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Novel Insights to Celiac Disease: A review article

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Abstract

Celiac disease is a chronic, systemic and autoimmune disorder of gastrointestinal track that involves approximately 1% of individuals of all ages throughout the world. The collaboration of environmental factor such as gluten proteins and genetic factors, notably HLA-DQ2 and/or HLA-DQ8 trigger the disease. Gluten-free diet is the simply and merely safe and proficient existing treatment. This article summarizes the latest trends in celiac disease.

Keywords: Celiac disease; Diagnosis; Epidemiology; Treatment

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Introduction

Celiac Disease (CD) is well defined as a complex, chronic, autoimmune and inflammatory gastrointestinal tract disorder caused by gluten intake, and insoluble prolamine polypeptides in wheat, rye, barley and closely-related grains, in genetically predisposed individuals (1-3). This contributes to villous atrophy of the small intestine and impedes with the absorption of vitamins including A, D, E, K, B12, B9 and iron (3, 4). Celiac disease is a multifactorial disease with potent genetic and environmental factors (5). It can be efficiently treated with a severe gluten-free diet; however, if it is not treated on time, it can lead to anemia, osteoporosis, growth failure, various autoimmune disorders, and malignancy (3, 6). CD affects 1% of the population and is one of the main prevalent gastrointestinal disorders occurring at any age with wide-range of symptoms (5, 6). In spite of advances in diagnosis, the majority of patients remain undiagnosed due to extra intestinal symptoms (6, 7). This review emphasizes on latest trends in epidemiology, genetic and environmental risk factors, clinical presentation, diagnosis, and treatment regarding the spectrum of celiac disease.

Epidemiology

The prevalence of CD is generally reported to be about 0.6 to 1.0% worldwide and about 1% in the United States. There are emerging data to propose it may really be increasing rate in some developed countries (8). The Saharawi people of Africa with the frequency of 5% for celiac disease have been reported to have the highest prevalence for this disease (3). A recent comprehensive study in Europe found great differences in CD occurrence showing the lowest prevalence rate (0.3%) in Germany and the highest in Finland (2.4%) (9). Many developing countries have shown an increasing frequency rate of celiac disease. In the northern part of India, CD disease is highly prevalent with around (1.04%) predominance. This disease is predominant (about 4.8 %) in the first-degree relatives of the patients (10-12). Genetic history is of great importance in the disease predisposition and it has been reported that the children are more at risk (7.2%) compared to their parents (1.8%) (10-12).

About 90% of celiac disease patients express HLA-DQ2 haplotype (DQA1 0501/DQB1 0201) and approximately 5% express HLA-DQ8 haplotype (DQA1 0301/DQB1 0302) (11, 13). Children under 5 with HLA haplotype DR3-DQ homozygote are high risk for celiac disease. In the Infants having the family risk of developing CD, the HLA-DQ2 haplotype affect the early gut microbiota composition which may be related to the intestinal dysbiosis and may assist in the disease risk determining (13, 14). Most patients are carriers of the HLA-DQ2/DQ8 genes but these genes also exist in around 40% of the general population, and only 2-5% grows CD. This show that the HLA-DQ genotype

is essential but not uniquely responsible for the expansion of the disease (10, 11).
Celiac disease has become so prevailing over the past 5 decades and diagnosis rate has also increased in the past 20 years. About 2 million Americans and 3.5 million European suffer from this disease; around 83% of whom are not diagnosed yet (6). An important awareness, exclusively in the United States, has been proved to be responsible for the improved diagnostic rates, but reliable epidemiological data present a true rise in incidence worldwide, and this rate doubles approximately every 20 years (8, 12). Environmental factors are also known to be responsible for such a fast increase among which, some may be more complicated, like higher wheat consumption and early-life infections but this theory is yet to be completely certain and clear (6, 11).
According to some American and European studies, incidence of CD is estimated to be 3 to 13 cases per 1000; the overall prevalence of CD is around 1% of the general population. Though according to the evidence, only 10% to 15% of this population (children and adults) have been detected and treated. Until the last decade CD was reported to be rare in Iran with the prevalence rate of 0.5% to 12% (3, 8, 15).
Developments in our understanding of the epidemiological data and disease spreading have been achieved through studying serological indicators (Table 1). Serum tissue transglutaminase (tTG) IgA antibody levels have been utilized widely as a high resolution screening tool (9, 16).

