

## REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

# Celiac disease – a comprehensive review

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## SUMMARY

Celiac disease is a multisystemic autoimmune disease induced by gluten in wheat, rye, and barley. It is characterized by polygenic predisposition, prevailing prevalence in members of the white population (1%), especially in close relatives (5–15%), very heterogeneous expression and frequent association with other autoimmune diseases (3–10%), as well as selective deficiency of IgA and Down, Turner, and Williams syndromes. The basis of the disease and the key finding in its diagnostics is gluten-sensitive enteropathy, i.e., non-specific inflammation of the small intestinal mucosa which resolves by gluten-free diet. In addition to enteropathy, whether symptomatic or asymptomatic, the disease is also characterized by various extraintestinal manifestations, and even very serious complications. Therapy is based on a lifelong gluten-free diet, so that the disorder, if diagnosed in time and treated consistently, has an excellent prognosis.

**Keywords:** celiac disease; pathogenesis; clinical forms; diagnostics

## INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease induced by gluten of wheat, rye, and barley in genetically predisposed individuals [1, 2, 3]. It occurs in all population groups, and most often in members of the white race (1:100) [3–6]. As to other autoimmune diseases, it is more frequent in people of the female versus male sex (1.5:1 to 2:1) [7, 8, 9]. It is particularly common in first- and second-degree relatives (5–15%) [10]. With a slightly lower frequency (3–10%) it occurs in patients with other autoimmune diseases, selective IgA deficiency and Down, Turner, and Williams syndromes [1, 3, 6, 11–16].

The main feature of the disease and the basis of its diagnosis is non-specific inflammation of the small intestinal mucosa that resolves on a gluten-free diet [1, 3, 6, 17, 18]. In addition to damage of the small intestinal mucosa, which can be symptomatic or asymptomatic, the disease is also characterized by numerous extraintestinal manifestations and in cases diagnosed too late or treated inconsistently, permanent consequences and sometimes very serious complications [3, 4, 9, 19–25].

## PATHOGENESIS

The pathogenetic basis of CD is polygenic predisposition and exposure to gluten containing cereals [2, 3, 26]. Gluten is a complex water

insoluble protein that comprises about 75–80% of the total proteins of wheat, rye, and barley flour [27]. It is characterized by a high content of glutamine and proline-rich polypeptide residues resistant to efficient gastrointestinal proteolysis, which, after passing into the submucosa of the small intestine, lead to inadequate immune reactions in genetically predisposed individuals [2, 26, 28]. In addition to gluten, gastrointestinal infections, alteration of the intestinal microbiota, some medications, and other factors play an important role in the occurrence of the disease, which explains its incomplete prevalence in monozygotic twins (83–86%) [3, 10, 11, 17, 29, 30]. Longer breastfeeding and continuation of breastfeeding after gluten introduction delay the onset of CD [31]. Evidence of the prevalent role of polygenic inheritance in the occurrence of the disease, its highly variable frequency in different populations, as well as its high presence in identical twins and first-degree relatives (~10%) [10, 11, 13, 32]. The human leukocyte antigens (HLA) class II genes *DQ2* and *DQ8* (6p21.32), which are present in 98–99% of patients, play a central role in the hereditary predisposition to the disease [6, 10, 26, 33]. HLA *DQ2* molecules are registered in 85–95% of patients, and HLA *DQ8* in 5–15% [34, 35, 36]. In addition, HLA *DQ2/DQ2* homozygotes have a particularly high risk of developing CD, as well as its earlier onset and more severe form of manifestation, including more frequent occurrence of complications, such as “celiac crisis,” refractory type of the disease

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and enteropathy-associated T-cell lymphoma [3, 9, 29, 37]. However, apart from HLA *DQ2* or *DQ8* genes and exposure to gluten, the presence of one or more of the approximately 40 non-HLA genes (e.g., *TAGAP*, *IL18R1*, *RGS21*, *PLEK*, and *CCR9*) that have been verified so far is indispensable for the appearance disease [3, 11, 13, 26].

