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Celiac Disease and Other Autoimmune Disorders

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1. Introduction

Celiac disease (CD) is an autoimmune condition affecting the small intestine, triggered by the ingestion of gluten, the protein fraction of wheat, barley, and rye. There is a strong linkage between CD and HLA-DQ2 and HLA-DQ8 haplotypes. As in other autoimmune diseases, CD results from of an immune response to self-antigens, leading to tissue destruction plus the production of autoantibodies and has a complex pattern of inheritance with influence from both environmental as well as additive and non-additive genetic factors [1, 2]

A significantly increased prevalence of other autoimmune diseases has been reported in individuals with CD and their first-degree relatives as compared to controls. This chapter provides an overview of the pathogenesis of CD and reviews the literature regarding associations between CD and other autoimmune diseases, including the potential effects of gluten-free diet therapy on the prevention or amelioration of associated diseases. It has been speculated that these associations might share a pathogenic basis that involves the same environmental triggers, genetic predisposition, compromise of the intestinal barrier secondary to the failure of tight junctions, leading to greater permeability of the intestine, and perhaps mechanisms yet to be identified [1, 2].

2. Autoimmune disorders

The decline in physiological tolerance against “self” antigens gives rise to autoimmune disorders. While various mechanisms might participate in this process, faulty regulation of B-cell and T-cell activation as well as of inflammation pathways are plausible [3]. Predisposition to autoimmune diseases has been related to genetic, epigenetic, and environmental factors. With modern genetic-analysis techniques, our grasp of autoimmunity is steadily improving.

To date, over 30 genome-wide association studies (GWAS) have examined an array of autoimmune diseases (AID) while studies have identified hundreds of common variants that represent protection or risk [4].

The genetic bases of autoimmunity are just starting to be uncovered, while several susceptibility genes have been identified in the most common autoimmune diseases. In addition, structural variants (insertion/ deletion polymorphisms, copy number variations, etc.) are also likely to play a significant role in determining susceptibility to autoimmune disorders [3-4].

Although on the genetic level, immune-related diseases still differ, e.g. in the number of disease-susceptibility loci, the effect sizes associated with each locus, and the environmental factors involved in the various diseases [5], there is clearly a remarkable overlap of susceptibility factors between various immune-related diseases [6-8]. The complex inheritance pattern implies the involvement of several genes. Despite that the same genes are unlikely to account for susceptibility to all autoimmune disorders, one gene complex (major histocompatibility complex, MHC, in the human leukocyte antigen, HLA) has invariably been involved as a key genetic risk factor and might explain why the autoimmune diseases co-exist [9].

This overlap clearly implies the involvement of shared pathways in multiple autoimmune diseases and, most importantly, suggests that general treatment modalities might be feasible for some immune-related diseases [9].

3. Celiac disease as an autoimmune disorder

Celiac disease (CD) is one of the best-understood immune-related diseases. CD is frequent with a prevalence of about 1:100, and it occurs selectively in individuals expressing HLA-DQ2 or HLA-DQ8. The prevalence of CD in the western world is probably underestimated, since not all cases of CD are symptomatic and thus go undiagnosed [1]. As in patients with organ-specific autoimmune disorders, patients with CD have autoantibodies and suffer from the destruction of a specific tissue-cell type by CD8+ T cells [2, 10]. The presence of highly disease-specific transglutaminase 2 (TG2)-specific autoantibodies allows the diagnosis of the disease. These autoimmune features require the presence of gluten, and HLA-DQ2- or HLA-DQ8-restricted gluten-specific CD4+ T-cell responses have a central role in disease pathogenesis [10, 11]. On the basis of CD, it bears considering that exogenous antigens may drive autoimmune disorders.

The pathogenesis of CD reveals a complex interplay between environmental factors, genetics, the adaptive and innate immune systems, and the presence of autoantigens, in a process which has still not been fully elucidated.

It is a multifactorial disease caused by many different genetic factors acting in concert with non-genetic causes. Similar to other autoimmune diseases, CD is a polygenic disorder for which the MHC locus is the single most important genetic factor. The MHC locus accounts for 40 to 50% of the genetic variance in the disease. A genetic association between CD and the HLA class II genes in the major histocompatibility complex (MHC) has been documented [12,

13]. Although the HLA component of CD susceptibility is well characterized, little is known about the possible role of other genes than HLA [14–16]. Recently, various non-MHC genes have been found to be susceptibility factors. To date, researchers have described 39 loci having 57 independent association signals [17]. Of these genes, many are associated with immunity, especially with T-cell and B-cell function. All these loci together account for an estimated 14% of all genetic variance of CD [17].

