Coexistence of coeliac disease and type 1 diabetes

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Abstract

There is a selective review of the literature concerning the coexistence of coeliac disease and type 1 diabetes mellitus. This review focuses on the principles of serological tests towards coeliac disease in patients with type 1 diabetes mellitus and metabolic control measures as a result of a gluten-free diet.

Coeliac disease (CD) and type 1 (T1) diabetes mellitus belong to the group of autoimmune illnesses, the pathogenesis of which involves the body’s immune system destroying its own cells and tissues. In recent years, a dynamic increase of autoimmune illnesses morbidity has been observed, especially in the paediatric population. Autoimmune illnesses may affect almost all systems and organs of the body [1]. CD involves damage to the mucous membrane of the small intestine manifested by the atrophy of intestinal villi, crypt hyperplasia and intra-epithelial lymphocyte infiltration caused by gluten from ingested wheat, rye and barley. Type 1 diabetes mellitus involves the destruction of β pancreatic cells, which produce insulin [2].

CD and T1 diabetes occur in genetically predisposed persons. Genetic predisposition for CD is mainly associated with class II HLA genes of histocompatibility complex on chromosome 6p21 (CELIAC 1). The majority of patients with CD have the HLA DQ2 antigen coded by alleles DQA1*0501 and DQB1*0201, and the rest of them have HLA DQ8 coded by alleles DQA1*0301 and DQB1*0302. Fewer than 1% of patients suffering from CD lack any of the HLA alleles associated with predisposition to the illness. However, HLA-associated genes that predispose to CD are found in as much as 30–40% of healthy people. Thus, their presence seems to be essential, but indecisive for the occurrence of CD. Other genes, not associated with HLA but involved in the pathogenesis of CD as well, include the following: COELIAC 2 (5q31-33), COELIAC 3 (2q33) and COELIAC 4 (19p13.1) [3].

Class II HLA genes are also responsible for 40–50% of the genetic risk of T1 diabetes occurrence. The highest risk for the occurrence of T1 diabetes mellitus is genotype DR3-DQA1*0501-DQB1*0201/DR4-DQA1*0301-DQB1*0302, whereas – DR15-DQA1*0102-DQB1*0602 is associated with dominant protection [4]. Antigen HLA DQ2 occurs in 80% of patients with T1 diabetes and CD, and 49% of patients with T1 diabetes without CD. This means that patients having antigen HLA DQ2 or HLA DQ8 are the most predisposed to the co-existence of CD and T1 diabetes [5].

Studies conducted in recent years have revealed seven new HLA-independent loci associated with CD and T1 diabetes, including RGS1 on chromosome 1q31, IL18RAP on chromosome 2q12, TAGAP on chromosome 6q25, PTPN2 on chromosome 18p11, CTLA4 on chromosome 2q33, SH2B3 on chromosome 12q24 and 32-bp ID variant on chromosome 3p21, which additionally confirms the shared genetic predisposition for both illnesses [6].

The overall prevalence of CD evaluated on the basis of epidemiological population studies appears to be around 1/160 [7]. In some countries (e.g. Finland and the USA) the prevalence of CD shows an increasing tenen-
In the paediatric population, a sudden increase of T1 diabetes incidence rates has been observed, and it is most evident among the youngest children. In the years 1989–2005 the T1 diabetes mellitus incidence rate in the region of Upper Silesia (population representative of Poland) increased by over 260% [9].

According to medical literature, the prevalence of CD is 5–7 times higher in diabetic patients compared to the overall population. The percentage of diabetic children with histopathologically confirmed CD varies from 2.4% in Finland to 16.4% in Algeria (Table I) [10–32].

In Polish studies, the prevalence of serum anti-endomysial antibodies ranges from 7.1% to 9.6% among children with T1 diabetes mellitus and from 3.48 to 6.5% among children with histopathologically confirmed CD [33–38] (Table II).

The clinical presentation of CD in patients with T1 diabetes mellitus is diverse. The diagnosis of CD may be preceded or followed by the diagnosis of T1 diabetes. Sometimes both conditions are diagnosed concurrently [35]. The onset age of diabetes in children with CD is usually significantly lower than in those without CD [36].