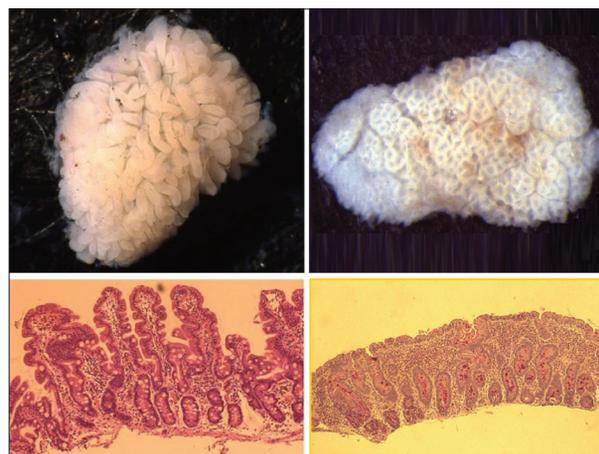
The importance of *DQ2* and *DQ8* glycoproteins present on antigen-presenting cells (dendritic cells and macrophages) in the pathogenesis of CD is reflected in their ability to activate intestinal CD4+ T-cells after binding with deaminated gluten polypeptide hydrolysates [2, 3, 11]. The deamidation of gluten hydrolysates, which increases the affinity of their binding to HLA *DQ2* and *DQ8* molecules, is performed by tissue transglutaminase (tTG). Proinflammatory cytokines released by activated CD4+ T-cells parallel activate intraepithelial cytotoxic CD8+ T-cells which lead to enterocyte apoptosis and infiltrative or infiltrative-destructive inflammation of the small intestine mucosa and the differentiation of B lymphocytes into plasma cells and the production of antibodies against gluten peptides and autoantibodies to endomysium (EMA) and tTG [10, 26].

## ENTEROPATHY

Enteropathy (morphological damage to the mucosa of the small intestine) is most pronounced in the duodenum and the proximal part of the jejunum and progressively decreases towards the ileum [38]. In some cases, however, evident mucosal lesions may be present only in the duodenal bulb [1, 6, 17]. According to the modified Marsh criteria, inflammation of the small intestine mucosa is classified into three basic forms: infiltrative (I), infiltrative-hyperplastic (II), and destructive (III) [39]. In the first form of mucosal damage, there is an increased number of intraepithelial lymphocytes with  $\gamma/\delta$  receptor properties, as well as lympho-plasmocytic infiltration of the stroma, while the height of the intestinal villi and the depth of the crypts remain preserved. In the second type of damage, in addition to more pronounced infiltrative changes, there is hyperplasia of the crypts, while in the third, with additional accentuated infiltration and hyperplasia of the crypts, shortening and/or loss of villi occurs. According to the degree of mucosal damage, destructive enteropathy is further classified into partial (IIIa), subtotal (IIIb), and total (IIIc) (Figure 1). Apart from that, a fourth form of damage is also possible, which is characterized by complete atrophy of the villi, but without crypt hyperplasia and typical signs of mucosal inflammation.

## CLINICAL FORMS OF THE DISEASE

Observed from the aspect of manifestation, there are two basic clinical forms of CD: symptomatic and asymptomatic (subclinical) [1, 2, 17]. Within the framework of the symptomatic disease, forms with classic and non-classical clinical presentation are distinguished [1, 2, 17]. The classical



**Figure 1.** Stereomicroscopic and pathohistological appearance of the normal small intestinal mucosa (left) and in the state of the most severe damage (Marsh IIIc) (right); the right stereomicroscopic image shows a lack of intestinal villi with crypt hyperplasia with pronounced lympho-plasmocytic infiltration of the lamina propria (original recordings were made by the authors)



**Figure 2.** A two-year-old boy with the classic form of celiac disease; on the left and in the middle in the diagnostic phase, and on the right after 12 months of a gluten-free diet and the first two weeks of lactose restriction; the images in the diagnostic phase, along with the typical clinical aspect, show hypoproteinemic edema on the lower extremities, conspicuous loss of muscle and fat tissue in the gluteal region ("tobacco bag phenomenon") and perianal erythema as a consequence of secondary lactose intolerance (original recordings were made by the authors with parental permission and consent)

form of the disease is characterized by chronic diarrhea followed by malabsorption and secondary malnutrition, while the clinical picture of the non-classical disease is dominated by extraintestinal manifestations [1, 2, 17, 22, 23]. The classic form of the disease is most often seen in infants and young children, and the non-classical in later ages and in adults [11, 17, 23]. In the symptomatic form of the disease, along with evident enteropathy, autoantibodies to tissue transglutaminase (AtTG) and EMA, as well as the HLA *DQ2* and/or *DQ8* genotype, are almost regularly registered [1, 2, 12, 33, 35]. However, despite the presence of all these indicators, in most cases, CD remains unmanifest for a long time, and this form of the disease is called subclinical ("silent CD") [1, 2]. In addition, potential CD has an asymptomatic character, which differs from the

previous one in the normal appearance of the small intestine mucosa [1, 2, 33]. In a significant number of patients with potential CD, enteropathy is also registered later [1].