These non-HLA genes may be important determinants of disease susceptibility, as indirectly shown by the high disease concordance rate in monozygotic twins (70%) compared with only 30% in HLA identical twins [18]. Mounting evidence suggests a genetic relationship between the *CTLA4* locus and various autoimmune disorders. CTLA4-Ig blockage of T-cell activation may determine some (though not all) immunological aspects of human CD [19]. A French case-control study [20] reported evidence of association between CD and *CTLA4* exon 1 polymorphism. Also, significant evidence for linkage to CD was found in a recent study on family-based linkage of the *CTLA4* region, as well as 39UTR polymorphisms and exon 1 [21].

More than 60% of CD-associated susceptibility loci are shared with at least another autoimmune condition such as type-1 diabetes and rheumatoid arthritis [22], suggesting common pathogenic mechanisms. In particular, the recognition of peptides by HLA molecules, posttranslational modifications required for optimal peptide binding, and immune mechanisms leading to tissue damage have been found [23].

One of the most important factors triggering CD is dietary gluten, a storage protein present in wheat and related grains (hordein in barley, secalin in rye, and avenin in oats). CD is an excellent model for studying the contribution of genetic factors to immune-related disorders because: (1) the environmental triggering factor is known (gluten); (2) as in other autoimmune diseases, in which specific HLA types (HLADQA1 and HLA-DQB1 are critically involved; (3) there is involvement of non-HLA disease-susceptibility loci, many of which are shared with other autoimmune diseases; (4) there is an elevated incidence of other immune-related diseases both in family members and individuals; and (5) both the innate and the adaptive immune responses play a role in CD [24, 25].

The tendency for multiple autoimmune disorders to occur over the lifetime of a CD patient has been well described. The co-existence of autoimmune diseases with CD is striking, and there is an association of the disease with type-1 diabetes, Sjögren's syndrome, autoimmune thyroid disorders, connective-tissue diseases and IgA deficiency. The role of protein complexes formed between exogenous and endogenous proteins in the formation of autoantibodies, and a CD8+ T cell response directed against altered-self and mediated by NK receptors in CD is an autoimmune reaction [8].

3.1. Pathogenesis

The main factors in CD pathogenesis include defective antigen processing by epithelial cells, along with the intrinsic properties of gliadins in addition to the individual's HLA-DQ haplotype [26]. This disorder is closely related to HLA class-II genes which map to the DQ locus. CD has been associated with the expression of both HLA-DQ2 and HLA-DQ8 expression

[27, 28]. A number of studies [29] have shown that most CD patients carry DQ2 (DQA1*05/DQB1*02), while the rest display an association with DQ8 (DQA1*0301/DQB1*0302). These HLA genes collectively represent as much as 50% of the genetic risk of developing CD. Studies on independent genome-wide linkage have found scant overlap among linkage regions, except for the HLA region on chromosome 6p21. According to linkage studies, besides the HLA region, the two likeliest regions are 19p13 and 5q32 [30-32].

The polymorphisms associated with autoimmune diseases appear to be primarily in genes that have immune functions. These polymorphisms have presumably evolved for their advantages in combating pathogens. These polymorphisms, in the presence of foreign antigen gluten, may also help shape the immune response [33].

Gliadin peptide presentation and T-cell activation are critical events in the pathogenesis of CD. The toxic effects of these prolamins include the reduction of F-actin, inhibition of cell growth, premature cell death, the rearrangement of the cytoskeleton, and increased small-intestine permeability [34].

Gastric, intestinal, and pancreatic enzymes do not fully digest gluten peptides in individuals with CD. In these patients, a 33-mer peptide which has been isolated and has been identified as being the prime trigger of inflammation in reaction to gluten [35]. This peptide reacts with tissue transglutaminase (tTG), which is the main CD autoantigen, by which specific glutamine residues of gluten are deamidated to glutamic acid. [12, 36]. Antigen-presenting cells that express molecules of HLA-DQ2 and HLA-DQ8 show greater affinity for deamidated peptides. Afterwards, as the immunogenic peptides generated bind to HLA molecules, peptide complexes form and are capable of activating host-gluten-specific CD4+ T cells found in the lamina propria. When these T cells are activated, a number of cytokines are produced, in turn promoting inflammation and damage to the small-intestine villi from metalloproteinases released by inflammatory cells and fibroblasts [35, 29]. Activated gluten-specific CD4+ T cells are also capable of stimulating B cells to produce anti-gluten and anti-TG2 antibodies. It is believed that the IFN-gamma production from these gluten-specific T cells may be the main cause of mucosal intestinal lesion [35, 12]. Furthermore, shifts in intestinal permeability, secondary to changes in tight junctions or in food-antigen processing, have recently been associated also with a loss of gluten tolerance [29].

