Systemic autoimmune disorders in celiac disease

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Purpose of review

Celiac disease is an immune-mediated disorder clinically characterized by a multitude of symptoms and complications. The comorbidity between celiac disease and other autoimmune disorders has been clearly established.

Recent findings

Two main theories have been postulated to explain this comorbidity: (1) linkage disequilibrium between the genes responsible for celiac disease and those responsible for the coexpressed autoimmune diseases or (2) untreated celiac disease leading to the onset of other autoimmune diseases. This article reviews the current literature supporting either theory and places the current knowledge in the field within the context of the most recent data on the pathogenesis of celiac disease.

Summary

The current literature did not clearly establish which of the two theories explain the comorbidity between celiac disease and other autoimmune disorders. There is, however, growing evidence that the loss of the intestinal barrier function typical of celiac disease could be responsible of the onset of other autoimmune disease. This concept implies that the autoimmune response can be theoretically stopped and perhaps reversed if the interplay between autoimmune predisposing genes and trigger(s) is prevented or eliminated by a prompt diagnosis and treatment.

Keywords

autoimmunity, innate immunity, intestinal permeability, tight junctions, Toll receptors

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Abbreviations

EMA	antiendomysium antibodies
GFD	gluten-free diet
ICA	islet cell antibody
NOD	nonobese diabetes
T1D	Type 1 diabetes
TAI	thyroid autoimmunity
TLR	Toll-like receptor
tTG	tissue transglutaminase

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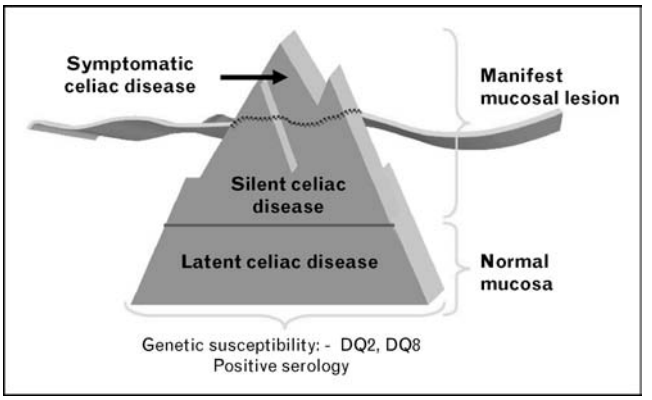
Introduction

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye and barley) in genetically susceptible persons. Celiac disease has several autoimmune features, including the production of highly disease-specific IgA and IgG autoantibodies to tissue transglutaminase (tTG) when patients are on a gluten-containing diet, and the presence of small intestinal intraepithelial lymphocytes which can mediate direct cytotoxicity of enterocytes expressing MIC molecules in an antigen-nonspecific manner [1•]. Similar to typical autoimmune disorders, celiac disease has a multifactorial etiology with complex genetics and comorbidity with autoimmune diseases. Celiac disease is, however, a unique example of autoimmunity, since early serological diagnosis and dietary treatment can revert the autoimmune process and can prevent its severe, sometimes life-threatening complications. Therefore, the common wisdom among experts in the field supports the notion that individuals affected by celiac disease should be treated, irrespective of the presence of symptoms and/or associated conditions. Well-designed prospective clinical studies to address this point have, however, not been performed, nor can they be conceived, given the ethical implications of such a proposition. Celiac disease can manifest itself with a previously unappreciated range of clinical presentations (the so-called celiac iceberg, Fig. 1), including the typical malabsorption syndrome (chronic diarrhea, weight loss, abdominal distension) and a spectrum of symptoms potentially affecting any organ system [2]. Since celiac disease often presents in an atypical or even silent manner, many cases remain undiagnosed, their diet treatment is significantly delayed and, consequently, the risk of long-term complications increases. While evidence-based data support the causative effect of untreated celiac disease for some of these complications, for

Figure 1 The celiac iceberg



The clinical outcome of the interplay between celiac disease genetic makeup and exposure to gluten, the environmental trigger of the disease, is typically represented by the iceberg model, with the symptomatic forms present at the visible part of the iceberg and the silent and potential forms being submerged below the water line.

other conditions this association remains questionable. One of the most controversial issues concerning possible complications of untreated celiac disease involves the association between celiac disease and other autoimmune disorders.

Celiac disease comorbidity with other autoimmune diseases: serendipitous association or calculated design?