In youngest children aged 9–36 months, CD almost regularly occurs in the clinical classic form [9, 17]. It is characterized by a relatively short period after the introduction of gluten into the menu, a gradual onset and a progressive course manifested by chronic diarrhea, anorexia, occasional vomiting, abdominal distension, apathy and irritability [17]. As a consequence of insufficient intake and malabsorption of nutrients, global malnutrition occurs, accompanied by sideropenic anemia, loss of fat tissue and reduction of bone and muscle mass (Figure 2) [40, 41]. In the most severe cases, secondary lactose intolerance, isolated hypertransaminasemia (“celiac hepatitis”), and sometimes the appearance of hypoproteinemic edema is registered [20, 41]. Within the first 6–9 months after birth, the disease usually has a rapid and severe clinical course. In rare cases, the so-called “celiac crisis” characterized by total gastrointestinal insufficiency followed by severe dehydration, metabolic acidosis, meteorism, drastic weight loss and hypoproteinemic edema [9].

The onset and course of the disease in preschool children is predominantly non-classical (atypical) [17]. Compared to earlier age, gastrointestinal disturbances are less often present or absent. Recurrent abdominal pain and constipation, sometimes diarrhea, and often sideropenic anemia, poor appetite, malnutrition, stagnation in longitudinal growth and a change in the child’s personality are encountered.

In the symptomatology of the disease in later childhood and adolescence mono or oligosymptomatic extraintestinal manifestations dominate [17]. In addition to the manifestations seen in preschool age, there are others, such as maturation delay, enamel hypoplasia, recurrent aphthous stomatitis, chronic malaise, dermatitis herpetiformis, osteopenia, arthralgia, myalgia, cerebellar ataxia, polyneuropathy, epilepsy and others [3, 6, 17, 22, 42].

The most frequent symptoms of CD in adulthood are: anemia, chronic fatigue, weight loss, recurrent abdominal pain, bloating, flatulence, constipation, mouth ulcer, headaches, depression, and osteopenia or osteoporosis [19, 43, 44]. In addition, women have an increased risk for infertility, miscarriage, and early menopause [19].

In about 1–1.5% of total cases of CD, mostly in adulthood, refractory CD (RCD) occurs [3, 11]. This type of disease is characterized by malabsorption, weight loss, as well as persistent villous atrophy and after a year a strict gluten-free diet [2, 6]. RCD may be categorized in two subtypes – type 1, where the phenotype of the intraepithelial lymphocyte population is normal (CD3+CD8+); type 2, where it is abnormal [3, 11]. RCD, particularly type 2, is associated with serious complications, such as ulcerative jejunitis and enteropathy-associated T-cell lymphoma [3, 19, 45].

Although the classic form of the disease is the most often described and best studied entity, today it is known that it represents only the “tip of the celiac iceberg” and that the largest number of patients, both children and adults,

are those with a non-classical and asymptomatic form of the disease [17].

## ASSOCIATION WITH OTHER DISEASES

In addition to the high frequency among close relatives of the patient, especially those of the first degree, CD is characterized by a high association (3–10%) with other autoimmune diseases, such as diabetes mellitus type I, autoimmune thyroiditis, Addison’s disease, rheumatoid arthritis, juvenile idiopathic arthritis, Sjögren’s syndrome, systemic lupus erythematosus, autoimmune liver diseases, IgA nephropathy, myasthenia gravis, psoriasis, dilated cardiomyopathy, autoimmune pericarditis, and others [1, 6, 11–15]. Approximately the same prevalence of the disease occurs in selective IgA deficiency, as well as in Down, Turner, and Williams syndrome [1, 3, 13]. Therefore, serological screening for CD is indicated in first degree relatives, as well as in the mentioned autoimmune and chromosomal patients [3, 6, 16, 17, 33, 46].

