

Celiac Disease: A Brief Review of Current Literature

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General Background

Celiac disease (also known as celiac sprue or gluten-sensitive enteropathy) is a systemic immune-mediated inflammatory disease triggered by permanent sensitivity to dietary gluten in genetically disposed people. Gluten is a protein complex found in wheat, rye, and barley, which are degraded into antigenic peptides that stimulate an immunologic reaction; characterized by a wide array of clinical symptoms; including diarrhea, malabsorption, eventually nutritional deficiencies and failure to thrive and variable damage to the mucosa of the small intestines [1].

The description of Celiac disease dates back to the 1st century AD, however the disease trigger was first defined by the Dutch pediatrician; Willem Karl Dicke, who noted that children with celiac disease had a great improvement in their condition during the World War II when there was a lack in cereals and bread [2].

Celiac disease is a common genetic disorder, with a prevalence of 0.5 to 1.0% in many populations worldwide with extensive area differences in Europe (e.g., the prevalence is 0.3% in Germany and 2.4% in Finland) and the United States for explanations that are poorly understood. Celiac disease is also common in developing countries, particularly in the Middle East and North Africa. The incidence of celiac disease is growing in

many developing countries because of the new eating and lifestyles which adapt the western diets, modifications in wheat production and preparation, better alertness of the disease, or a blend of these elements [3, 4].

Serologic screening studies have revealed that only a small proportion of cases of celiac disease are clinically documented (21%). The prevalence is 1.5 to 2 times higher among women rather than men, clusters in families, and first-degree relatives of affected patients (10 to 15%). Incidence of the disease increases in people with type 1 diabetes (3 to 16%), Hashimoto's thyroiditis (5%) or other autoimmune diseases, Down's syndrome/Trisomy 21 (5%), Turner's syndrome/45, XO (3%), and IgA deficiency (9%). The variability in presentation and delay in onset of symptoms probably lead to the disease being under or misdiagnosed [3, 4].

Genetic predisposition plays a major factor in the susceptibility to the disease. The HLA-DQ2 haplotype (DQA1*0501/DQB1*0201) is expressed in the majority of patients with celiac disease (90-95%), and the remainder 5% of patients with celiac disease express the HLA-DQ8 haplotype (DQA1*0301/DQB1*0302). DQ2 and DQ8 haplotypes expressed on the surface of antigen-presenting cells (APC) can bind activated gluten peptides, activating an immune response. The DQ2 and DQ8 haplotypes are essential but not sufficient for the progress of celiac disease. Until this time, approximately 39 non-HLA genes that pass a predisposition to the disease have been recognized, most of which are largely involved in inflammatory and immune responses [4, 5].

Pathogenesis

The pathogenesis of celiac disease is now quite understood. When the exogenous gluten (antigen); a mixture of gliadin and gliadin polypeptides is ingested, it becomes degraded into small residues by gastric, pancreatic, and intestinal enzymes which causes changes in intestinal permeability. In most cases, these residues represent the suitable stimulators of the immune system because they are not large enough to bind MHC molecules. Nevertheless, gluten contains a proline-rich peptide of 33 amino acids (33-mer) that endures the passage through the gastrointestinal tract and arrives intact in the small intestines. This peptide passes through the gastrointestinal lining into the subepithelial space. Such mechanisms are usually prevented by the tight junctions of the gastrointestinal epithelium. However a number of factors may damage the epithelial barrier, such as infections or mechanical stress. In the subepithelial space, the peptides are modified, including Tissue Transglutaminase (TTG) [5], that increase their antigenicity, and then they are transferred by the APC to CD4 T cells, which initiate an inflammatory reaction that is self-perpetuating in the presence of gluten and harms the gastrointestinal tract. The TTG enzyme makes the peptide more antigenic during the process, and has been identified as an autoantigen during the course of the disease. The HLA DQ2 and HLA DQ8 interplay with other factors to underpin the immune mediated response seen in patients with celiac disease. After presentation of the immunologic peptides to CD4 T cells, an inflammatory response is started; characterized by a CD4 TH1 response, with IFN- γ as the chief cytokine in action. Examination of gastrointestinal lesions often show penetration of the intestinal lining by both CD4 lymphocytes coming from the lamina propria and CD8 T cells coming from the intraepithelial space. The innate immune system may also be triggered by gluten. There is evidence that gluten derived peptides induce the secretion of IL-15 by epithelial cells in the intestines [6]. IL-15 stimulates antigen-presenting dendritic cells in the lamina propria and also causes an up regulation of expression of the cell-surface protein MIC-A by epithelial cells. Cytotoxic CD8 intraepithelial lymphocytes in the mucosal epithelium can be stimulated via the NKG2D receptors, which recognize MIC-A,