3.2. Clinical presentation

The clinical profile of CD is extremely varied. In children, the disorder is often reflected in anemia, abdominal distension, chronic diarrhea, steatorrhea, delayed puberty, and short stature. Common adult symptoms include abdominal distention and pain, chronic diarrhea, malabsorption, and general weakness [9]. Nevertheless, many individuals have few or no gastrointestinal symptoms, but present features such as neurological problems, anemia, osteoporosis, dermatitis herpetiformis, and fertility problems among others [29, 12]. Therefore, instead of primarily a gastrointestinal malady, CD should be considered more as a multisystem disorder. Whereas some non-intestinal symptoms of CD, e.g. osteoporosis or anemia, are due chiefly to nutritional deficiencies resulting from mucosal injury, others imply a far more complex relation to CD involving immunological as well as genetic factors.

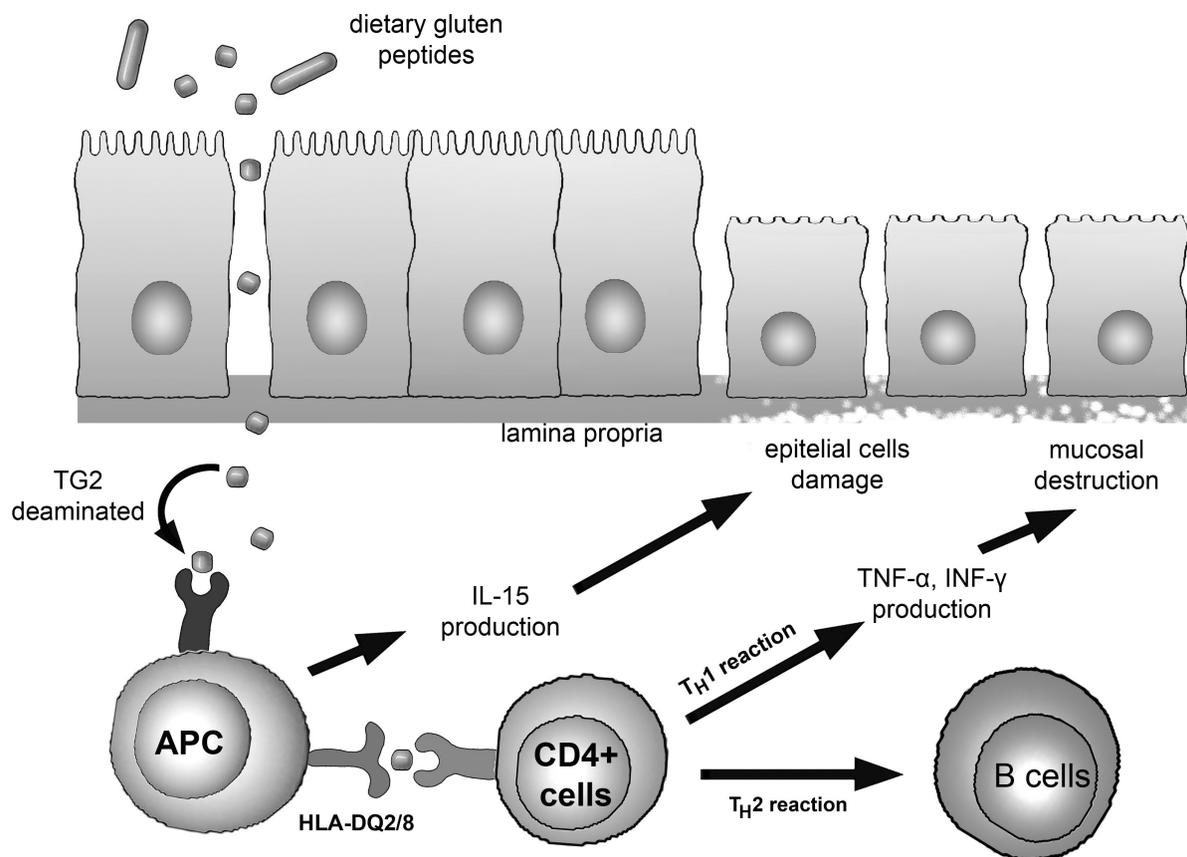


Figure 1. Schematic representation of CD pathogenesis. (Re-drawn of Sollid LM et al. Nature Reviews Immunology 13, 294-302. 2013)

3.3. Diagnosis

CD can be diagnosed according to the current guidelines, given that an intestinal biopsy is the only diagnostic procedure with broad consensus. CD diagnosis should follow the criteria laid out by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) or the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) [37].[38]. Figure 2 summarizes CD diagnosis.

3.4. Immune (oral) tolerance

The intestinal tract is the major immunological organ of the human body and plays an essential role in the induction of oral tolerance. Given that immunologically mediated reactions to foods can affect almost all organ systems, some extrinsic factors, such as gluten, can perturb the immune regulation in autoimmune disorders. The immune system of the intestine is exposed to innumerable antigens from foods, and endogenous as well as exogenous microbes [39]. Oral tolerance involves a lack of immune responsiveness towards food and bacterial antigens of the gut flora. Many mechanisms at the cellular and molecular levels participate in regulating this basic aspect of the intestinal immune system [40].