Table 1. Celiac disease and serologic indicators.

Serologic test	Sensitivity	Specificity	Notes
Anti-tTG IgA	98 (74-100)	97 (78-100)	Used for screening
Antiendomysium IgA	90 (75-96)	98 (91-100)	Highest specificity
DGP-IgG	(80.1-98.6)		Used in children aged <2 y
DGP-IgA	(80.7-95.1)		

DGP; Deamidation of Gliadin Peptides

Environmental factors

The role of environmental factors on risk of celiac disease

Age of gluten exposure
Many studies confirm that infant feeding in the first year of life is one of the environmental factors in celiac disease. The introduction of gluten into infant requires a long time and before starting it should be tested in this area (17).

Infectious agents
Infections are other environmental factors for celiac disease. For example, *H. pylori* infection is one of these factors. The risk of celiac for infants born by Caesarian is more than infants delivered vaginally. Other environmental factors such as vaccination, use of some medications like antibiotics, and also individual metabolism could increase the risk of developing celiac disease (18, 19).
Evidences show a difference between gut bacterial communities in treated and untreated celiac patients and also children and adults who suffer from the disease. Some infectious agents are attributed to CD development, among these pathogens, adenoviruses, Hepatitis C virus, Rotavirus and Enterovirus were expressed as case reports (19).

Genetic of celiac
Genetic susceptibility plays a critical role in CD and recently fairly large progress has been made in recognizing responsible genes for CD susceptibility.
Generally, two groups of loci are known to be associated with celiac disease.

1. HLA as a critical target gene
It is widely known that CD is firmly related to a particular HLA class II genes. These genes have been known as HLA-DQ2 and HLA-DQ8 which are placed on chromosome 6p21. The DQ2 and DQ8 are celiac-linked heterodimer proteins included alpha and beta chains. These chains have been encoded by particular variants of HLA-DQA1 and HLA-DQB1.
In the lamina propria, gluten peptides which are deamidated and negatively charged, attach to DQ2 and DQ8 complexes fixed on antigen-presenting cells (APCs) plasma membrane. Activated T-helper cells by identifying deamidated gluten peptides linked to DQ2 or DQ8, release cytokines such as interferon

gamma (IFN-γ), cause inflammatory response and finally villous damage and malabsorption. Following intestinal tissue inflammation, plasma cells produce antibodies including anti-endomysial, anti-gliadin and autoantibody against tTG (20).

2. Other biomarker loci

Although the HLA locus has been contributed to 25-40% of the genetic variation in CD, but these genes are not sufficient alone for causing the disease. Currently, 43 loci related to CD (Non-HLA loci) has been recognized by GWAS, that increase the disease risk for 15% (20, 21); the most of these loci are common SNPs located in regulatory regions, for example, two associated classes of variants in the 3′ UTR of the PTPRK gene, a TGF-beta target gene that is required in CD4+ T cell development (22). Also, exome sequencing studies have revealed protein-altrering SNPs in NCF2, MMEL1, SH2B3 and IRAK1(23). Biological effects of these SNPs on the celiac disease are still unidentified.

In addition, two large studies have shown that some of the CeD-associated SNPs intersect with transcription factors binding sites on genome. In the first research STAT1, PPARG, IRF1, GR, TP53, POU2F1, IRF9, and MEF2a have been reported by Maurano et al. (24) ; and in the second study, Farh et al. has presented STAT1, IRF4, SRF, STAT3, BATF, BCL11A, OCT2, and POU2F2 (25). An enormous regulatory non-coding RNAs including miRNA and lncRNA has been detected to be associated with CD. For instance, down-regulation of long noncoding RNA 13(lnc13) in inflamed intestinal biopsy samples of the celiac patients has been suggested by recent studies (26). Furthermore, there are some differences between gene expression profiles of celiac disease patients from children to adults (27).

