REVIEWS

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Celiac Disease and Diabetes Mellitus

Celiakia a cukrzyca

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Abstract

Celiac disease is a multifactorial disease involving both genetic and environmental factors. It is characterized by the presence of DQ2(DQA1*0501, DQB2*201) heterodimer in 90% of patient with celiac disease. The prevalence of celiac disease is about 1%. Autoimmune conditions such diabetes mellitus, *dermatitis herpetiformis* and thyroid disease may coexist with celiac disease. In individuals with type 1 diabetes mellitus prevalence of celiac disease range 10%, but in people with type 2 diabetes mellitus the frequency is similar to that of the general population. It is associated with the HLA markers B8 and DR3. Early detection of celiac disease and early treatment with a gluten-free diet may avoid many complications like: malnutrition, folic acid deficiency, anaemia, bone disease and malignancy especially lymphoma. Patients with diabetes mellitus and not-treated celiac disease have increased risk of symptomatic hypoglycemia. During taking gluten-free diet mean daily insulin requirement is higher, metabolic control is better and more seldom hypoglycemia occurs. Now, it is proposed that every patient with type 1 diabetes mellitus should be investigated for celiac disease, because clinical symptoms of celiac disease not always are clear, and early treatment allows avoiding many severe complications (**Adv Clin Exp Med 2007, 16, 2, 297–301**).

Key words: celiac disease, diabetes mellitus type 1, genetic predisposition.

Streszczenie

Celiakia jest wieloczynnikową chorobą, na której występowanie mają wpływ zarówno czynniki genetyczne, jak i środowiskowe. U 90% osób chorych na celiakię występuje haplotyp DQ2(DQA1*0501,DQB1*0201). Częstość występowania celiakii wynosi około 1%. Współistnieją z nią inne choroby autoimmunologiczne, takie jak: cukrzyca typu 1, *dermatitis herpetiformis* lub choroby tarczycy. Wśród pacjentów z cukrzycą typu 1 celiakia występuje u prawie 10%, a u pacjentów z cukrzycą typu 2 z częstością podobną jak w populacji ogólnej. Jest to związane ze wspólnym podłożem genetycznym celiakii i cukrzycy typu 1 – antygenami HLA B8 i DR3. Wczesne rozpoznanie choroby trzewnej i stosowanie diety bezglutenowej pozwala uniknąć wielu powikłań, takich jak: zaburzenia neurologiczne, niedokrwistość, osteoporoza i nowotwory złośliwe, a wśród nich szczególnie chłoniaki. U pacjentów z cukrzycą typu 1 i nieleczoną celiakią istnieje zwiększone ryzyko objawowej hipoglikemii. Podczas stosowania diety bezglutenowej poprawiały się wskaźniki gospodarki węglowodanowej i rzadziej występowały epizody hipoglikemii. Obecnie proponuje się wykonywanie badań przesiewowych u wszystkich pacjentów z cukrzycą typu 1 ze względu na to, że nie zawsze obraz kliniczny współistniejącej choroby trzewnej jest klarowny, a wczesne rozpoznanie celiakii pozwala uniknąć poważnych powikłań (**Adv Clin Exp Med 2007, 16, 2, 297–301**).

Słowa kluczowe: celiakia, cukrzyca typu 1, predyspozycja genetyczna.

Celiac disease is a malabsorption condition caused by gluten intolerance. Gluten, acting as an antigen, creates immune complexes in the mucous membrane of the intestine, causing the aggregation of T lymphocytes. These lymphocytes make lesions in the mucous membrane, which results in villous atrophy of the small intestine and crypt hyperplasia. Celiac disease has a broad spectrum of clinical manifestations. It can occur in the classic form with symptomatic malabsorption syndrome and in asymptomatic and atypical forms [1]. The prevalence of celiac disease is probably higher than estimates based on screening tests because of its asymptomatic forms. Its frequency in the USA is similar to that in Europe and is about 1% [2]. The prevalence of celiac disease in Poland shows

regional differentiation: the classic form is diagnosed most often in Silesia (1 : 1000), but very rarely in the Warsaw region (1 : 10,000). Silent celiac disease, diagnosed by serological tests, is much more common (1 : 112–1 : 500) [3].