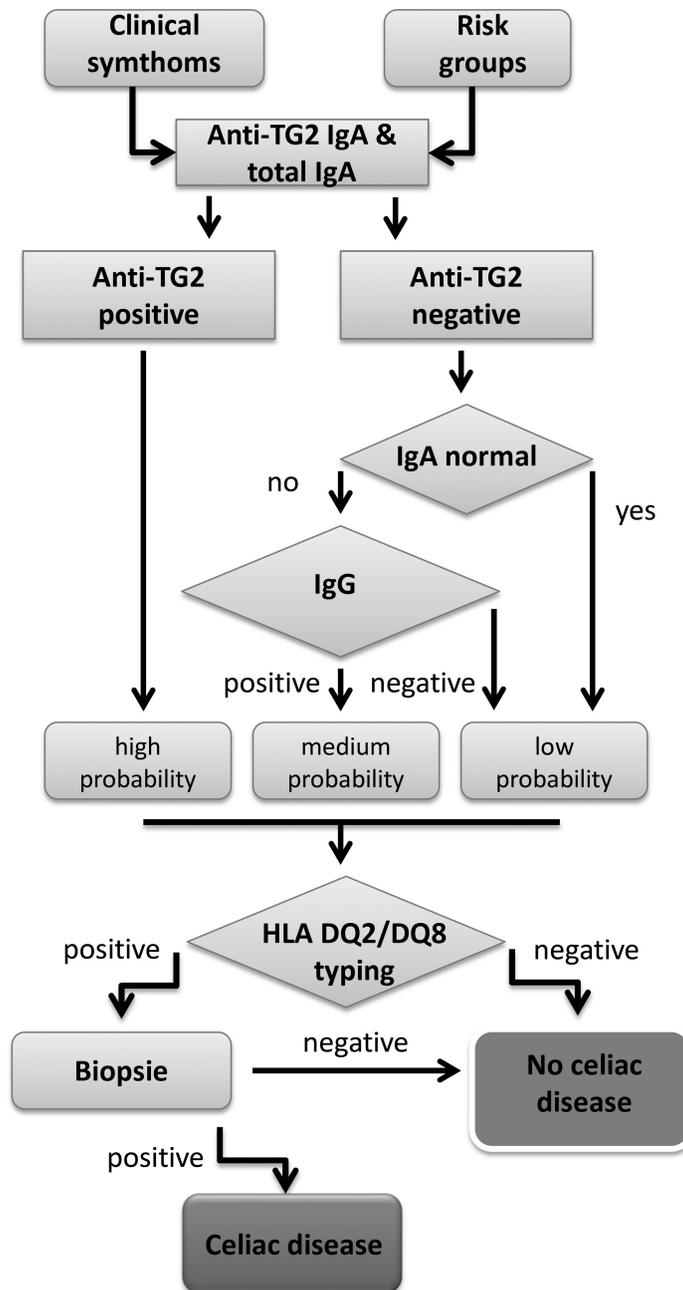


Figure 2. Algorithm for the diagnosis of celiac disease (Re-drawn of Mayo Foundation for Medical Education and Research (MFMER))

The most widespread food-sensitivity pathology in humans, CD results from defective immune tolerance (oral tolerance) to gluten (wheat) and the prolamins (rye and barley). Researchers have identified numerous gluten peptides that gut T cells recognize [41]. A major event in the CD pathogenesis involves the activation of gluten-reactive T cells. A high percentage of intraepithelial T cells that bear a gamma-delta chain of antigenic T-cell receptors ($\gamma\delta$ IEL) characterizes the mucosa in CD patients [42].

When ingested, the agent that triggers the disorder, gliadin, may penetrate the epithelial barrier to trigger a harmful immune response mediated by T cells. Immature dendritic cells, having characteristically low MHC class-II expression as well as co-stimulatory molecules, can modulate tolerance apparently by inducing Treg cells (T regulatory cells) [43]. Furthermore, Treg-cell-released IL-10 can mediate the activity of immature dendritic cells, inhibiting their differentiation, and thus locally favoring the presence of “tolerizing dendritic cells” [44]. Anergy of effector T cells is induced by IL-10-modulated dendritic cells through an as yet unknown process that requires contact between cells.

The immune-response shift towards tolerance or immunity is determined by the maturation stage and functional aspects of the dendritic cells. The unresponsiveness stage of immature dendritic cells can be overcome with the participation of gliadin peptides by inducing the functional and phenotypic maturation of dendritic cells, promoting more effective gliadin peptide processing and presentation to specific T lymphocytes [45]

A mouse model that overexpressed IL-15 in the lamina propria, at amounts comparable to those found in CD subjects, in cooperation with retinoic acid, was demonstrated to break oral tolerance to dietary antigens, triggering the differentiation of inflammatory dendritic cells that produce proinflammatory cytokines IL-12p70 and IL-23 and prompting the differentiation of IFN- γ -producing T cells (TH1 immunity)[46]. Also, Type-I IFNs are upregulated in the intestinal mucosa of subjects having active CD [47]. By activating dendritic cells, Type-I IFNs promote TH1-type immunity, causing oral tolerance to be lost, and might be an alternative pathway, triggering the loss of gluten tolerance.