The classic form of the illness may also be observed, with common gastrointestinal symptoms such as chronic diarrhoea, lack of appetite, body mass deficiency, abdominal pain and flatulence. However, uncommon forms (manifesting as short stature, iron deficiency anaemia or delayed puberty) and silent forms are definitely more frequent. It is estimated that the clinical signs of CD are present in only 50% of T1 diabetes patients (36% – diarrhoea, 16% – recurrent abdominal pain). The remaining patients suffer from non-intestinal symptoms or are asymptomatic [39]. In the studies recently published by American authors it has been shown that up to 71.4% of children with T1 diabetes do not have any gastrointestinal symptoms when the CD-specific antibodies are detected [40]. However, British authors point out the fact that some patients with T1 diabetes may present with non-characteristic or mild symptoms of CD such as poor appetite or low body mass and height, which may be overlooked by doctors and patients themselves. Of the

| Geographic location | First author and year of publication | Number of patients with DM | Age [years] | Rate of patients with CD |
|---------------------|-------------------------------------|---------------------------|------------|-------------------------|
| Europe              |                                     |                           |            |                         |
| Finland             | Saukkonen 1996 [10]                 | 776                       | 2–21       | 2.4                     |
| Austria             | Crone 2003 [11]                     | 157                       | 14.8       | 5.1                     |
| Denmark             | Hansen 2006 [12]                   | 106                       | 10.8       | 10.4                    |
| Great Britain       | Goh 2007 [13]                      | 113                       | 12.1       | 4.42                    |
| Sweden              | Larsson 2008 [14]                  | 300                       | 9.2        | 9.67                    |
| Italy               | Salaridi 2008 [15]                 | 331                       | 8.1 ±4.3   | 6.65                    |
| Portugal            | Mont-Serrat 2008 [16]              | 120                       | Children   | 2.5                     |
| Greece              | Karavanaki 2009 [17]               | 144                       | 12.3 ±4.6  | 3.37                    |
| Serbia              | Djurić 2010 [18]                   | 121                       | 10.8       | 5.79                    |
| Spain               | Vicuña Arregui 2010 [19]           | 463                       | –          | 3.02                    |
| Estonia             | Uibo 2010 [20]                     | 271                       | –          | 4.06                    |
| Romania             | Gabriel 2011 [21]                  | 119                       | 11 ±4      | 9.2                     |
| North America       |                                     |                           |            |                         |
| USA                 | Aktay 2001 [22]                    | 218                       | 4–21       | 4.6                     |
| Canada              | Gillett 2001 [23]                  | 233                       | Children   | 7.7                     |
| South America       |                                     |                           |            |                         |
| Brazil              | Baptista 2005 [24]                 | 104                       | 10.5 ±4.3  | 4.8                     |
| Africa              |                                     |                           |            |                         |
| Algeria             | Boudraa 1996 [25]                  | 116                       | 1–19.5     | 16.4                    |
| Libya               | Ashabani 2003 [26]                 | 234                       | 12.8 ±5.4  | 10.3                    |
| Egypt               | Salah 2005 [27]                    | 200                       | 11.2       | 4.0                     |
| Tunisia             | Mankai 2007 [28]                   | 205                       | 11         | 5.3                     |
| Australia           | Smith 2000 [29]                    | 218                       | 9.9 ±3.8   | 5.7                     |
| Near East           |                                     |                           |            |                         |
| Saudi Arabia        | Al-Ashwail 2003 [30]               | 123                       | Children   | 4.9                     |
| Iran                | Fallahi 2010 [31]                  | 96                        | 12         | 6.2                     |
| Asia                |                                     |                           |            |                         |
| India               | Bhadada 2001 [33]                  | 189                       | –          | 11.1                    |
T1 diabetic patients studied by them, 86% did not initially report any clinical symptoms. However, when small intestine biopsy was performed the percentage fell to 22% [41].

It is also pointed out in medical literature that an increase in the frequency of hypoglycaemic incidents and a reduction of insulin demand constitute a dominant symptom of CD in patients with T1 diabetes; however, not all authors confirm this claim. According to some authors, the introduction of a gluten-free diet can decrease the frequency of hypoglycaemic episodes [12].

Recommendations concerning screening tests for CD in patients with T1 diabetes differ between countries. The American Diabetes Association (ADA) [42] and the National Institute of Health and Clinical Excellence (NICE) [43] recommend conducting screening tests for CD in all patients with T1 diabetes, and introducing a gluten-free diet in all patients with histopathologically confirmed CD. Similar recommendations were published by experts of the International Society for Paediatric and Adolescent Diabetes (ISPAD) [44] and the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [45]. However, they admit that cases of short-term improvement in the course of T1 diabetes in asymptomatic patients are scarce. On the other hand, the Canadian Diabetes Association (CDA) [46] currently recommends conducting tests for CD only on symptomatic patients and informing them that the treatment of asymptomatic patients with CD is controversial. According to the Polish Diabetes Association, which published its recommendations in 2011 [47], screening tests for CD should be conducted in diabetic children and teenagers once a year.