Celiac disease is a multifactorial disease involving both genetic and environmental factors. Its manifestation and intensity of clinical symptoms depend on various combinations of risk factors and their possible accumulation as well as the overlapping of environmental factors [4]. A genetic factor influencing the appearance of celiac disease was suggested based on observations of cases of the disease among family members. About 10–15% of first-degree relatives of affected individuals develop celiac disease [5]. In Poland this is 5.6% [3]. It has also been observed that if the disease appears in one twin, the second twin will suffer from the disease in 70% of monozygotic twins but in only 20% of dizygotic twins. [6]. The higher percentage of disease coincidence in monozygotic twins than in siblings having the same HLA type (30–40%) suggests that monozygotic twins may also have one or more non-HLA genes that are responsible for the occurrence of the disease [7, 8].

Celiac disease has been shown to be strongly associated with HLA alleles. Ninety percent of patients with celiac disease carry the HLA haplotype DQ2(DQA1∗0501, DQB1∗0210) [9, 10]. This is found in the *cis*-position in DR3-positive patients or in the *trans*-position in heterozygotic DR5/DR7 patients [4]. Most other patients carry the HLA haplotype DQ8(DQA1∗0301, DQB2∗0302) in the *cis*-position in DR4 patients [11]. Among the patients with DQ2, in the DQB1∗0201 homozygotes the risk of the disease is significantly higher [11, 12]. DQ2 homozygots have a predisposition for earlier development of the disease and more severe clinical symptoms [14]. Patients with celiac disease carrying the DR3 and DR4 alleles are strongly predisposed to developing malignant neoplasms of the alimentary tract [15]. In patients without DQ2 and DQ8 antigens, the risk of the celiac disease is very small.

There is an association between celiac disease and genes at q26 on chromosome 15 (on this chromosome is also the locus responsible for susceptibility to diabetes mellitus type 1), on chromosome 5, and probably on chromosome 11 [16]. On chromosomes 9 and 19 (19p13, where the locus CELIAC 4 is located) and on chromosome 6 (6q21-22) are also loci associated with celiac disease [17, 18].

There is an association between celiac disease and another autoimmune diseases, such as type 1 diabetes and dermatitis herpetiformis. Screening tests for celiac disease among type 1 diabetic patients showed different frequencies for these two diseases depending on the population (from 1.1–1.3% in children from Germany and Switzerland to 7–8% in adult Italians and 4–9% among adult Irish people) [19]. In Poland it is about 6% [3]. This suggests the same genetic pathogenesis. Celiac disease among patients with non-insulin-dependent diabetes is the same as in the general population [20]. Celiac disease and type 1 diabetes have a common genetic background connected with the HLA antigens B8 and DR3 [21].

There are over 17 loci (IDDM1-IDDM17) responsible for susceptibility to diabetes mellitus type 1. The most important genes are part of major histocompatibility complex (MHC) HLA class II, located on chromosome 6 at the locus p21. They are responsible for 45% of the genetic susceptibility to diabetes mellitus type 1 (IDDM1) [22]. Diabetes mellitus type 1 is strongly connected with the DQB allele combined with DQA, with the most important haplotype being DQA*03--DQB1*0201. This haplotype, found in the *trans* configuration (DR3-DQ2/DR4-DQ8 in most people, but DR3-DQ2/DR9-DQ9 in Chinese people) or in *cis* configuration (DR7-DQ2 in African Americans), is strongly connected with the occurrence of diabetes mellitus type 1 [23]. Diabetes mellitus type 1 is a polygenic disturbance connected not only with HLA loci, but also another genes. In nearly 10% of people susceptible to this illness there is a correlation to the IDDM2 gene located on chromosome 11 at position p5 [24]. Another site connected with the occurrence of diabetes mellitus type 1 in some populations is the gene IDDM12 located on chromosome 2q33 [25]. There is a high risk of suffering diabetes mellitus type 1 among persons with HLA DRB1: 0401, 0402, 0405, HLA DQA1: 0301, HLA DQB1: 0302 and HLA DRB1: 0301, HLA DQA1 0501, and HLA DQB1 0201 [26].

A connection has been observed between the duration of diabetes mellitus type 1 and increased frequency of celiac disease. In most cases, celiac disease presents no or atypical symptoms, which is the cause of delayed diagnosis and has negative consequences for the course of diabetes [27]. Silent celiac disease may not only coincide with diabetes mellitus, but can also precede it. There were suggestions that a late diagnosis of celiac disease may be connected with a higher risk of further advance of diabetes mellitus type 1. In a group of patients in whom celiac disease was diagnosed and treated in early childhood, the percentage of patients who developed diabetes mellitus type 1 was lower than in those in whom celiac disease was diagnosed in late childhood or adulthood [28].