The two most accredited theories to explain this comorbidity propose: (1) untreated celiac disease leads to the onset of other autoimmune disorders in genetically susceptible individuals or (2) this association is secondary to linkage disequilibrium of genes predisposing for both celiac disease and the associated autoimmune disease(s). The first hypothesis is supported by the evidence that tTG, the recognized autoantigen involved in the pathogenesis of celiac disease, seems to be only one of the autoantigens involved in gluten-dependent autoimmune reactions. Other autoantigens which are normally 'cryptic' can be unmasked and cause a self-aggressive immunological response following the gliadin-initiated inflammatory process [3]. In fact, persistent stimulation by some pro-inflammatory cytokines such as interferon-γ and tumor necrosis factor-α can cause further processing of autoantigens and their presentation to T lymphocytes by macrophage-type immunocompetent cells (so-called antigen-presenting cells). The phenomenon of antigen spreading has been described in well-defined natural models such as Type 1 diabetes (T1D), whose clinical manifestations appear after the patient has produced an autoimmune response to various autoantigens (i.e. anti-insulin, anti-β cell, etc.) and might also be present in celiac disease. This would explain the high incidence of autoimmune diseases and the presence of a large number of organ-specific autoantibodies in a certain number of celiac subjects on a gluten-containing diet.

The report by Ventura *et al.* [4] that studied the prevalence of autoimmune disorders in celiac disease in relation to the duration of exposure to gluten seems to support this theory. Over a 6-month period, 909 pediatric patients with celiac disease, 1268 healthy controls and 163 patients with Crohn's disease were evaluated for the presence of autoimmune disorders. The authors [4] detected a prevalence of autoimmune disorders among celiac disease patients higher than in controls, but similar to that detected in Crohn's disease patients. Prevalence of autoimmune disorders in celiac disease was increased with increasing age at diagnosis. In a logistic regression model, age at diagnosis was the only significant predictor variable of the odds of developing an autoimmune disorder [4]. Based on this evidence, the authors concluded that the prevalence of autoimmune disorders in celiac disease is related to the duration of exposure to gluten. The same group [5] screened sera from 491 subjects with T1D, 824 relatives and 4000 healthy control subjects for antiendomysium antibodies (EMA), followed by confirmatory intestinal biopsy in positive subjects. The authors found that the prevalence of celiac disease was 5.7% among diabetic patients and 1.9% among relatives – values significantly higher than those found among control subjects [5]. The prevalence of autoimmune disorders in diabetic patients with celiac disease was significantly higher than in subjects with T1D alone. The prevalence of autoimmune disorders in relatives that were diagnosed with celiac disease was significantly higher than in those who tested negative for EMA. The authors concluded that it would be appropriate to routinely screen diabetic patients and their relatives for celiac disease in order to prevent the onset of additional autoimmune disorders.

A report from Cataldo and Marino [6] suggest that the increased prevalence of autoimmune disorders is also increased in first-degree relatives of celiac disease patients. The authors reported a 6-fold increase of autoimmune diseases among relatives – a risk that increased with age. A subgroup of these relatives was diagnosed with silent celiac disease and their prevalence of autoimmune disorders as compared to first-degree relatives not affected by celiac disease was significantly higher with an odds ratio of 6.3 [6]. The authors concluded that first-degree relatives of celiac disease patients have an increased risk of autoimmune disease, most likely related to unrecognized and, therefore, untreated celiac disease.

Different conclusions were reached by Sategna Guidetti *et al.* [7], whose results favor the linkage disequilibrium hypothesis. The authors screened for the presence of autoimmune disorders in 605 healthy controls (16–84

years old) and 422 celiac disease patients (16–84 years old) that had been on a gluten-free diet (GFD) for at least 1 year. A logistic regression analysis, setting the prevalence of autoimmunity as the dependent variable, was employed to control for independent covariates as predictors of the risk of autoimmunity. The authors found a 3-fold higher prevalence of autoimmunity in patients as compared to controls. Mean duration of gluten exposure was 31.2 and 32.6 years for patients with or without autoimmunity. Logistic regression showed that increased age at diagnosis of celiac disease was related to the prevalence of autoimmune disease, whereas 'actual gluten exposure', which takes into account diet compliance, follow up and age at diagnosis of autoimmune disorders, was not predictive for the risk of developing autoimmune diseases [6]. Therefore, the authors concluded that the increased prevalence of autoimmune diseases in patients with a late celiac disease diagnosis does not correlate with duration of gluten intake nor does gluten withdrawal protect patients with a late diagnosis from autoimmune diseases.