Of special interest in CD is the expression of soluble HLA-G, as this molecule is key in immune-tolerance induction. We suggest that in CD a greater expression of soluble HLA-G could help to restore gluten tolerance. That is, HLA-G appears to interact with an inhibitory receptor (ILT), leading to the development of tolerogenic dendritic cells, inducing immunosuppressive and anergic T cells, and inhibiting dendritic-cell maturation/activation. Inflammatory stimuli and cytokines tightly control the expression of ILT receptors in dendritic cells [48]. Torres MI et al. found a correlation between higher levels of soluble HLA-G expression and CD associated with other autoimmune diseases, this depending on a genetic link of these diseases through HLA genes[48].

3.5. Autoimmune features of celiac disease

3.5.1. Autoantibodies

Untreated CD patients (on a wheat-containing diet) usually have higher levels of antibodies against wheat gluten, several other food antigens, and autoantigens present in the mucosa. In some autoimmune disorders, autoantibodies can specifically interfere with the biologic activities of a specific antigen, while in others they can cause tissue injury by forming immune complexes that activate the complement system. High titers of autoantibodies against tissue transglutaminase 2 (TG2) in patient sera TG2-specific immunoglobulin A (IgA) is the most characteristic aspect of CD and can be used to diagnose the disorder, reaching specificity and sensitivity of almost 100%. Even subjects with negative serum TG2-specific antibodies still

seem to produce these antibodies locally, as reflected by small-intestine deposits [49]. In the small-intestine mucosa of untreated cases, it has in fact been demonstrated that, with CD, roughly 10% of all plasma cells prove to be TG2-specific [50]. The anti-TG2 antibodies in CD have been shown to be capable of interfering with TG2 activity and hamper the differentiation of epithelial cells [51, 52]. In addition, anti-TG2 antibodies also reportedly increased the permeability of epithelial cells in an intestinal cell line and activated monocytes on binding to Toll-like receptor 4, perhaps contributing to gut injury [53].

In CD subjects, although autoantibodies are directed mainly against the activated Ca²⁺ (extracellular) form of TG2, calreticulin and actin antibodies also appear [54, 55]. Antibodies to TG2 include IgA as well as IgG isotypes, whereas IgA antibodies are more specific than IgG antibodies, and it is also thought that this Ab is produced primarily in the mucosa of the intestine [56]. A weak inhibitory effect of the antibodies on certain TG2-catalyzed reactions has been reported [57, 58]. TG2 is involved in the formation of active TGF- β by the crosslinking of the TGF- β binding protein. Indirect inhibition of TGF- β activation can have broad effects, including dysregulation of enterocytes and immune cells [59]. TG2 participates in the motility as well as attachment of fibroblasts and monocytes through interactions with fibronectin and integrins. The cause of CD villous atrophy could be the activity of TG2 autoantibodies upsetting fibroblast and epithelial cell migration to the tips of the villi from the crypts [60].

Also, anti-TG2 antibodies may play a part in certain non-intestinal symptoms of CD, by interacting with TG2, in addition to cross-reaction with other transglutaminases. Deposits of anti-transglutaminase antibody have in fact been detected in the brainstem and cerebellum of a patient showing cerebellar ataxia, and, in fact, gluten sensitivity. In certain idiopathic, neurological, and psychiatric disorders, these antibodies proliferate, moving some researchers to examine the potential of their cross-reactivity to neural antigens. In addition, anti-gliadin antibodies reportedly bind to neural cells and also cross-react specifically with synapsin I [61].

3.5.2. Autoreactive intraepithelial lymphocytes

Leukocyte accumulation is common in autoimmune lesions. Similarly, leukocyte infiltration occurs in CD lesions, in the lamina propria as well as in the epithelium [62]. CD8⁺ T cells, called intraepithelial cytotoxic lymphocytes (IE-CTLs), predominantly infiltrate the epithelium. The lamina propria shows greater density of different cell types, including antigen-presenting cells (dendritic cells and monocytes), plasma cells, and CD4⁺ T cells.