The age of patients who are diagnosed with both celiac disease and diabetes mellitus is higher than the age of patients diagnosed with only diabetes mellitus. The increased duration of autoimmune disease such as diabetes mellitus type 1 may increase the risk of developing celiac disease [29].

Developing celiac disease, with or without the typical symptoms, may lead to serious health problems. Malignant neoplasm can be the first sign of silent celiac disease [30]. Each form of celiac disease may threaten with the onset of serious complications, and this is the reason why in such cases a gluten-free diet aimed at preventing autoimmune illnesses developing in the future should be considered [31]. Antibodies active against pancreatic islet cells are often present in cases of untreated celiac disease, but they tend to disappear when a gluten-free diet is used [32]. Some symptoms of celiac diseases, such as diarrhea or flatulence, could be wrongly interpreted as connected with diabetes mellitus complications (autonomic nervous system enteropathy), which causes a delay in diagnosing a possibly present celiac disease. Early diagnosis of celiac disease makes it possible to avoid many of its complications, such as neurological disorders, osteoporosis, and malignant neoplasm, particularly lymphomas. Alimentary tract lymphomas were reported in 10–15% patients diagnosed with celiac disease but who did not fully comply with the rules of a gluten-free diet. The elimination of gluten from food can delay or prevent the development of some of these complications and improve the treatment results of coexisting illnesses [33–35].

In the past, when the screening tests used for diagnosing celiac disease were not easy to use in patients with diabetes mellitus type 1, the presence of celiac disease was suspected based on low body mass and diarrhea, which are standard signs of celiac disease. This could lead to a wrong diagnosis, because similar signs are presented by patients with diabetic neuropathy. Shannan et al. observed that the illness most often coinciding with celiac disease was poorly controlled diabetes mellitus, with characteristic episodes of hypoglycemia. The authors suggested that an irregular course of diabetes mellitus may be a sign of coinciding celiac disease. A gluten-free diet improves the metabolic balance in diabetes mellitus in these cases and hypoglycemic episodes become rare [21].

Currently there is a trend to perform celiac disease screening tests in patients with diabetes mellitus type 1 because celiac disease occurs in this group 10 times more often than in the general population. Diabetes mellitus type 1 occurs most often in patients who are less than 30 years old. Early diagnosis of existing silent celiac disease makes it possible to institute a gluten-free diet early and to avoid the consequences of advanced celiac disease. Some authors recommend performing screening tests repeatedly every few years. Genetic tests identifying HLA type could eliminate the need to perform repeated tests with antibodies against transglutaminase in the 60% of the population in whom the risk of celiac disease is low (DQ2- or DQ8-negative). However, it must be remembered that almost 20–30% of the healthy population are HLA DQ2 positive. Celiac disease and diabetes mellitus type 1 occur not only because of the presence of some HLA genes, but are also influenced by the presence of other genes located in other regions of the human genome and their interactions with environmental factors.

Patients with celiac disease are also at a higher risk of developing diabetes mellitus type 1. The risk probably grows with increasing duration of celiac disease, but because diabetes mellitus type 1 develops most often in patients who are under 30 years old, their coincidence is not often encountered. The diabetes mellitus type 1 concordance rate (measured in 100,000 people per year) is increasing both in Poland and in most other countries and is currently above 9. The diabetes mellitus type 1 morbidity rate in Poland is approximated to 0.3%. In this group, the celiac disease morbidity rate (6%) is higher than in the general population [3, 36, 37].

For many years there was some conflict over celiac disease screening tests. The supporters of performing the tests routinely stated that celiac disease could be handled as other illnesses that are advised by the WHO to be diagnosed using screening tests, because 1) it is difficult to diagnose it at an early stage using only clinical symptoms and signs (silent disease course), 2) it is found often (1% of the general population), 3) good screening tests (of high sensitivity and specificity) are available, and 4) it can be treated effectively. It was also stressed that if celiac disease remains untreated, some serious, even life-threatening, complications may occur. The adversaries of performing the tests were more against screening the whole population than against testing limited to high-risk groups, mainly diabetes mellitus patients. The need for such tests is no longer in question [38].

The problem of early diagnosis of celiac disease appears important and efforts to make medical professionals of all specialties aware or it are worthwhile.

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