

Celiac disease as an autoimmune condition

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Abstract

*Autoimmune diseases have become a major medical problem of recent years. Celiac disease is an autoimmune disease model. The aim of our study was to follow the changes in the clinical autoimmunity picture of the celiac disease from recent years. The study of autoimmunity in celiac disease has focused on associated diseases with the aforementioned disease: type 1 diabetes mellitus, thyroid autoimmunity disease, Graves' disease, Hashimoto's disease, systemic lupus erythematosus, systemic sclerosis, spondyloarthritis, hyperprolactinemia, Turner syndrome, Addison's disease, sensory neuropathies. Immune reactivity to tissue transglutaminase targeted autoantibodies and other autoantigens, including transglutaminase 3, actin, ganglioside, collagen, calreticulin or zonulin which have been reported in the celiac disease. New research directions given by celiac disease autoimmunity, interleukin 1, interleukin 2, protein tyrosine phosphatase non-receptor type 22, CD4+CD25+ T lymphocytes, cytotoxic T-lymphocyte antigen 4, infection with *Necator americanus* and definitive identification of pathogenic T cell epitopes, seem to provide a solution in celiac disease treatment.*

Key words: diagnosis, autoimmunity disease, research direction.

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Introduction

In the United States, the increase in prevalence of celiac disease (CD) during a 15-year period was attributable to the increasing number of the subjects who lost the immunological tolerance to gluten in their adulthood [1]. In Europe, CD is widespread in the Western countries [2]. A clear environmental trigger has been identified in CD [3], namely gluten from wheat, barley, and rye [4]. Patients with CD are continuously exposed to the exogenous dietary antigen gluten [5]. Therefore, CD is a self-perpetuating autoimmune condition [6], influenced by disorders of the gut microbiota [7]. Why is it necessary to study separate autoimmune phenomena from CD? Innate gluten sensitivity, adaptive gluten sensitivity and autoimmunity are independent phenomena and are all essential in the development of CD [8].

Material and methods

In a recent study we have analyzed the immune response and new immunological challenges in CD [9]. The aim of our study was to follow the changes in the clinical autoimmunity picture of CD from recent years. We conducted the study on the PubMed database. Eligibility criteria consisted of data found in articles indexed in the PubMed database about autoimmunity in CD.

Results and discussion

Clinical presentation

Gluten exposure in infants genetically susceptible to CD leads to an immune response against gluten. These are more common than at-risk infants, in which gluten exposure occurs late until 12 months of age [10]. The single life-long treatment is a gluten-free diet (GFD) [11]. Some study showed an increased incidence and prevalence of CD in developed countries [12]. However, autoimmune disease prevalence including CD was 1.4% in older women (95% CI: 1.3%, 1.5%), which is the evidence that GFD is beneficial [13]. But gender differences were also found in CD [14].

The prevalence of type 1 diabetes mellitus (T1DM) among CD families was 0.9% [15]. Within the framework of polyglandular disorders, T1DM can coexist with CD. But in CD organ-specific autoantibodies can occur [16]. Children diagnosed with T1DM before the age of 6 had a major risk of developing CD, compared with those diagnosed after this age [17]. After long-term monitoring of diabetes [18], CD appearance in the T1DM was identified as one of the autoimmune morbidities [19]. Researchers analysed three functional 5' un-translated region β -defensin 1 (DEFB1) single nucleotide polymorphisms (SNPs) in a group of 170 T1DM patients. They found no association of DEFB1 SNPs with the onset of thyroid autoimmunity disease (TA), CD,

and both TA and CD in T1DM patients [20]. But the prevalence of CD is 5.4% in patients with TA [21]. Thyroid autoimmunity disease appeared to be as common in paediatric and adolescent patients with CD on a GFD as in controls [22]. Another recent study highlighted the fact that there is a prevalence of 1.2% of CD for Graves' and 1.2% for Hashimoto's diseases [23].

Integrin, alpha M (complement component 3 receptor 3 subunit) and its related 'predisposing' variant (rs1143679, Arg77His) are predicted to alter the tertiary structures of the ligand-binding domain and can play a key role in systemic lupus erythematosus (SLE) pathogenesis. A group of researchers evaluated case-control associations between rs1143679 and autoimmune diseases ($n = 18,457$) including CD. The conclusions were that integrin, alpha M (complement component 3 receptor 3 subunit) could not possibly be a general autoimmunity gene but this variant could eventually be associated with SLE and systemic sclerosis [24].

In CD, bone metabolic changes are more frequently associated with inflammatory joint disorders. Several disorders have been revealed as associated diseases/extraintestinal manifestations, including rheumatological diseases [25]. According to Iqbal *et al.*, a high rate of spondyloarthritis could not be observed in CD patients but increased rates of T1DM, TA, SLE, and psoriasis could [26]. Another possible association with CD, namely the risk of psoriasis was found in CD patients with vitamin D deficiency (7% vs. 3%, $p = 0.04$) [27].