Clinical presentation

Celiac disease is currently being recognized as a systemic disease that will have an effect on people of all ages, races and ethnic groups. Clinical signs of CD are very variable and consist of both gastrointestinal and non-gastrointestinal features. There are also some individuals with no symptoms who have positive CD serology and characteristic histologic alterations on small intestinal biopsy. These cases are identified mainly through screening the groups who are at amplified risk for CD (5, 10).

The symptoms include weight loss, iron deficiency anemia, aphthous ulcers, osteomalacia, dermatitis herpetiformis (a rash as a result of gluten-sensitivity), and gastrointestinal signs, as well as diarrhea and abdominal bloating. The identification of CD can be challenging because the clinical range of the disease varies, and some people demonstrate mild features (28). Others have signs and positive serological test results but do not initially have the distinctive histological features of mucosal hurt. If such individuals continue on a regular diet, most will finally demonstrate the mucosal changes found in CD over time. The precise definition of CD has resulted in much debate, because these alterations are different in clinical and laboratory discoveries (3).

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition describes CD as, an immune-mediated systemic disease caused by gluten and associated prolamines in genetically susceptible people which is determined by a variable combination of gluten-dependent appearances, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy (12, 13).

Celiac disease has some subgroups as follows: typical, atypical, latent, silent and potential CD. The typical CD is described by symptoms such as diarrhea, weight loss, steatorrhoea and hypoalbuminemia which are the result of enteropathy and consequent GI malabsorption (6, 10).

The “atypical” form does not include weight loss and diarrhea but the clinical expression can still involve the GI, liver or organs other than the GI skin, nervous system, bones, metabolism, and reproductive system. Oslo descriptions discourage the term “silent” CD because it is the same to asymptomatic CD (5).

In the forms below, the starting point of clinical findings which their symptoms are not enough to fall in the CD diagnostic procedure, are suggested to be categorized as “subclinical CD”.

The Oslo definitions shows the misunderstanding which may be caused by the term “latent” CD and discourage its use. They, instead suggest the term “potential” CD to be used for individuals without intestinal impairment who are in high risk for the disease due to the presence of CD autoantibodies (3).

Clinical appearance of celiac disease differs greatly according to age group. Pediatric patients of CD are more often found with typical signs than adult patients. A research has publicized that diarrhea is the presenting disease features in 74% of children compared with 58.7% of adolescent/adults. More than 50% of adult patients with celiac disease demonstrate atypical signs. Other symptoms of CD are chronic fatigue, aphthous stomatitis, short stature and reduced bone mineral density (3, 5, 9). Individuals suffering from CD also have some nutritional shortages such as iron, vitamin D, folate, vitamin B12, vitamin B6 and zinc. Iron deficiency is reported in 50 percent of recently diagnosed adults and can be a screening marker for CD (29).

Celiac disease patients with anemia are more expected to have severe villous atrophy and low bone

mass density compared with those diagnosed with the symptoms of diarrhea. Uncommon symptoms of CD are dermatitis herpetiformis, gluten ataxia and celiac crisis; a rare life-threatening syndrome in children (14). Peripheral neuropathy, seizure disorders, ataxia and impaired cognitive function are among the neurological disorders which are less frequent in adults with CD than in children. Hypertransaminasemia is a common subclinical discovery but severe liver disease can hardly be associated with CD (5). Though celiac disease is fundamentally an inflammatory disorder of the small intestine and gastrointestinal symptoms are protuberant, they may, in many cases, be minor or absent, whereas the signs and symptoms outward of the intestinal tract can be major (9, 10).

An alteration of performance symptoms from gastrointestinal (still called typical) to extra intestinal (atypical) has been observed in many geographic regions during the past decades and looks to be a common trend, along with a larger part of patients recognized as having potential CD and a move toward older ages at appearance. At first thought only children are affected by demonstrating diarrhea and presenting a malabsorptive picture (3,9,12,13,38,28)

CD was later verified to affect adults as well, happening at any age. Table 2 reviews the main symptoms of CD performance in its gastrointestinal and extra intestinal or atypical forms (3, 12, 14, 30).

Table 2. Gastrointestinal and extraintestinal presentations of celiac disease (31-34).

