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Celiac Disease and Diabetes Mellitus Type 1

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1. Introduction

A significant increase in autoimmune disease morbidity has been observed in recent years, including disorders manifesting in childhood, concurrent with decreased age of patients at the time of diagnosis. Autoimmune diseases can involve almost every organ system but the endocrine, connective tissue and gastrointestinal systems are the most commonly affected [1, 2, 3].

In terms of epidemiology, autoimmune thyroid diseases (AITD) and diabetes type 1 (T1DM) come to the fore among autoimmune diseases related to the endocrine system, whereas among those unrelated to the endocrine system celiac disease (CD) is one of the more common. These diseases, apart from bronchial asthma, are among the most frequent chronic diseases affecting infants and children and often occur together [1, 3, 4].

Autoimmune polyendocrinopathy syndrome (APS) or polyglandular autoimmune diseases (PGAD) concern primary deficits in two or more endocrine glands and manifest themselves, except for Graves' disease, as organ hypofunction. The main autoimmune endocrinopathies are: type 1 diabetes mellitus, autoimmune thyroid diseases, autoimmune adrenal failure (Addison disease), hypergonadotropic hypogonadism (premature ovarian failure), autoimmune hypoparathyroidism, and pituitary defects (lymphocytic hypophysitis) [5, 6, 7]

Those syndromes are often associated with other non-endocrine autoimmune diseases [5, 6, 7].

For descriptive purposes three to four different types of APS or PGAD have been described. Addison disease is a common element of the first two types i.e. APS-1 Blizzard syndrome, APS-2 Schmidt's syndrome (Carpenter's syndrome). APS-3, on the other hand, is characterised by the presence of autoimmune thyroid disease and diabetes type 1 (3a), pernicious anaemia (3b) or vitiligo, alopecia or other organ specific autoimmune disease (3c).

Some authors also distinguish type 4 disease/syndrome, which comprises varied combinations of autoimmune diseases with the exception of those mentioned above as types 1 and 2. A patient with diagnosed T1DM and CD can be included in this group [5, 6, 7].

In 1969, Walker-Smith and Grigo[8] described a child with T1DM and CD for the first time, highlighting the frequent coexistence of these two diseases. What makes CD unique among autoimmune diseases is the fact that the external or initiating factor is known, which is not the case in T1DM or AITD.

2. Pathophysiology

Recent studies have shown that, apart from environmental causes, such as the ingestion of gluten in celiac disease, other less understood factors like in T1DM, and recent advances in our understanding of genetic predisposition factors, many autoimmune disorders are associated with either primary or secondary disturbances in gastrointestinal mucosal permeability.

Gastrointestinal epithelial cells form the largest body surface area interfacing between an organism and its external environment. Thanks to tight junctions (TJ), a healthy intestinal mucosa serves as a barrier against toxic macromolecules. Under physiological conditions, only a few immunologically active antigens can traverse this barrier. Almost 90% of the proteins that penetrate the barrier via the epithelium are reduced to non-immunogenic, short linear peptides due to the action of lysosomal enzymes. Only a few remain unchanged and are transported by M cells or between the enterocytes through TJ. Breaching of the epithelial barrier by these antigens often results in the development of immunological tolerance rather than triggering the immune response or autoimmunisation [9]. An immature or damaged mucosa makes the mucous barrier more permeable, which can result in an allergic or autoimmune reaction in genetically predisposed individuals [9, 10]. Uibo et al. [11] detected the lowest expression of tight junction protein 1 (TJP1) mRNA in small bowel mucosa samples from celiac patients with diabetes mellitus type 1, indicating an increase in intestinal permeability. Furthermore, these samples displayed the highest expression of forkhead box P3 (FoxP3) mRNA, a marker of regulatory T cells, when compared with controls and celiac patients [11]. Antigen presenting cells (APC), which present antigens to T cells of the intestinal mucosa, are vital to the immunological processes. On their surface, they present glycoproteins encoded by major histocompatibility complex (MHC) class I and II antigens [12, 13]. Almost 50 different conditions, including CD and T1DM, are associated with specific MHC class I or II antigen presentation pathways [13]. Apart from genetic predisposition, the disease or disorder develops when the immune system is exposed to the antigen. This process may be enhanced by increased permeability of the mucosa due to damaged TJ. According to Fasano et al. [14, 15, 16, 17] an excessive production of zonulin stimulated by gluten, increases permeability of TJ. In CD, this process is presumed to be mediated by gliadin binding to the chemokine receptor CXCR3 [18].