An association between active CD and hyperprolactinemia was found suggestively higher in patients with active CD than in patients with an inactive one [28]. A 2.7% prevalence of CD in Turner syndrome (TS) [29] was found. The most common clinical features of TS are short stature and gonadal dysgenesis. Grossi *et al.* presented a unique case of mosaic TS with a complex rearrangement involving a partial deletion of chromosome 2q and duplication of chromosome 10p. Thyroid autoimmunity disease was associated with a group of multiorgan autoimmunity-related manifestations including Hashimoto's thyroiditis, CD, T1DM. Their conclusion was that timely genetic analysis in TS patients with complex associations of multiorgan autoimmune manifestations would enable a detailed diagnostic classification [30].

Another rare, chronic endocrine disorder in which the adrenal glands do not produce enough steroid hormones is autoimmune Addison's disease (AAD). In AAD, a 3.5% prevalence of CD [31] was identified. Celiac disease was occasionally associated with a neurologic disease (4 patients among 70 CD patients), and with antibody reactivity to neuronal antigens [32]. But a recent study described CD as one of the autoimmune diseases most often associated with sensory neuronopathies [33].

Diagnosis

Tissue transglutaminase (tTG) is a deamidating enzyme that can increase the immunostimulatory effect of

gluten, and a target autoantigen in the immune response [34, 35]. Autoantibodies to tTG showed high CD specificity and sensitivity [36]. Immune reactivity to other autoantigens, including transglutaminase 3, actin, ganglioside, collagen, calreticulin or zonulin has also been reported in CD [37]. The small-bowel mucosa and other tissues deposited CD specific tTG-targeted autoantibodies. Therefore, extraintestinal manifestations of the CD [38] have been reported. Marwaha *et al.* found high positivity of anti-glutamic acid decarboxylase and anti-tTG antibodies, i.e. 6.9 and 12.5 per cent in subjects among cases compared to 3.5 per cent ($p = 0.015$) and 4.3 per cent ($p = 0.001$) in controls, among subjects with TA [39]. The researchers observed a slight and probably irrelevant increase in IgG tTG antibody in patients with rheumatoid arthritis treated with adalimumab [40]. Tissue transglutaminase has also been associated with angiogenesis disturbance in CD [41].

One or more CD HLA-DQ heterodimers increased the risk of developing CD ($p < 0.001$) [42]. The HLA-DR3-DQ2 haplotype in children with T1DM was associated with CD in the extended family ($p < 0.001$) [43]. By stratifying the HLA-DQ, Östensson *et al.* identified a new genome-wide significant risk locus covering the DUSP10 gene [44].

New immunological research directions

Interleukin-1 β has a systemic influence on the loss of immunological tolerance and NALP3 inflammasome was directly involved in the pro-inflammatory cytokine production. Pontillo *et al.* highlighted an association of NLRP3 rs358294199 SNP to CD ($p = 5 \times 10^{-4}$). They hypothesized that variations in NLRP3 could belong to a predisposing genetic background that triggers autoimmune diseases development [45]. The increase in Th1 serum cytokines could possibly be associated with CD in offspring [46]. The associations for interleukin-2 gene polymorphisms and its α - and β -chain receptor (IL2RA and IL2RB) variants of different autoimmune diseases including CD were also suggested [47]. Protein tyrosine phosphatase non-receptor type 22 (PTPN22) is a strong susceptibility gene spread among many autoimmune diseases. PTPN22 showed a negligible association with CD [48].

Hmida *et al.* isolated intraepithelial lymphocytes (IELs) and lamina propria lymphocytes (LPLs) from duodenal biopsy specimens of CD patients and controls. CD4+CD25+ T lymphocytes (Tregs) were purified from blood. They tested responses of IELs, LPLs and peripheral lymphocytes (PBLs) to suppression by Tregs. Their results indicated that effector T lymphocytes from active CD become resistant to suppression by Tregs. Their conclusion was that this resistance might cause loss of tolerance to gluten, but also to self-antigens [49]. The level of soluble CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4), also known as CD152 (cluster of differentiation 152) was evaluated in the sera of CD patients with overlapping autoim-

mune diseases (obliterative airway disease (OAD), T1DM, TA, inflammatory bowel diseases, and autoimmune polyendocrine syndromes). The results showed a statistically significant association for serum sCTLA-4 levels with associated autoimmune disease (i.e. OAD) in CD patients vs. patients with CD only [50].

The infection with *Necator americanus* remains a challenge, which elicited parasite-specific immunity and modified the host's immune response to gluten: mucosal IL-1 β and IL-22 responses were enhanced, but IFN- γ and IL-17A levels and circulating regulatory T cells following gluten challenges were suppressed [51]. The biggest challenge remains the definitive identification of the pathogenic T cell epitopes, which would outline the antigen-specific immunotherapy in CD [52].

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