## DIAGNOSIS

The diagnosis of CD, except in cases explained in the following text, is based on an enterobiopsy with pathohistological examination of the small intestine mucosa [1, 3, 6, 17, 18]. Biopsies are obtained from the duodenum via an upper gastrointestinal endoscopy, whereby one or two from the bulb and  $\geq 4$  from the distal duodenum [1, 3, 17]. Such a diagnostic approach is necessary because the histologic changes may be patchy in distribution and confined to the duodenal bulb. In order for the conditions for pathohistological analysis to be adequate, the correct orientation of the biopsies is required [47, 48].

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), as part of the recommendations published in 2012, unlike earlier ones, considers that enterobiopsy is not necessary in patients with symptoms and/or signs consistent with CD, and in addition, they have an IgA titer antibodies to tissue transglutaminase (AtTG-IgA)  $\geq 10$  times above the upper reference value, positive anti-endomysial antibodies of the same class (EMA-IgA) and “celiac HLA” (*DQ2* and/or *DQ8*) [1]. The clinical recovery of the patient and the disappearance of AtTG are part of the confirmation of the disease, i.e., the justification for the introduction of a gluten-free diet without a previous enterobiopsy. This attitude in the diagnosis of CD is based not only on the high sensitivity and specificity of AtTG-IgA as a serological marker of the disease ( $> 95\%$ ), but also on the highly significant correlation of their titer with the degree of damage to the mucosa of the small intestine, as well as the almost inevitable correlation ( $> 98\%$ ) presence of HLA *DQ2* and/or *DQ8*. An additional difference compared to the previous position is that even in children under two years with an exact diagnosis of CD, provocation of gluten tolerance with pathohistological analysis of the small intestine mucosa is not required. However, in patients in

whom a gluten-free diet was introduced without a previous enterobiopsy, as well as in cases where the morphological damage of the mucosa was not typical or the samples were inadequate for a reliable interpretation, the final confirmation or exclusion of CD is based on the enterobiopsy and pathohistological findings during the provocation of gluten tolerance. Because it can endanger the quality of permanent teeth, this procedure is not recommended before the age of six, and because of the side effects on the child's growth and development during puberty.

ESPGHAN, as part of the additional modification of the criteria for the diagnosis of CD, published in January 2020, does not consider enterobiopsy with pathohistological analysis of small intestine mucosa samples necessary even in asymptomatic patients with a serum level of AtTG-IgA class  $\geq 10$  times above the upper reference level values and positive EMA-IgA in a second serum sample [33]. Also, bearing in mind the almost absolute association of CD and HLA *DQ2* and/or *DQ8* in these patients, as well as in those whose diagnosis was established by enterobiopsy, testing in this sense is not necessary. However, in all other cases, the diagnosis of CD requires strict adherence to the 2012 criteria. It is additionally recommended that, as part of the initial serological screening for CD, with prior verification of normal serum IgA for age, AtTG-IgA should be used, and not EMA and antibodies to deamidated gliadin peptide (AtDGP). However, if it is a suspected patient with IgA deficiency, tests based on IgG class antibodies (AtDGP, EMA or AtTG) should be used for this purpose. If there is a discrepancy between the level of AtTG-IgA and the pathohistological findings, it is necessary to re-evaluate the appearance of the biopsy or consult another pathologist. Patients with elevated serum levels of AtTG-IgA and EMA-IgA in whom normal or minimally damaged mucosa of the small intestine (Marsh 0/I) was registered, require strict monitoring.

Except in the mentioned exceptions, serological tests for CD have no diagnostic value [1, 6]. Hence, they are primarily used in the detection of asymptomatic and non-classical forms of the disease and in the assessment of the consistency of the elimination diet in patients in whom it has been established [1]. When interpreting serological screening, it should be borne in mind that it can be positive even without the characteristic damage of the small intestinal mucosa, which is seen in other autoimmune diseases and other pathological conditions [1]. Contrary to this, due to the immunological immaturity of children under two years, AtTG may be negative despite evident enteropathy [6, 17]. For this reason, when screening children under two years of age for CD, the IgA tTG test should be combined with AtDGP (IgA and IgG) [6, 17]. In the last ten years in the detection of CD, as well as gluten-free diet monitoring, the tTG-based commercial rapid whole blood test is widely used, which is less invasive, more practical and cheaper than the serological test [49].

