

CELIAC DISEASE – ASSOCIATION WITH AND IMPACT ON DIABETES MELLITUS

Spomenka Ljubić, Željko Metelko

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SUMMARY

The main culprit for celiac disease (CD) is intolerance to gliadin, a fraction of gluten. Ingestion of gluten causes chronic inflammatory reaction in the upper small intestine leading to malabsorption. The onset of celiac disease together with type 1 diabetes or autoimmune polyendocrine syndrome affects glycemic control, and more precisely the development of hypoglycemia. These diseases share a similar genotype. The only treatment is a gluten-free diet. Failure to implement a strict diet may result in two major complications, osteoporosis and malignancy. ADA recommendation is that persons with type 1 diabetes and symptoms pointing to CD be screened for CD-associated transglutaminase and endomysial autoantibodies.

Corresponding author: Spomenka Ljubić, MD, Vuk Vrhovac University Clinic, Dugi dol 4a, HR-10000, Zagreb, Croatia
E-mail: spomenka.ljubic@idb.hr

INTRODUCTION

Celiac disease (CD) is a gastrointestinal disease accompanied by inflammation. It is more common than was previously thought (1). The disease is genetically determined, but also develops in interaction with environmental factors. CD can develop in both children and adults (2). Today, there are reliable serologic tests in the diagnosis of CD in people with gastrointestinal symptoms or symptoms related to malabsorption, such as anemia and steatorrhea. In the United States, more than 60,000 people are diagnosed annually with CD (3). Several serologic screening studies performed in Europe, South America and USA have shown that approximately 0.5%-1% of these populations may have undiagnosed CD (4). It is considered at present that CD and type 1 diabetes have a similar genetic background, and that CD is the most common genetically predetermined condition in humans, with a prevalence of 0.5%-1% in the tested population (5). Symptoms of CD attenuate during a period of starvation, as has been observed in children during World War II (6).

PATHOGENESIS

Ingestion of gliadin, found in food such as wheat, rye and barley, causes inflammation in susceptible persons. The inflammation can result in mucosal damage, primarily in the upper small intestine and consequent malabsorption of valuable nutrients (3). The gliadin fraction of gluten causes an abnormal T cell-mediated immune response, followed by inflammatory injury in the small intestine (6). Genetic markers on chromosome 6, HLA (human leukocyte antigen)-DQ2 and HLA-DQ8 are very frequent in these persons. T-cells, together with HLA-DQ2 and HLA-DQ8, stimulate the production of cytokines by stimulating plasma cells, the consequence of which is a further production of antibodies to gliadin, tissue transglutaminase and endomysium (7). The predisposing genotypes HLA-DQ2 and HLA-DQ8 have been found in approximately 98% of patients. The risk of CD is also higher in persons with first-degree relatives with CD (5). Genetic factors, however, do not explain the development of CD because the disease is concordant in only 60% to 70% of identical twins (8).

CLINICAL MANIFESTATIONS

Celiac disease presents most commonly in either childhood or third or fourth decade of life, with twice as many females diagnosed in adulthood (4). Important symptoms of CD include anemia, arthralgia, fatigue, infertility, weight loss, and especially gastrointestinal symptoms such as abdominal pain, anorexia, bloating, constipation and diarrhea (3,6). In children, clinical picture is more typical: they can suffer from abdominal distension, diarrhea, edema, impaired growth and vomiting. Symptoms could be divided into those caused by intestinal inflammation and others caused mainly by malabsorption (8). The onset of CD is connected with the presence of cereals in diet (6). In severe cases of CD, pubertal delay, anemia, iron, folate, calcium and vitamin D deficiency can also be present, as can elevated transaminase level (5).

A severe form of CD is refractory sprue, a symptomatic severe enteritis. Such patients are at a high risk of enteropathy-associated T-cell lymphoma and they need to be treated with corticosteroids and immunosuppressants (6). Nowadays, the proportion of patients with CD presenting with gastrointestinal manifestations is decreasing (5). The widely used serologic tests are the reason that more “mild” and asymptomatic cases of CD are also diagnosed at a later age, and this trend is expected to continue in the future (6).