The screening tests for CD that are currently recommended include the indirect immunofluorescent method (enzyme-linked immunosorbent assay, radioimmunossay or other) using purified or recombinant TG2 antigens or tissue sections/fluids containing TG2 [48]. This choice is based on numerous scientific studies that have confirmed the high sensitivity and specificity of both types of antibodies for CD diagnosis, which for EmA IgA are estimated to be 95% and 99%, respectively [39]. Other types of antibodies (e.g. antigliadin antibodies) and other methods of antibody marking (e.g. the ELISA method for detecting anti-endomysial antibodies) are currently not recommended for the diagnosis of CD [48].

It is suggested that in patients with complete or partial IgA deficiency (the prevalence of which in patients with CD is estimated at 1 : 39–1 : 57), screening tests for endomysial or tissue transglutaminase (TTG) antibodies of class IgG should be conducted [39]. The value of an-

| First author and year of publication | Number of patients with DM | Age [years] | Rate of patients with positive serological tests | Rate of patients with biopsy-proven CD |
|--------------------------------------|---------------------------|-------------|-----------------------------------------------|--------------------------------------|
| Karczewska 1996 [33]                 | 201                      | 3–17        | 7.46                                          | 3.48                                 |
| Nazim 2004 [34]                      | 380                      | 8/12–23     | 7.1                                           | 6                                    |
| Szaflarska-Popławska 2006 [35]      | 446                      | 1.3–21      | 9.6                                           | 5.16                                 |
| Grzenda-Adamek 2007 [36]             | 459                      | 13.7        | 8.3                                           | 5.7                                  |
| Galicka-Latała 2009 [37]             | 109                      | 18–52       | –                                             | 9.71                                 |
| Szypowska 2010 [38]                  | 249                      | 0.9–17.8    | 7.5                                           | 6.5                                  |

Figure 1. Screening schema for patients at risk for coeliac disease
tibodies against deamidated forms of gliadin peptides (DGP) in the diagnostics of CD in children younger than 2 years of age needs to be confirmed in prospective studies [48]. A patient with abnormal serological test results should be referred to a gastroenterologist, who ought to consider conducting a small intestine biopsy collecting numerous bioplates from different parts of the duodenum (Figure 1) [39].

The need to repeat serological tests in patients with T1 diabetes is also widely discussed in medical literature. There are numerous cases described of patients with T1 diabetes mellitus who were initially seronegative and who then presented with antibodies and changes in the membrane of the small intestine typical for CD [49, 50]. In the study by Barera et al. [49] the prevalence of CD at the time of appearance of T1 diabetes was 3.6% and it increased to 6.2% in subsequent years of patient observation. Similar results were obtained by Mäki et al. [50], who initially estimated the prevalence of CD in T1 diabetes patients to be at 2.1%, but based on the results of further serological screening they diagnosed CD in another 11 patients, which made the percentage of patients with both CD and T1 diabetes grow to 6.7%. The authors of both publications unanimously recommend testing patients for CD once when they are diagnosed with T1 diabetes and then once a year for at least several consequent years, even if no symptoms are observed. Similar recommendations were published by the American Diabetes Association (ADA) [42], the North American Society for Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [45] and the International Society for Paediatric and Adolescent Diabetes (ISPAD) [44], which recommend conducting screening tests for CD more frequently if a child with T1 diabetes is a first degree relative of a CD patient or if there are any other indications.