The role of gluten as a trigger of autoimmunity

Funda *et al.* [8] explored the role of gluten as a trigger of the autoimmune process outside celiac disease using the nonobese diabetes (NOD) mouse model for diabetes. The authors showed that the early introduction of a GFD substantially lowered diabetes incidence in NOD mice (15%) compared to mice on the standard diet (64%). In addition, mice on the GFD developed diabetes significantly later (244 ± 24 days) compared to those on the standard diet (197 ± 8 days). Based on these results, the authors concluded that a GFD both delayed and to a large extent prevented diabetes in NOD mice that had never been exposed to gluten. These results have been recently confirmed by Maurano *et al.* [9•], who demonstrated that NOD mice fed a standard diet showed reduced villous height, increased intraepithelial infiltration by $CD3^+$ cells and enhanced expression of H2-IA and interferon-γ mRNA when compared with mice on the GFD. The cumulative diabetes incidence at 43 weeks of age was 65% in the latter and 97% in the former ($P < 0.01$). Mice fed a wheat-containing diet also showed increased epithelial infiltration and a higher incidence of diabetes [9•].

The role of gluten exposure in T1D pathogenesis has been also confirmed in human studies. Early introduction of gluten to children at high risk for T1D produces T1D-associated islet autoantibodies [10]. Feeding gluten-containing foods in the first 3 months of life yields a 4-fold greater risk of developing islet cell autoantibodies (and potentially subsequent diabetes) than exclusive breast feeding [10]. Children starting gluten foods between 4 and 6 months of age demonstrated no such association [10]. Similarly, in the absence of overt clinical symptoms of T1D, some celiac disease children produce diabetes autoantibodies in a gluten-dependent manner [11]. In diabetic patients, intestinal challenge with gluten produces mucosal recruitment of lymphocytes, similar to that seen in celiac disease patients [12]. The most direct evidence of the role of gluten as an 'instigator' of the autoimmune response in T1D has, however, been recently provided by Sblattero *et al.* [13••]. The authors monitored the effects of a GFD on anti-tTG antibody synthesis in the intestinal mucosa of a patient with T1D and a subjects at high risk of diabetes [anti-islet cell antibody (ICA)-positive], both carrying HLA-DQ2/DQ8, but lacking serum anti-tTG [13••]. Intestinal specimens from both subjects and samples of peripheral blood lymphocytes were used to make phage-antibody libraries to look for lymphocytes synthesizing anti-tTG antibodies. In both subjects, positive tTG antibody clones were isolated only from the intestinal lymphocyte libraries. After 12 months of GFD the subject at risk of T1D sero-converted from ICA-positive to ICA-negative. In both subjects, biopsies were normal, and analysis of new phage antibody libraries showed complete elimination of anti-tTG clones in the T1D subject and 90% reduction in the subject at risk of T1D [13••]. In this subject, reduced response to tTG and elimination of ICA after GFD suggest that an early intervention may abort and then revert the autoimmune process, indicating a possible temporary protection from the disease if a GFD is promptly implemented.

Autoimmune diseases associated with celiac disease

The celiac disease-associated autoimmune disorders can be either organ-specific, in which the autoantibodies are specifically directed against antigens localized in a particular organ and are often detected in circulation (e.g. Hashimoto's thyroiditis and T1D), or nonorgan-specific autoimmune disorders characterized by the presence of autoantibodies directed against ubiquitous antigens (e.g. systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and scleroderma) [14]. The focus of this review will be on the celiac disease–organ-specific autoimmune disorders association, since this association has been extensively studied.

Type 1 diabetes

A 10-year, age-matched study [15] found a highly significant correlation between endocrine disorders in celiac disease patients versus controls and concluded that celiac disease patients have a significantly higher prevalence of T1D. More recent studies [16,17] show a similar incidence of celiac disease in T1D patients. Early identification of celiac disease and subsequent treatment improves growth and diabetic control in children with T1D [18,19]. This comorbidity suggests possible genetic

polymorphisms that may dictate the risk of celiac disease in subjects with T1D. To address this hypothesis, Sumnik *et al.* [20•] investigated whether the susceptibility to celiac disease in diabetic children is modified by positivity for HLA-DQB1*02-DQA1*05 and DQB1*0302-DQA1*03, and by alleles of single nucleotide polymorphisms within the genes encoding several cytokines. The authors compared genotypic data between 130 case subjects (children with T1D and celiac disease) and 245 control subjects (children with T1D only). The best-fitting model showed that risk of celiac disease is increased by presence of HLA-DQB1*02-DQA1*05 [odds ratio 4.5 (95% confidence interval 1.8–11) for homozygosity and 2.0 (1.1–3.7) for a single dose] and also independently by tumor necrosis factor –308A [1.9 (1.1–3.2) for phenotypic positivity], whereas interleukin-1α –889T showed a weak negative association [0.6 (0.4–0.9)] [20•]. These results indicate that the risk of celiac disease in children with T1D is significantly modified both by the presence of HLA-DQB1*02-DQA1*05 and by a variant of another gene within the major histocompatibility complex, i.e. tumor necrosis factor –308A.