ASSOCIATED CONDITIONS

The most common cutaneous manifestation of CD is dermatitis herpetiformis, present in approximately 25% of CD patients, while 90% of patients with dermatitis herpetiformis also suffer from CD (2). Longer exposure to gluten can result in a higher incidence of autoimmune hepatitis, autoimmune thyroid disease, connective tissue disease (Sjögren syndrome, rheumatoid arthritis), Addison’s disease and type 1 diabetes mellitus (2). About 15%-30% of patients with type 1 diabetes also have autoimmune thyroid disease, 4%-9% have CD and 0.5% Addison’s disease, whereas approximately 5%-10% of patients with type 1 diabetes are found to be positive for endomysial and transglutaminase autoantibodies (9). CD, together with type 1 diabetes, can also be part of the autoimmune polyendocrine syndrome II (APS II). This might be due to CD and other disorders sharing the same autoimmune mechanism or gene. It is possible that chronic lymphocyte stimulation in CD acts as a trigger for other autoimmune diseases (10). Untreated patients suffer from more serious autoimmune diseases, probably because the risk of developing antibodies is associated with gluten exposure. The diagnosis of CD should be made in diabetic patients because mucosal atrophy and inflammation can change the absorption of nutrients, also affecting glycemic control and thus causing hypoglycemia (5). Changes in body mass index are also present, affecting glycemic regulation (11). The diagnosis of CD can be made prior to, at the diagnosis of, or after the diagnosis of type 1 diabetes, but usually within 5 years after type 1 diabetes has been diagnosed

(1). In patients with type 1 diabetes, hypoglycemia and diarrhea can serve as an indication for the diagnosis of CD (12). As a consequence of primary malabsorption, osteoporosis is also observed (4). Osteoporosis together with malignancy could be considered as two major complications of CD (13). Clinical disorders associated with CD are presented in Table 1. It has been observed that people with CD have less symptoms of extraintestinal disease during an appropriate diet, and improvement has also been observed in echocardiographic parameters, neurologic symptoms and transaminase concentrations (3). An important observation is that timing of gluten introduction and cessation of breast-feeding influence the risk of developing CD (4).

Table 1. **Clinical disorders associated with celiac disease**

Gastrointestinal	Hemopoietic
Liver disease	Anemia
Aphthous mouth ulcers	Coagulation disorders
Irritable bowel disease	IgA deficiency
Lymphocytic gastritis	Hyposplenism
Small bowel adenocarcinoma	T-cell lymphoma
Neurologic	Locomotor
Peripheral neuropathy	Osteopenia
Epilepsy	Arthralgia
Ataxia	Psychiatric
Endocrine	Depression
Type 1 diabetes	Schizophrenia
Infertility	Dental
Recurrent abortion	Defect in tooth enamel
Thyroid disorders	Genetic
Addison's disease	Down syndrome
Renal	Cardiovascular
IgA nephropathy	Cardiomyopathy
Dermatologic	Other
Dermatitis herpetiformis	Alopecia areata
Psoriasis	Sjögren syndrome
Brown pigmentation of the face	Finger clubbing
	Pharyngeal and esophageal carcinoma

DIAGNOSIS

Serologic tests have to be performed prior to introducing a diet. IgA-tissue transglutaminase (IgA-tTG) and total serum IgA can first be determined, as IgA is frequently deficient in CD (9). In case the first tests are negative despite a high clinical suspicion, IgA antiendomysial antibody (IgA-EMA) test should be used in the diagnostic procedure. Endomysium is a connective tissue protein found in the collagenous matrix of human and monkey esophagus (14). IgA antigliadin antibody (IgA-AGA) and IgG antigliadin antibody (IgG AGA) tests should also be added to the diagnostic work-up (15). Nevertheless, these antibodies can also be found in healthy people (6). The combination of tTG and EMA has been established as being sensitive and specific in 99%-100% of cases. It has recently been reported that measurement of antitissue transglutaminase antibodies might be an alternative and a more objective method (8). Genetic markers HLA DQ2 and HLA DQ8 are important in the diagnostic procedure, but tissue biopsy of the second or third sections of distal duodenum remains the gold standard.

TREATMENT

The only treatment for CD is a gluten-free diet. Strict adherence to gluten-free diet results in the absence or attenuation of both intestinal and extraintestinal manifestations of CD (3). Persistent symptoms despite adherence to diet may be associated with disorders like colitis or irritable bowel disease. In addition to gluten-free diet, patients can benefit from calcium and vitamin D supplementation, as well as from the addition of iron and folates (16). Persons with CD have to be educated that they need to adhere to a gluten-free diet for life in order to improve the symptoms of the disease. Appropriate food improves not only the symptoms of CD, but also those of other extraintestinal manifestations of the disease.

ADA recommendation is to screen for CD-associated autoantibodies at the diagnosis of type 1 diabetes and when symptoms pointing to CD are present (9).

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