There is no doubt that patients with T1 diabetes and CD (even with mild symptoms of it) should be treated with a gluten-free diet. However, whether the diet should be used in asymptomatic T1 diabetes patients is still controversial. Taking into account that untreated CD can lead to deficits of body mass and/or height, disorders of pubertal development, deficiency anemia, osteopenia, osteoporosis, neurological disturbances, changes in insulin demand, frequent hypoglycaemias and other serious distant complications such as gastrointestinal neoplasms (cancers and lymphomas), it seems that a gluten-free diet should be recommended to all patients with T1 diabetes and CD. Experts of ISPAD, ADA and NASPGHAN also support this view [42, 44, 45]. Such an approach seems even more justified if we consider that Galili-Tsianopoulou et al. [51] found anti-GAD and IA-2 antibodies in most newly diagnosed patients with T1 diabetes and in as much as 23% of children and young adults with CD. Thus, they suggested that a strict gluten-free diet might have a protective effect on the islets of Langerhans and delay the onset of diabetes. Ludvigsson et al. [52] showed that early diagnosis of CD (children below 2 years of age) decreases the risk of T1 diabetes onset before the age of 20 years compared to the group of patients with CD diagnosed between the age of 3 and 20 years. Only the Canadian Association of Gastroenterology (CAG) leaves the decision on introducing dietary treatment in patients with coincident T1 diabetes and CD to the patients themselves, recommending that they be informed that following a gluten-free diet in asymptomatic patients is controversial [46].

Table III. Metabolic control measures after implementation of gluten-free diet in patients with coeliac disease and type 1 diabetes mellitus

| First author and year of publication | Number of patients with DM | Number of patients with DM and CD | Age [years] | Growth improvement effect | HbA1c changes | Hypoglycaemic effect |
|-------------------------------------|---------------------------|----------------------------------|-------------|---------------------------|---------------|---------------------|
| Saadah 2004 [54]                    | 42                        | 21                               | 1.6–12.9    | Height NS                |BMI ↑↑         | NS –               |
| Sanchez-Albisua 2005 [57]          | 263                       | 9                                | 12 ±5       | Height ↑↑                 |BMI NS         | NS –               |
| Rami 2005 [55]                      | 195                       | 98                               | 10.0 ±5.4   | Height NS                |BMI NS         | NS –               |
| Hansen 2006 [12]                    | 236                       | 33                               | 1.5–16      | Height NS                |BMI ↑↑         | NS –               |
| Sun 2009 [58]                       | 49                        | 49                               | 60 ±4.1     | Height NS                |BMI NS ↑↑     | –                  |
| Goh 2010 [56]                       | 58                        | 29                               | No data     | BMI NS                   |NS             | –                  |
Following a gluten-free diet by patients with CD is difficult. Estimates are that the percentage of patients strictly following dietary recommendations ranges between 23.8% and 81%, the highest being for patients with overt CD diagnosed in early childhood, and the lowest for adults diagnosed during screening tests [39]. In small groups of patients with CD and T1 diabetes studied by Westman et al. [53] and Saadah et al. [54] (20 and 21 subjects, respectively) only 25–30% of patients strictly followed a gluten-free diet. In the most extensive questionnaire study conducted so far, Rami et al. [55] reported that in a group of 74 patients with coincident CD and T1 diabetes mellitus, 55.4% confessed to not following a gluten-free diet.

Difficulties with following a gluten-free diet result from numerous factors, including limited availability of gluten-free products and their unsatisfactory taste, insufficient support from family and other people around, a lack of complaints after eating gluten-containing food, inadequate knowledge of the harmfulness of not following the gluten-free diet, and the high relative cost of such a diet (in Canada the cost of a gluten-free diet was estimated to be approx. 242 ±212% higher than that of a traditional diet) [39]. In the case of patients with T1 diabetes it is probably also the controversy over the effectiveness of dietary treatment that discourages them from following a gluten-free diet. Most authors point out the lack of effect of a gluten-free diet on the metabolic control in patients with T1 diabetes [54–56]. The results of the studies are also discrepant as regards the positive effect of dietary treatment on weight and body mass index [11, 54–59] (Table III).

There is little data in medical literature concerning CD-dependent complications in patients with T1 diabetes mellitus. In most of the studies published so far, decreased bone density and consequent increased risk of osteoporosis was found independently in both CD and T1 diabetes patients. However, the results of studies comparing the occurrence of decreased bone density in patients with coincident T1 diabetes and CD and those only with T1 diabetes are contradictory [39].

Furthermore, there is no data as regards the risk of enteropathy-associated T-cell lymphoma in patients with CD and T1 diabetes mellitus. The risk of this kind of tumour is 50 times higher in the population of CD patients than in the overall population. The only study published so far on this issue did not confirm any increased risk of this type of lymphoma in patients with T1 diabetes mellitus [59]. Also, there is no data in medical literature concerning the impact of T1 diabetes mellitus on well-documented complications of untreated CD, such as disturbances in reproduction and increased mortality risk [39].

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