD.

Another proposed approach, currently at the experimental stage, is to bind gluten and prevent its further metabolism using poly (hydroxyethylmethacrylate-co-styrenesulfonate). This method has been shown to reduce the digestion of wheat gluten and barley hordein, as well as attenuate the immune response to gluten in food mixtures in rodents (Pinier et al., 2012). In contrast, Kaperchan et al. proposed a series of gluten peptides in which the proline residues were replaced by azidoprolines. These peptides bind to HLA-DQ2 with an affinity similar to that of the natural gluten peptide. Some of these peptides are non-immunogenic and block gluten-induced immune responses. Therefore, they could potentially be used to develop HLA-DQ2-blocking peptides (Kapoerchan et al., 2008).

Technolodzy próbują też wykorzystać możliwości modyfikacji genetycznej to reduce immunotoxic components of gluten (Ghazanfar et al., 2023; PubMed, 2024).

3 Conclusion

Celiac disease is an immune-mediated disorder influenced by genetic variants, with MHC variants explaining most of the

heritability of CD. In addition to genetic factors, external factors also play a role in increasing the risk of the disease.

Nutritional factors are one such external factor, however, while several links have been suggested between a Western-style diet and CD development, this area has not yet been fully investigated. It is recommended to avoid large amounts of gluten in the first month after gluten introduction, but there is no evidence to support the protective properties of breastfeeding or the timing of gluten introduction. The composition and function of gut microbiota have been linked to CD and common gastroenterological infections have been shown to increase the risk of developing CD. The type of delivery is not an independent factor in the development of CD or CD autoimmunity. What is interesting, it has been found that smokers have a significantly lower risk of developing CD compared to non-smokers.

Currently, the GFD is the only widely accepted treatment for CD, although there is ongoing research for novel therapies. The investigations focus on reducing immunogenic gluten peptides, blocking the immune response to gluten peptides, and immunotherapy to restore gluten tolerance. Novel therapies also include probiotic therapy and modulators of tight junctions that regulate intestinal permeability. It is thought that a cure for CD, which would offer an alternative to the gluten-free diet with its many restrictions, is becoming more attainable as our understanding of the causes and factors of CD increases. However, most of the available options appear to complement a gluten-free diet and offer the opportunity to improve gastrointestinal symptoms among patients, rather than being a direct substitute for a gluten-free diet.

4 Statement and declarations

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Author contributions

KS: Writing–original draft, Writing–review and editing. SH: Writing–original draft, Writing–review and editing. FT: Writing–original draft, Writing–review and editing. AR: Writing–original draft. AR: Writing–original draft. RS: Writing–review and editing. AD: Funding acquisition, Writing–review and editing. AG: Writing–review and editing. IK-K: Conceptualization, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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