Gastrointestinal presentation	***Diarrhea***	
	Anorexia	
	Vomiting	
	Failure to thrive or weight loss	
	Abdominal pain, bloating	
	Constipation	
Extraintestinal presentation	***Constitutional***	Fatigue
	Hematologic	Iron deficiency anemia
	Dermatologic	Dermatologic herpetiformis
	Oral	Dental enamel hypoplasia
		Aphthous ulcers
	Musculoskeletal	Arthritis
		Arthralgia
		Ostepenia or osteoporosis
		Fractures
	Liver	Mildly elevated AST, ALT levels
	Endocrinology	Short stature
		Delayed puberty
		Unexplained infertility (in women)
		Miscarriage
	Neurologic	Cerebellar ataxia
		Recurring headaches
		Peripheral neuropathy
		Seizures
	Psychiatric disorders	Anxiety, Pain attacks, depression

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

The frequency of symptoms in children with extraintestinal expressions, becomes more widespread as the age increases. As revealed, because CD first and foremost involves the gastrointestinaltract, the clinical presentation is stilldescribed as typical affects gastrointestinal signs (3, 8, 30). The numerous interactions of symptoms, serological markers, and duodenal pathologic disorders have encouraged the CD arrangements currently in use, which are abridged in Table 3 (5, 16).

Table 3. Categorization of celiac disease (33-35).

Type	Age (Most Often Affected)	Symptoms	Anti-tTG IgA and Antiendomysium IgA serological Markers	Pathologic Type
Typical	Toddler, young child	Abdominal pain, distention, diarrhea, vomiting, anorexia, constipation	+	2-3
Atypical	Older child, adult	Mostly extraintestinal	+	1-3
Silent	Adult	None	+	1-3
Potential	Any age	None, gastrointestinal, extraintestinal	+	0-1
Latent	Adult	None, gastrointestinal, extraintestinal	+/-	0-1, History of gluten dependent enteropathy

Advances in diagnosis

Due to extensive clinical spectrum of CD, precise histological and serological testing is crucial for accurate diagnosis. Therefore, lifelong commitment to a gluten-free diet in related patients will terminate.

Histopathological analysis

The mucosal injury in celiac disease expands gradually to severe atrophy. The lesion is usually scored by grouped classification. But this grouping has manifested weak reproducibility, particularly in borderline cases (36-38) and interpretation of samples may differ considerably among pathologists (37). One more exact method is advance morphometry in which the proportion of villous height-crypt depth and intraepithelial lymphocyte count are measured separately. In this method reproducibility and reliability are remarkably outstanding (38).

Serological and other biomarker candidates

Serological testing is considered as the initial stage in the diagnostic algorithm of celiac disease. The primary tests measure antibodies against reticulin (ARA), endomysium (EmA) and gliadin (AGA) (39). These tests are according to indirect immunofluorescence and laborious. The identification of transglutaminase type 2 (TG2) as the auto-antigen is targeted by ARA and EmA facilitated more objective assays and was the preferred serological assays in CD (40). The disadvantages with this test are lower specificity in comparison with EmA and showing low positive TG2 antibody values in individuals with other autoimmune conditions (41). In line with this condition, serum antibodies from celiac patients have been manifested torecognize a specific conformational epitope in TG2 which is not recognized by TG2 antibodies derived from individuals with other autoimmune diseases (42). The next stage in celiac pathogenesis is the TG2-catalyzed deamidation of gliadin peptides (DGP) (43). Some studies showed that this test have higher sensitivity than TG2 antibodies in detecting CD in early childhood (44). Combination tests that measure antibodies against both DGP and TG2 simultaneously show promising accuracy (45).

Besides, there are also a few commercial rapid fingertip tests for celiac disease. The first point of care tests has 97% sensitivity and specificity for uncured celiac disease and it is based on the liberation of internal TG2 from RBC by hemolysis (46). Its drawback is false negative result in the presence of selective IgA deficiency. Another POCT(Point of Care Testing) is based on the measurement of DGP combination antibodies of IgA and IgG class for more accuracy (47). This test is recommended to be performed by health care professionals (47).