Inhibitory and activating NKG2 natural killer (NK) receptors tightly regulate normal intraepithelial lymphocytes (IELs). These receptors recognize non-classical HLA molecules, which are induced by IFN- β (HLA-E) and stress (MIC) exerted on epithelial cells of the intestine [63, 64]. CD, when untreated, characteristically has increasing density of proliferating TCR $\gamma\delta$ ⁺ CD8⁺ CD4⁻ and TCR $\alpha\beta$ ⁺ CD8⁺ CD4⁻ cells in the villous epithelium, and this upregulates the selectively activating NKG2 receptors [63, 65]. The upregulation of these NKG2 receptors seems to be driven by IL-15, which is expressed by CD enterocytes [63, 66]. IL-15 seems to play a critical role in the expansion of IELs [66], and in the induction of MIC molecules on intestinal epithelial cells [67].

As suggested by Sollid *et al.*, in order for IE-CTLs to kill, need two independent but related changes in the mucosa of the intestine: 1) an epithelium that is under stress and expresses high IL-15 levels and non-classical MHC class-I molecules; and 2) activated gluten-specific CD4+ T cells [68]. The way in which B-cell immunity, an adaptive anti-gluten T-cell immunity, epithelial stress, and TG2 activation interact to determine the acquisition of a killer phenotype by IE-CTLs remains to be elucidated.

3.5.3. *Gluten-free diet and autoimmune disorders*

Numerous papers have investigated the effect of CD treatment on the incidence and prognosis of various autoimmune disorders [69]. A prospective study by Ventura *et al.* examining 90 adults with biopsy-proven CD determined the autoimmune antibody levels associated with type-1 diabetes (glutamic acid decarboxylase, islet cell, anti-insulin) as well as autoimmune thyroiditis (anti-thyropoxidase); the examination was at CD diagnosis, and later, while on a gluten-free diet (GFD), at intervals of as much as 2 years [70]. As all antibodies normalized after 2 years without gluten intake, the authors concluded that a GFD was therapeutic against related autoimmunity [70]. In a study by Cosnes *et al.*, autoimmune-disease incidence proved lower in the gluten-free-diet group compared to the gluten-intake group [71]. In the same study, subjects with their first CD diagnosis at more than 36 years of age displayed a lower cumulative risk of autoimmune disorders vs. subjects diagnosed at 16 to 36 or under 16 years of age. The authors suggest that because CD manifests autoimmune dysregulation, celiac patients who are older may be less prone to autoimmunity or CD [71]. Also, a later onset of CD is related to greater intestinal-barrier integrity, thus diminishing antigen triggers in the case of several autoimmune diseases. Other large-scale prospective studies would be helpful to elucidate the way in which CD is related to other autoimmune conditions and to clarify the possible influence that GFD exerts in this context. Further clarification of these relationships would provide a fuller comprehension of specific disorders and of general autoimmunity.

4. Other autoimmune disorders associated

4.1. Associated autoimmune endocrine diseases

4.1.1. *Type 1 Diabetes (T1D)*

The association between CD and autoimmune insulin-dependent diabetes mellitus is one of the most intensely studied relationships. The prevalence of CD among patients with type-1 diabetes has been estimated in approximately 4% and this risk is highest with diabetes onset in childhood but also with a longer diabetes duration. It is known that T1D and CD both have autoimmune origins [72]. Also, both disorders have been associated with the major histocompatibility complex class-II antigen DQ2 encoded by the alleles, DQA1*501 and DQB1*201, this offering a genetic basis in common for the expression of these disorders. A recent study has also demonstrated that 7 shared non-HLA loci are associated with T1D as well as CD, including a 32-bp insertion-deletion variant on chromosome 3p21, *CTLA4* on chromosome

2q33, *SH2B3* on chromosome 12q24, *PTPN2* on chromosome 18p11, *TAGAP* on chromosome 6q25, *IL18RAP* on chromosome 2q12, and *RGS1* on chromosome 1q3 [73].

The ADA (American Diabetes Association) recommends screening T1D patients for CD and placing all children with a confirmed diagnosis of CD on a gluten-free diet (GFD) [74]. The screening of T1D patients for CD and a GFD is recommended by the NASPGHAN (the North American Society for Pediatric Gastroenterology and Hepatology) for children without symptoms but with an associated condition such as T1D. However, the ADA recognizes that meager evidence exists for suggesting that a GFD provides short-term improvement of diabetes. Furthermore, it remains to be clarified whether asymptomatic patients derive long- or short-term health benefits, or both, from a GFD [75]. No clinical studies available have monitored the natural progress of CD in asymptomatic patients, so that no beneficial effects for asymptomatic CD and T1D patients strictly following a GFD are known. A GFD may affect the lipid profile, HbA1c, glycemic values, insulin needs, and perhaps even diabetes complications over the long term. Furthermore, GFD could alter, for example, growth rate, body-mass index (BMI), height, and/or weight, although no consensus is available on the ultimate results of such a diet. Hence, it is important to evaluate the impact of a GFD on metabolic control, growth and nutritional status in children with T1D and CD [76]