and they then kill MIC-A-expressing epithelial cells. This innate immune responses adds to the damage of intestines, and may also prompt the co-stimulatory molecules required for initiating an antigen-specific CD4 T cell response to other parts of the α -gliadin molecule. The ability of gluten to stimulate both innate and adaptive responses may explain the uniqueness nature of celiac disease and the difficulty in applying highly effective treatments [7].

Clinical Appearance

Children with celiac disease typically come to attention between 6-24 months of age, presenting with diarrhea, abdominal distension and pain, malabsorption, weight loss (40-50%), dehydration, short stature, high aminotransferase levels, chronic fatigue, vomiting, constipation, and decreased bone mineral density. Once thought a disease correlated with children, now recognized as a systemic disorder that affects people of any age or ethnic group. Adults also develop celiac disease, with a very common manifestation of iron deficiency anemia that does not respond to oral therapy. Gastrointestinal problems such as flatulence and diarrhea are predominant [5].

Other atypical symptoms of celiac disease include hypoplasia of the dental enamel of the permanent teeth, osteopenia/osteoporosis, delayed puberty, dermatitis herpetiformis, an intensely itchy rash with pathogenic cutaneous IgA deposits, gluten ataxia, a random form of ataxia with positive serologic markers for gluten sensitization, and celiac crisis, a life-threatening syndrome, mostly witnessed in children, that is characterized by severe diarrhea, hypoproteinemia, and marked disruption in electrolyte balance; which requires immediate treatment with intravenous corticosteroids. Serological testing has been increasingly used to detect clinically silent celiac disease [6, 8].

Untreated celiac disease leads to significant illness and increased risk of mortality. Children with celiac disease are most likely to show growth problems and reduced bone mineralization, which can be corrected on gluten-free diet. Women with untreated celiac disease can develop complications

characterized in infertility, recurrent abortions, and infants of low birth weight and shorter duration of breast feeding. Lastly, celiac disease mortality rates are increased due to cancer, primarily enteropathy-associated-T-cell lymphoma and adenocarcinoma of the jejunum [6].

Chronic refractory celiac disease is confirmed when there are persistent or recurrent malabsorption symptoms with signs of atrophy detected using biopsy in spite of adherence of a strict gluten-free diet for more than 12 months. Refractory celiac disease can be categorized as type 1 (normal intraepithelial lymphocytes) or type 2 (abnormal intraepithelial lymphocytes; clonal intraepithelial lymphocytes lacking surface markers CD3, CD8, and T-cell receptors; or both). Type 2 is linked to a higher risk of ulcerative jejunoileitis and lymphoma than type 1 [8].

History

The sequence of events at which celiac disease symptoms appear varies greatly between patients. Longitudinal data suggest a classic order of proceedings: the appearance of celiac antibodies, intestinal enteropathy, beginning of symptoms, and development of complications. However, not all of these events may occur. The timeline of each phase may range from weeks to years. Presence of celiac autoantibodies in the serum in patients characterize a possible celiac disease candidate with a normal intestinal mucosa on biopsy. Evident intestinal damage develops over time in a subgroup of these patients [9]

Furthermore, in comparison to previous suggested theories which explained that the immunologic and mucosal changes normally develop at an early age (as soon as the subject is exposed to gluten), more updated long-term reports show that the conversion to celiac autoimmunity might occur at any age. This remark suggests that the genetic predisposition and ingestion of gluten are essential, yet not sufficient for the loss of gluten tolerance and the appearance of celiac disease [10, 11].