Thyroiditis

Thyroiditis has been repeatedly associated with celiac disease [15,21–23]. A highly significant association exists between celiac disease and autoimmune thyroiditis (Graves' disease and Hashimoto's thyroiditis), as evidenced by elevated EMA antibodies in these thyroid conditions [23]. In addition, abnormal liver enzymes (transaminases) are common in both thyroid disorders and subclinical celiac disease [24]. Mainardi *et al.* [25] specifically studied the association of celiac disease with autoimmune thyroid disease. The authors evaluated the prevalence of celiac disease in 100 patients with thyroid autoimmunity (TAI). They found that the prevalence of celiac disease in patients affected by autoimmune thyroid disease was 2% and that the serologic markers for celiac disease became undetectable 6 months after beginning a GFD, while thyroid autoantibodies did not change following the implementation of the diet. More recently, da Silva *et al.* [26] have studied 52 patients with celiac disease, nine of which were on a GFD. The patients were divided into four groups: Group 1, without thyroid involvement ($n = 30$), and Groups 2A–C, with thyroid involvement ($n = 22$) [Group 2A, subclinical hypothyroidism ($n = 11$); Group 2B, clinical hypothyroidism ($n = 10$) and Group 2C, other thyroid disorders ($n = 1$)]. Increased levels of thyroid-stimulating hormone and/or anti-thyroperoxidase antibodies were detected in Groups 2A (21.1%) and 2B (19.2%). The patients of Group 2B presented clinical symptoms of hypothyroidism before the diagnosis of celiac disease and five of these patients were receiving levothyroxine. There was a statistically significant correlation between the age when thyroid disease was diagnosed (current age) and the age of celiac disease diagnosis when Groups 1 and 2B were compared. Patients with thyroid involvement presented associated diseases such as T1D, Down's syndrome, ulcerative colitis and dermatitis herpetiformis.

Different conclusions were reached by Sumnik *et al.* [27], who performed a multicenter retrospective case-control study comparing data from 84 diabetic children with celiac disease (Group 1) to 167 diabetic children without celiac disease (Group 2), matched by age at T1D onset, duration of T1D and center. Markers of TAI, thyroid function and HbA1c were recorded. The TAI follow-up lasted 4.9 ± 2.8 years. TAI was diagnosed in 13% of children in Group 1 and 19% of children in Group 2. Diabetes control was not influenced by TAI in either group [27]. These results prompted the authors to conclude that occurrence of TAI in diabetic children is not related to coexisting celiac disease.

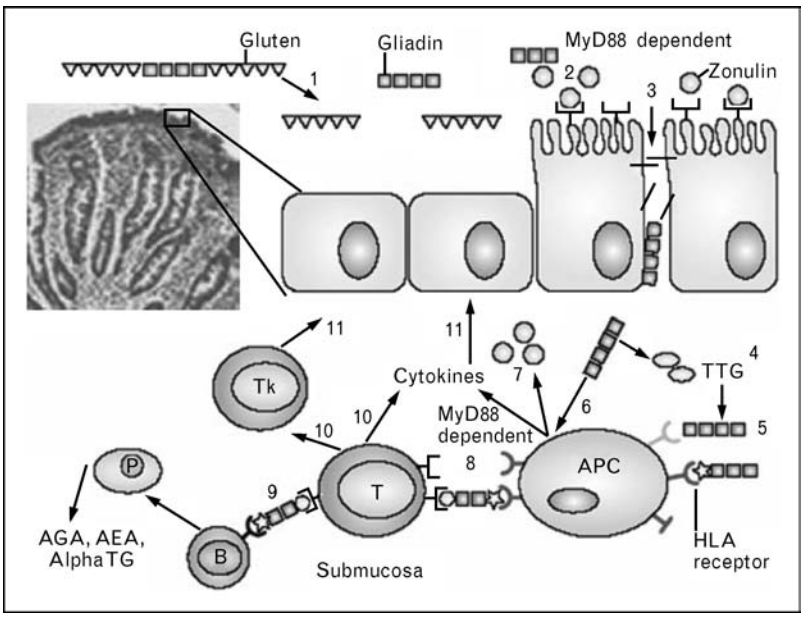
Celiac disease as a paradigm shift in the pathogenesis of autoimmune diseases

A common denominator of autoimmune diseases is the presence of several pre-existing conditions leading to an autoimmune process [28•]. The first is a genetic susceptibility for the host immune system to recognize, and potentially misinterpret, an environmental antigen presented within the gastrointestinal tract. Second, the host must be exposed to the antigen. Finally, the antigen must be presented to the gastrointestinal mucosal immune system following its paracellular passage (normally prevented by the competency of intercellular tight junctions) from the intestinal lumen to the gut submucosa [29,30]. In many cases, increased permeability appears to precede disease and causes an abnormality in antigen delivery that triggers the multiorgan process leading to the autoimmune response [31••].