Gliadin has lately been speculated to be one of the environmental causes of T1DM. Gliadin, which contains relatively high levels of glutamine and proline, is a source of polypeptides that can penetrate the damaged TJ and presented to T cells by dendritic cells. Activated Th1 lymphocytes can be stimulated to secret gamma interferon (INF-γ) and tumor-necrosis factor-alfa (TNF-α), Th2 lymphocytes to secrete Interleukin-4 (IL-4) and Th17 cells to secrete Interleukin-17A (IL-17A). All these cytokines can stimulate a local inflammatory response, which further augments the permeability of the mucosa [19, 20], hence resulting in a vicious circle that perpetuates damage to the intestinal mucosa.

It seems that the development of CD is dependent on the dose, type, timing and method of gluten ingestion. Breastfeeding and small amounts of gluten administered with breast milk are associated with a reduced risk of developing CD [21, 22]. Breastfeeding favours the growth of beneficial bacteria, such as *Bifidobacterium,* and therefore decreases the proliferation of others, including those less beneficial, like *Bacteroides*.

Diet (and gluten intake) related disorders of the intestinal microflora and permeability of the intestinal mucosa appear to play a significant role in the development of T1DM [23]. According to Visser et al. [24], the influence of gluten on the development of T1DM is as follows: a high gluten diet is favourable for *Bacteroides,* while a gluten-free casein diet reduces their number. The predominance of *Bacteroides* over *Bifidobacterium* and *Lactobacillus,* which occurs in breastfed babies, stimulates zonulin release [25]. In CD zonulin release is enhanced by gliadin binding to the chemokine receptor CXCR3 [18]. An excessive concentration of zonulin and its receptor in the enterocyte changes the structure of TJ proteins and increases the passage of antigens from the intestinal lumen to the *lamina propria* where antigens are presented to the T cells by the APC. In conjunction with a genetic predisposition, this may lead to the trafficking and/or activation of autoaggressive T cells, which may provoke autoimmune responses, including destruction of beta cells in T1DM.

A significant role of gliadin in the etiology and pathogenesis of CD and T1DM has also been hypothesized by Barbeau et al [26].

3. Epidemiology

Around 4.5% of children and almost 6% of adults with T1DM have concurrent CD [27]. This correlation between the two diseases seems to become stronger with increasing age and duration of diabetes. The epidemiological data vary depending on population characteristics as well as on diagnostics criteria. Prevalence of CD among Australian children with newly diagnosed T1DM was 1.2% according to Doolan et al.[28]. This prevalence was 2.7% among children with long-standing T1DM and 8.4% among adults.

In similar populations of children in the USA, the prevalence of CD was 5% percent according to Crone et al, and 3.2% according to Sanchez-Albisua et al [29, 30].

CD coexists with T1DM in only 1.4% of young adults in Wales [31], while the rate is 7.7% in children in British Columbia, 2% in adults in the Czech Republic [33], 2.6% in children and teenagers in Brazil [34] and 12.3% in adults in Denmark [35]. In Iraq it is 11.2% [36], and in Serbia 5.79% [37]. Triolo et al. have found tissue transglutaminase antibodies (anti-tTG) in 11.6% of diabetic children, of whom 24.6% had CD [4]. In a large study of 28,671 T1DM patients under the age of 30 from Germany and Austria, Warncke et al. [38] demonstrated the presence of anti-tTG in 10.7% patients, which was associated with the duration of T1DM. In a recent study form Greece, Kakleas et al. [39] found an 8.6% prevalence of anti-tTG IgA positivity among T1DM children associated with younger age and a shorter duration of diabetes. The highest prevalence of 13.8% was documented in Italy by Picarelli et al. [40]. This study also demonstrated the value of analysing IgA and IgG antibody concentrations simultaneously. The prevalence of CD in the patients with T1DM was 6.4% for IgA-EMA-positive, which increased to 13.8% when IgG1-EMA was also used for screening.