The update recommendations of the American College of Gastroenterology (ACG) on the diagnosis of CD in children and adults published this year do not differ from the current ESPGHAN recommendations [6, 33]. The American Gastroenterological Association also agrees with

the ESPGHAN and ACG guidelines in the diagnosis of CD in children, with the fact that in adults, for purposes of differential diagnosis, esophagogastroduodenoscopy with duodenal biopsy can also be performed [18]. However, the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition in its 2016 criteria for the diagnosis of CD includes endoscopic enterobiopsy as a mandatory [17]. This attitude is based on the fact that without an endoscopic diagnostic approach, comorbid conditions with CD, such as peptic and eosinophilic esophagitis or *Helicobacter pylori* gastritis, can be overlooked. The European Society for the Study of CD also advocates the necessity of enterobiopsy in the diagnosis of CD in adults [3].

## THERAPY

Patients with CD should adhere to a gluten free diet for life [1, 3, 6, 17, 18]. Most of them with a symptomatic form of the disease, especially the classical one, during the initial phase of treatment require the correction of micronutrient deficits, primarily iron and folate, and sometimes temporary restriction of lactose [6, 41]. In patients with "celiac crisis," in addition to the correction of hydroelectrolyte and acid-base imbalance and removal of edema, semi-elemental and/or parenteral nutrition is applied, and sometimes short-term glucocorticoid therapy [3, 9]. RCD therapy also requires parenteral nutrition and immunosuppressive therapy containing steroids, azathioprine, 6-mercaptopurine, and methotrexate, whereas RCD2 therapy is based on additional medications, including cyclosporine and chemotherapy such as cladribine and fludarabine associated with anti-CD52 monoclonal antibodies (alemtuzumab) [3, 11, 50]. RCD1 usually responds to a gluten-free diet, nutritional support, and immunosuppressive medications, while the therapeutic response in RCD2 is incomplete and, accordingly, prognosis is often poor [6, 45].

## PROGNOSIS

The prognosis of timely recognized and adequately treated CD is excellent [11, 39]. Delayed recognition of the disease or non-compliance with the elimination diet, however, can lead to serious consequences, including serious complications, both during the growth and development, and those that manifest in adulthood, such as enteropathy-associated T-cell lymphoma, small bowel adenocarcinoma, osteoporosis, miscarriages, infertility, and others [3, 9, 11, 19, 21, 23, 25].

## CONCLUSION

CD represents a polygenically determined autoimmune disorder induced by gluten of wheat, barley, and rye. It primarily occurs in Caucasians, and particularly often in close relatives of the diseased, as well as in patients with other autoimmune diseases, selective IgA deficit, and Down, Turner,

and Williams syndrome. The basis of the disease and the key finding in its diagnostics are formed by the non-specific inflammation of the small intestinal mucosa that resolves by gluten-free diet. Beside enteropathy, either symptomatic or asymptomatic, the disease is also characterized by various extraintestinal manifestations, and in neglected cases, serious complications. The therapy is based on lifelong gluten-free diet, and this disorder, if timely diagnosed and adequately treated, has an outstanding prognosis.

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## Целијачна болест – свеобухватан преглед

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### САЖЕТАК

Целијачна болест је мултисистемско аутоимунско обољење индуковано глутеном пшенице, ражи и јечма. Карактерише је полигенска предиспозиција, преовлађујућа преваленца код припадника беле популације (1%), посебно код блиских сродника (5–15%), веома хетерогена експресија и честа удруженост са другим аутоимунским болестима (3–10%), као и селективним дефицитом ИгА и Дауновим, Тарнеровим и Вилијамсовим синдромом. Основу болести и кључни налаз у њеној дијагностици чини ентеропатија осетљива на глутен,

тј. неспецифично запаљење слузокоже танког црева које се повлачи на дијети без глутена. Поред ентеропатије, било симптоматске или асимптоматске, болест карактеришу и различите екстраинтестиналне манифестације, па и веома озбиљне компликације. Терапија се заснива на доживотној дијети без глутена, тако да поремећај, ако се благовремено дијагностикује и доследно лечи, има одличну прогнозу.

**Кључне речи:** целијачна болест; патогенеза; клинички облици; дијагностика