One new biomarker being measured is the intestinal fatty acid binding protein (IFABP). IFABP is present in the cytoplasm of the intestinal epithelial cells and is rapidly released into blood by mucosal damage. High serum levels of IFABP may be also found in the Crohn's disease (48).

The next new biomarker is based on measuring the CYP3A4-catalyzed simvastatin metabolism (49). Cytochrome P450 3A4 (CYP3A4) is highly expressed in the epithelial cells on the villi and its expression is reduced in the villous atrophy condition (50). Therefore, celiac patients could show high concentrations of orally administered simvastatin in their circulation (49).

Recently a novel candidate biomarker based on the visualization of gluten reactive CD4+ T-cells in the blood has been established (51). This biomarker revealed that gut-homing gliadin-specific T-cells

were notably frequent in celiac patients than controls. The last but not least novel diagnostic biomarker for CD is the combination of the intestinal microbiota and particular microRNAs. However, studies failed to show the precise miRNA interfered in CD and more studies need to implement this strategy (52, 53).

Treatment
The Celiac disease results in damaging the small intestine mucus that leads to immune response against cereal proteins. Celiac therapy has various views that are mentioned below.

Approach 1: reducing the exposure to gluten
There are many discusses in processing of deformation of gluten: Cooking method can deform the protein content or it can reduce the gluten effect.

Approach 2: proteolysis of gluten peptides
Several strategy applied to degradation of celiac associated peptides through bacterial, fungal or cereal protease or the combination of them. This attractive technology can decrease or even remove the injurious prolamins from cereal grains.(19, 54).

Approach 3: inhibiting HLA-DQ2 to bind to the immunological peptides
Celiac is a genetic disease which almost has HLA-DQ2 and DQ8 haplotypes. Blocking HLA molecules by gliadin antagonist peptides could prevent from stimulation of cascade.

Approach 4: blocking of transglutamase 2
Effective approach for celiac therapy is selective blockade of TG 2 and inhibition of the deamidation process. Some studies investigate various competitive, reversible and irreversible TG2 inhibitors, which can be effective in neurologic disorders, and several cancers. (19, 55, 56).

Approach 5: modulation of inflammation
IBD and RA is kind of autoimmune disorders for which cytokine therapy is utilized to regulate cytokines.

TNF-α and anti-interferon-gamma
Increased Matrix Metalloproteinase (MMPs) levels result in stimulation of CD4+ T cell and IFN-γ secretion. So by inhibiting of cytokines the activation of MMPs can be prevented (57).

Anti-Interleukin 15
A recent study showed that responsive and refractory celiac disease could be treated by IL-15 targeting (58).

Integrin α4β7 and MADCAM1
During inflammation migration of lymphocyte and location of mucosal adhesion all adherence molecules in vascular endothelial cells are required. So some monoclonal antibodies can be beneficial (57).

Approach 6: gluten-sequestering polymer
A new strategy for reducing the immunotoxic effects of gluten relies on oral polymeric resin consumption, such poly (hydroxyethyl methacrylate-*co*-styrene sulfonate). This polymeric particle can bind to gluten proteins in simulated small intestine and reduced the mucosal toxicity induced by gliadin. This method can be replaced by complete treatment in minimal gluten exposure (59).

Conclusion
Celiac disease, a chronic and immune-mediated disorder in small intestine, develops as a response to gluten consumption in individuals with genetic susceptibility, as HLA-DQ2 or HLA-DQ8 positive individuals. Normally celiac patients have a long period of manifestations; thus has a delayed duration of diagnosis. The diagnosis is commonly based on serologic assays, biopsy of duodenal tissue, and monitoring responses to a GFD. The first step of treatment for celiac patients is GFD, avoidance of foods containing wheat, barley, and rye. Celiac disease is related to a raised risk of small bowel malignancies, unconventional signs such as anemia and osteoporosis. Furthermore, early diagnosis is notable because GFD prescription may preventthese problems.
To the best of our knowledge, several factors affect the prevalence of celiac disease. Although, revolutionary progression occurred in different areas of diagnosis and treatment in recent years, it seems that there is still a need for further the investigations in this field to obtain more definitive results.

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Author Contributions
Authors have the same contribution in this work.

Conflict of Interest
There is no conflict of interest.

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