The incidence of CD in Polish children with newly diagnosed T1DM was reported to be 5.7% and 9.4% in those with long-standing T1DM by Mysliwiec et al. [41]. There was no

significant difference between the positivity for anti-tTG IgA and IgG in those groups. Gorska et al. [42] reported 4.1% of newly diagnosed type 1 diabetic children to have positive antibodies and our study [43] showed this to be twice as high among girls (5.62%) than among boys (2.57%). These data are consistent with other studies i.e. the prevalence of CD is twice as high in females as in males.

Patients with CD also have a greater risk for developing T1DM (around 5%) [44] and diabetes-associated antibodies are more commonly detected in these individuals. Galii-Tsinopoulou et al. [45] detected anti-GAD and IA-2 antibodies in 23% of patients with CD. The same authors suggested that a strict gluten-free diet might protect the pancreatic β-cells and thus postpone the onset of T1DM. Initiation of a gluten-free diet in T1DM children is associated with a significantly reduced risk of autoimmunisation. According to Ludvigsson et al.[46], early diagnosis of CD (before the age of 2) reduces the risk of developing T1DM before the age of 20 when compared to a group diagnosed between the ages of 3 and 20. The differences, however were not statistically significant.

4. Genetic determinants and associations

Most estimates put the prevalence of CD at close to 1% of the general population [47], and recent evidence suggests that serologic prevalence rates have increased fourfold in the past 50 years [48]. The concordance rate for CD in monozygotic twins is 75% and it highlights the role of other factors besides genetic predisposition [49]. The MHC molecules HLA-DQ2 and HLA-DQ8 are risk factors in the disease. Almost 90% of CD patients carry HLA-DQ2 antigens while most of the rest carry HLA-DQ8 [50, 51]. HLA-DQ2 molecule is encoded by the DQA1*0501 and DQB1*0201 genes [52].

T1DM is strongly associated with HLA DR3-DQ2 and DR4-DQ8 MHC molecules, and associated with DQB1*0302, DQB1*0201, DRB1*0401 and HLA-B alleles [53]. Approximately 90% of CD patients share the HLA DR3/DQ2 configuration [54]. The prevalence of tissue transglutaminase antibodies has been reported to be as high as 32% in HLA DQ2 homozygous T1DM patients, compared with 2% in patients without DQ2 or DQ8 [55].

CD and T1DM also share a number of other genetic susceptibility loci. Out of 8 celiac susceptibility loci, 6 are associated with T1DM. On the other hand, out of 17 diabetes-susceptibility loci, 8 are associated with CD [56]. At least 8 loci appear to be common for both conditions (CCR3, CCR5, SH2B3, RGS1, TAGAP, PTPN2, IL18RAP, CTLA4) [57]. It has been suggested that the immune or inflammatory responses associated with many autoimmune diseases overlap with the function of genes specific for certain diseases, such as IL12A in CD and INS in T1DM [57]. Two new CD risk regions were recently identified at chromosomes 6q23.3 (OLIG3-TNFAIP3) and 2p16.1 (REL) [58]. Polymorphisms within the TAGAP gene are also related to another autoimmune disease: rheumatoid arthritis [59].

The coexistence of T1DM and CD could be explained by a common genetic factor in the HLA region [60, 61] or by molecular mimicry by which gliadin or tissue transglutaminase C activates T cells that are cross-reactive with various antigens. During active β-cell destruction, transglutaminase C, which is expressed in pancreatic islets, might be presented in an immunogenic form. Such inflammatory responses may have the capacity to persist in susceptible hosts and lead to chronic organ-specific autoimmune disease [62]. Furthermore, it

has been suggested that in the development of autoimmunity in T1DM, the failure to achieve tolerance to autoantigens is attributable to gut related issues [63].

5. Diagnosing CD in diabetic patients

At the time of writing this chapter, duodenal biopsy remains the gold standard for CD diagnosis. The diagnostic criteria devised by ESPGHAN in 1989 [64] and later modified, consist of finding villous atrophy and crypt hyperplasia in a patient who ingests a sufficient amount of gluten (the Marsh classification [65]) and achieves remission after discontinuing gluten from the diet. The diagnosis is further confirmed by positive serology. Highly sensitive and specific IgA and IgG antiendomysial antibodies (EmA) and tissue transglutaminase antibodies (anti-tTG) are most frequently used. Sometimes, deaminated gliadin antibodies (DGP) are also elevated.