4.1.2. Thyroid diseases

In subjects having autoimmune thyroid disease (i.e. Hashimoto's thyroiditis and Grave's disease), the CD rate reportedly accelerates, and its prevalence ranges between 2% and 7%. Similar findings have been reported in CD patients, whose serological signs of autoimmune thyroid disease (AITD) reached 26%, and in whom the detection of thyroid dysfunction reached 10% of the cases, and thyroid disease risk was some 3-fold higher than in control. Increased CD prevalence is known to occur in children and young adults who have AITD was caused by enrichment with patients with other co-morbidities associated with CD. In the absence of these co-morbidities or gastrointestinal symptoms, the prevalence of CD in AITD may not be sufficient to justify serological screening for CD in patients with AITD. A prevalence of positive tTG-IgA titers in patients with AITD was found to be higher than in a healthy population and a greater prevalence (2.3%) of biopsy-confirmed CD was noted in patients having AITD. [77]

The coexistence of CD and AITD has been explained by several mechanisms such as common genetic predisposition and the association of both diseases with the gene-encoding *CTLA4*, a gene causing susceptibility to thyroid autoimmunity. Several studies have suggested that *CTLA4* gene polymorphisms may be linked to autoimmune diseases, including T1D, CD, Addison's disease, and autoimmune thyroid disorders [78, 79]. *CTLA4* CT60 A/G polymorphism was reported to be strongly associated with autoimmune thyroid disease (AITD and an increased risk to develop a subsequent autoimmune disease in CD children [80]. This study in an Italian population showed that the risk of AITD in children with CD was substantially modified by the *CTLA4* CT60 A/G polymorphism, with the G allele in the homozygous state being the high-risk genotype. In this sense, *CTLA4* CT60 A/G polymorphism evaluation may

be useful for stratifying the frequency of testing celiac children for antibodies indicative of AITD [80].

4.2. Associated autoimmune liver disease

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are all considered to be autoimmune liver diseases, in which the end result is immune-mediated hepatocellular or hepatobiliary injury [81]. Clinical observations have demonstrated a link between CD and all three major autoimmune liver diseases, the association with primary biliary cirrhosis (PBC) being greatest. Disturbances in mucosal immunity may also be responsible for the hepatic manifestations of graft vs. host disease (GVHD) and IgG4-associated autoimmune pancreatitis [81].

The breakdown of gut-liver axis equilibrium plays a central role in the development of immune disorders involving the small bowel and liver in the context of genetic predisposition, and/or gut inflammation. Comsmensals or pathogenic bacteria may stimulate immune responses that fail to be suppressed by regulatory networks resulting in liver disease as a consequence of a breakdown in self-tolerance driven by molecular-mimicry or activation of innate immune pathways [82]. In celiac disease, immunologically active molecules generated from the cross-linking between tTG and food/bacterial antigens reach the liver through the portal circulation owing to the increased intestinal permeability and may contribute to triggering immune hepatic damage. This enterohepatic pathway is facilitated by the aberrant expression of adhesion molecules and chemokines that under normal conditions are restricted to either the gut or liver.

Celiac disease and primary biliary cirrhosis have several features in common, such as greater incidence in the female population, specific autoantibodies, and autoimmune comorbidities. For both diseases, reciprocal screening is advised, because early diagnosis followed by adequate treatment can enhance the outlook for such patients [82].

4.3. Associated autoimmune dermatological diseases

4.3.1. *Dermatitis herpetiformis*

Dermatitis herpetiformis (DH) is an inflammatory cutaneous disease with typical histopathological and immunopathological findings, clinically characterized by intensely pruritic polymorphic lesions with chronic relapse. DH patients reportedly undergo changes in the small intestine; later, these abnormalities prove similar to those found in subjects with CD. Currently this is considered more common than specific cutaneous manifestations of CD [83].

Although all DH patients present gluten sensitivity, a great majority are asymptomatic in terms of digestive symptoms [84]. The intestinal biopsy performed in DH patients could reveal signs of gluten sensitivity in 60% to 75%, ranging from normal-appearing epithelium to a flat mucosa (Marsh I to III). DQ8 and HLA DQ2 prevalence is the same level as in CD, giving strength to the idea that DH can be considered a cutaneous manifestation of CD. In fact HLA DQ2 is expressed in some 90% of DH patients (approx. 20% of controls), the other 10% being DQ8. It

is extremely rare to find patients who do not have the two predisposing HLA types [85]. These two types typify this disease, and consequently a lifelong strictly gluten-free diet is the most effective cure.