Therefore, the following hypothesis can be formulated to explain the pathogenesis of autoimmune diseases that encompasses the following three key points:

(1) Autoimmune diseases involve a miscommunication between innate and adaptive immunity.
(2) Molecular mimicry or bystander effects alone may not explain entirely the complex events involved in the pathogenesis of autoimmune diseases. Rather, the continuous stimulation by nonself antigens (environmental triggers) appears necessary to perpetuate the process. This concept implies that the autoimmune response can be theoretically stopped and perhaps reversed if the interplay between autoimmune predisposing genes and trigger(s) is prevented or eliminated.
(3) In addition to genetic predisposition and the exposure to the triggering nonself antigen, the third

Figure 2 Proposed role of abnormal intestinal permeability in the pathogenesis of celiac disease (reproduced from [28•])



Gliadin and its immunomodulatory/inflammatory fragments are present in the intestinal lumen (1), inducing an MyD88-dependent zonulin release (2) that causes opening of tight junctions and gliadin passage across the tight junction barriers in subjects with dysregulation of the zonulin system (3). Following tissue transglutaminase (TTG) deamidation (4), gliadin peptides bind to HLA receptors present on the surface of antigen-presenting cells (APC) (5). Alternatively, gliadin can act directly on antigen-presenting cells (6) causing MyD88-dependent release of both zonulin and cytokines (7). Gliadin peptides are also presented to T lymphocytes (8), followed by an aberrant immune response, both humoral (9) and cell-mediated (10) in genetically susceptible individuals. This interplay between innate and adaptive immunity is ultimately responsible for the autoimmune process targeting intestinal epithelial cells, leading to the intestinal damage typical of celiac disease (11). AEA, anti-endomysium antibodies; AGA, anti-gliadin antibodies; TG, thyroglobulin; Tk, T killer.

key element necessary to develop autoimmunity is the loss of the protective function of mucosal barriers that interface with the environment (mainly the gastrointestinal and lung mucosa).

Celiac disease represents the best testimonial of this t-heory. Early in the disease, tight junctions are opened [32,33], most likely secondary to zonulin upregulation [34] and severe intestinal damage ensues [33] (Fig. 2). The upregulation of the zonulin innate immunity pathway is directly induced by the exposure to the disease's antigenic trigger gliadin [35]. Gliadin has been shown to be also a potent stimulus for macrophage pro-inflammatory gene expression and cytokine release [36]. Our recent data suggest that signaling of both functions is independent of Toll-like receptor (TLR) 4 and 2, but is dependent on MyD88, a key adapter molecule in TLR/interleukin-1 receptor signaling [37•]. These data indicate that gliadin initiates intestinal permeability through a MyD88-dependent release of zonulin that enables paracellular translocation of gliadin and its subsequent interaction with macrophages within the intestinal submucosa (Fig. 2). Gliadin interaction with macrophages initiates signaling through a TLR-like pathway, resulting in the establishment of a pro-inflammmatory (T helper 1-type) cytokine milieu that results in mononuclear cell infiltration into the submucosa. This, in turn, may permit the interaction of T cells with antigen-presenting cells, including macrophages, leading ultimately to the antigen-specific adaptive immune response seen in patients with celiac disease. Once gluten is removed from the diet, serum zonulin levels decrease, the intestine resumes its baseline barrier function, the autoantibody titers are normalized, the autoimmune process shuts off and, consequently, the intestinal damage (that represents the biological outcome of the autoimmune process) heals completely [28•].

Conclusion

Based on recent findings concerning celiac disease, the classical paradigm of autoimmune pathogenesis involving specific gene makeup and exposure to environmental triggers has been challenged by the addition of a third element – the loss of intestinal barrier function. Whether the increased comorbidity between celiac disease and other autoimmune disorders is related to increased intestinal permeability causing the passage of environmental triggers responsible for the onset of the autoimmune processes or it is secondary to cosegregation of genes remains to be established.

Acknowledgements

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