When evaluating anti-EmA and anti-tTG antibodies only of the IgA class (which is often preferred due to the lower cost), it is important to note the IgA concentration as well, as the frequency of isolated IgA deficiency in celiac patients is almost 2% and 7.7% of patients with isolated IgA deficiency suffer from CD [66].

The above criteria are about to change. With exceptionally high levels of antiendomysial antibodies and positive genetic testing (HLA-DQ2, DQ8), CD might be diagnosed without histopathologic examination[67]. The use of three PCR reactions and a single electophoretic step for DQA1, DQB1 and DRB1 typing provides distinction of CD associated alleles and their homo- or heterozygous status. This analysis reduces reagent costs, personnel and instrument time, while enabling improved allelic assignment through HLA-DR-DQ haplotype association [68]. In case of doubt, when the levels of antibodies are low, duodenal biopsy is recommended to confirm the diagnosis.

6. Evaluation for celiac disease in diabetes mellitus type 1 patients

T1DM often coexists with CD. However, the latter is often latent, Larsson et al. suggest that T1DM patients should be screened annually [69].

There is no consensus as to whether all diabetic patients should implement a gluten-free diet, nor is it clear how often they should be screened for CD.

The ADA recommends screening diabetic patients for CD and placing all children with a confirmed diagnosis of CD on a gluten-free diet (GFD) [70]. ISPAD suggests that while it seems sensible to put an asymptomatic child on a GFD to avoid the development of disease complications, evidence supporting this is still not sufficient. Therefore, they recommend that children with confirmed CD and T1DM receive support from a paediatric dietician [71].

Classical presentation of CD can occur in T1DM patients, but many patients with CD and T1DM are either asymptomatic (silent CD) or present with only mild symptoms [72, 73]. In a recent study from a North American CD clinic, 71.4% of children with diabetes reported no gastrointestinal symptoms at the time of a positive screen [74]. Some patients are overweight or obese at diagnosis; 11.2% of children with CD had a BMI greater than the 90th percentile in a recent US study [72]. Based on these data, the ISPAD recommendations for the screening of all T1DM patients for CD appear to be adequate. Screening for CD should be carried out

at the time of diagnosis, annually for the first five years and every second year thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of CD or the child has a first-degree relative with CD [71].

It should be emphasised that both adults and children suffering from CD are at an increased risk for sepsis. The risk is highest for pneumococcal sepsis [75]. Therefore it is recommended to vaccinate these patients against pneumococci.

Patients with both CD and T1DM have gastrointestinal symptoms more often than those who suffer from diabetes only. These include stomach pain, bloating, diarrhea, failure to thrive, and decreased appetite. In the study by Naruli et al. [76], this difference was statistically significant ($p<0.0005$). The symptoms subsided after switching onto a gluten-free diet, which goes to show that CD was in fact not asymptomatic. Patients who observed the diet significantly improved their weight SD score ($p=0.008$) and BMI SD score ($p=0.002$) within a year.

In a study by Fröhlich-Reiterer et al. [77], patients with both T1DM and CD (confirmed by a biopsy) were diagnosed with diabetes at a younger age and were of a generally lower height and weight. Those features were statistically significant ($p<0.001$) and they continued for another five and a half years of observation.

According to Pitocco et al. [78], patients with both diseases are at higher risk of developing atherosclerosis compared to those presenting with diabetes or CD only.

Other recognised side effects associated with untreated CD in patients with T1DM include changes in insulin requirements, frequent hypoglycaemia, failure to thrive, delayed puberty, anaemia, osteopenia, osteoporosis and neurologic complications [79, 80, 81, 82].

The most clinically serious, but rare, complication associated with CD (usually the type resistant to treatment) is the development of small intestinal lymphoma[83]. The incidence of this malignancy in patients with both CD and T1DM, however, has not been adequately assessed.

In conclusion, it appears that despite being inconvenient and restrictive, a gluten-free diet should be implemented for all patients suffering from T1DM and CD. There is evidence that this diet might be effective in protecting the pancreatic β-cells and increasing the levels of insulin secretion in newly diagnosed patients [84, 85, 86]. A gluten-free diet is beneficial for diabetic patients. It improves the indicators of physical development, reduces the risk of atherosclerosis and sepsis (especially pneumococcal), and relieves the gastrointestinal symptoms associated with untreated CD.

We strongly suggest that annual screening for CD become part of routine practice in patients with T1DM.

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