An additional worthwhile observation refers to CD patients who have DH. That is, these patients not only have anti-TG2 antibodies but also have antibodies which target TG3, this being a transglutaminase expressed only in the dermal papillae of patients with dermatitis herpetiformis [86]

4.3.2. Psoriasis

Psoriasis is a chronic inflammatory disease characterized by well-demarcated, erythematous, scaly plaques. Epidemiological and clinical studies suggest that psoriasis is associated with celiac disease and celiac disease markers. Bhatia et al. [87] performed a meta-analysis to show that psoriatic populations have an approximately 2.4-fold increased risk of elevated levels of AGA compared with control subjects. These authors showed that IgA AGA antibodies were positive in about 14% of patients with psoriasis vs. 5% of healthy control subjects. CD antibody positivity has been positively correlated with psoriasis severity or psoriatic arthritis. Notably, these psoriasis patients with high counts of CD antibodies did not necessarily show a correspondence to biopsy-confirmed diagnosis of celiac disease [87].

The pathogenesis of psoriasis and celiac disease involves the interplay among multiple gene-susceptibility loci, the immune system, and various environmental factors and may involve shared biological mechanisms. Genome-wide association studies of psoriasis and CD have revealed that these two diseases share genetic-susceptibility loci at 8 genes, including at *TNFAIP3*, *RUNX3*, *ELMO1*, *ZMIZ1*, *ETS1*, *SH2B3*, *SOCS1*, and *UBE2L3*. [88-90]. Adaptive and innate immune responses are regulated by these genes. Despite that autoantibody formation that typifies the Th2 axis is associated with CD, immunological studies of CD show that gamma-delta T cells, Th17 cells, Th1 cells, and natural killer-like cells have key importance in disease pathogenesis [91-94]. Similarly, psoriasis has been related to gamma-delta T cells, Th17 cells, and T helper (Th1) cells. Further hypotheses that link CD to psoriasis involve greater intestinal permeability under both conditions, and the proposal that, in patients with CD, vitamin-D deficiency can provoke psoriasis [95-97].

Regarding the benefit of a GFD in patients with psoriasis, some case reports showed a decrease in serologic markers of celiac disease after GFD and a significant reduction in the Psoriasis Area Severity Index score. These case reports documented resolution of psoriasis after GFD [98].

4.4. Associated rheumatological disorders and connective-tissue diseases

4.4.1. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem disorder with manifestations including rash, arthritis, cytopenia, and renal disease. Some case reports have suggested the association between CD and SLE. Patients with CD were at a 3-fold increased risk of SLE compared to the

general population. Although this excess risk remained more than 5 years after CD diagnosis, absolute risks were low. SLE is a complex autoimmune disease characterized by dysregulated interactions between autoreactive T and B lymphocytes and the development of antinuclear antibodies [99].

This is striking because both disorders share the human leukocyte *HLA-B8* and *HLA-DR3* histocompatibility antigens, and a variety of antibodies including the detection of tTG IgA as well as antinuclear and anti-stranded DNA antibodies [100]. Piccoli et al. found a significantly higher frequency of anti-endomysium antibodies (IgA-EmA) in SLE patients than in controls, although the titers of antibodies were predominantly low [101].

4.4.2. Rheumatoid arthritis

Celiac disease (CD) and rheumatoid arthritis (RA) are two autoimmune diseases characterized by distinct clinical features but increased co-occurrence in families and individuals. In fact, rheumatoid arthritis shares many major features that have been identified in CD, such as HLA association, T-cell infiltration in target organs, disease-specific autoantibodies, and the specific targeting of modified antigens *in vivo* [102]. Therefore, case studies of CD should help in identifying disease-relevant T-cell epitopes in rheumatoid arthritis.

More specifically, key enzymes catalyzing the post-translational modification of different amino-acid residues in antigenic structures play a major role both in CD as well as RA — that is, distinct peptidyl arginine deiminase (PAD) isoforms in RA [104] and TG2 in CD [103]. These enzymes plus other features shared by CD and RA, include immune targeting of modified proteins, target organ T-cell infiltration, autoimmune phenomena, HLA association, and the importance of post-translational modification regarding peptide binding to disease-associated HLA molecules.

Also, in CD as well as in RA, genome-wide association studies (GWAS) have identified the HLA region and 26 non-HLA genetic-risk loci. Research has demonstrated that, of the 26 CD and 26 RA risk loci, six are common to the two disorders, including *TAGAP*, *TNFAIP3*, *IL2-IL21*, *ICOS-CTLA4*, *REL*, and *MMEL/TNFRSF14* eliminate, and [105-107]

5. Conclusions

Celiac disease is categorized as an autoimmune disorder. In this context, it is noteworthy that celiac disease has been associated with various autoimmune disorders, but there are no reliable data to establish a cause and effect relationship between celiac disease, gluten, and these autoimmune conditions. In any case, there are more similarities between celiac disease and typical autoimmune diseases, such as type-1 diabetes and rheumatoid arthritis, than previously suspected. It has been proposed that such relationships might be accounted for by the common pathogenesis that involves similar environmental triggers, genetic predisposition, and the loss of intestinal barrier secondary to dysfunction of tight junctions leading to greater gut permeability, and perhaps other mechanisms yet to be discovered.

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