Loss of gluten tolerance may be reversible in some patients. It has been reported that 49% of children who are genetically predisposed for celiac disease had sero-conversion from positive

tests for IgA anti-tissue transglutaminase antibodies to negative tests, even with sustained ingestion of gluten. In some case reports, it was documented that patients who were diagnosed to have celiac disease early in life, showed negative serologic tests and normal villous feature when they re-introduced gluten in their diets. Nevertheless, patients with reverted serologic findings to negative titers, should still be followed up and tested, because the serologic and intestinal status might change with time [8, 12, 13].

Diagnosis

Serum Tests and Serological Markers

The development of highly sensitive and specific serologic tests for detection of celiac disease has significantly aided in the diagnosis. Serologic screening is suggested in all first-degree family members of patients who obtain a diagnosis of celiac disease. Serologic testing is also very crucial to monitor compliance with gluten-free diet. Several different serologic tests are in use; for initial screening, measurement of serum IgA anti-Tissue Transglutaminase (anti-TTG) antibodies is recommended in people who do not have associated IgA deficiency because of its high sensitivity (94%) and high specificity (97%) [11]. IgG anti-tissue transglutaminase antibodies can be tested in people with IgA deficiency. Measurement of IgA antiendomysial antibodies is nearly 100% specific for active celiac disease, but it should only be used as a confirmatory test in borderline cases positive or possibly false positive for anti-tissue transglutaminase antibodies, which occurs in other autoimmune diseases, as type 1 diabetes. Tests for IgA antiendomysial antibodies are expensive and observer-dependent and are therefore subject to error. Positive results of anti-TTG and anti-endomysial IgA antibody are almost 100% conclusive in predicting celiac disease lesions in symptomatic patients. Measurement of anti-gliadin IgG antibodies are less predictive, because they are found positive in patients with inflammatory bowel disease and in healthy subjects; but this class is reported to have better specificity and sensitivity in screening for celiac disease patients who are IgA deficient.

Moreover, the sensitivity of serologic testing is evidently decreased in patients following a gluten-restricted diet; consequently patients should not control their diet before testing [7, 8, 14, 15].

Biopsy

Regardless of the serologic findings, all suspected celiac disease subjects should be confirmed by a biopsy of the small intestine. The characteristic histologic changes include an increased number of lymphocyte infiltration (>25 per 100 enterocytes), crypt hyperplasia, and partial to total villous atrophy. However, false positive results and false negative results may occur. The recognition of sub-epithelial anti-tissue transglutaminase antibody IgA deposits using double immunofluorescence is useful in patients with an indefinite diagnosis, as seen in patients with negative serologic results and positive results on biopsy. It is important to note that recent recommendations from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition suggest that a biopsy of the small intestine may not be essential in children with classic symptoms, in regards that a high titer of anti-tissue transglutaminase antibodies and predisposing HLA genotypes is sufficient to confirm a diagnosis [11, 14, 16].

Genetic Testing

Testing for HLA-DQ2 and HLA-DQ8 may be useful as a prophylactic measure in people at high risk (e.g., close family members of patients with celiac disease). This test has a high negative predictive value, which means that the disease is improbable to develop in people who are negative for both HLA-DQ2 and HLA-DQ8.15 [11].

Other less frequently diagnostic procedures such as double-balloon enteroscopy, capsule endoscopy, and magnetic resonance imaging are not commonly indicated, but might be helpful in complicated cases [17-19].

Treatment

The treatment for celiac disease is lifelong adherence to a gluten-free diet. A wide range of gluten-free wheat substitutes are specifically manufactured for patients with celiac disease in some countries. But this is challenging to comply with and is also expensive. Additionally, this lifestyle represents a new burden in other countries, such as in the Middle East and North Africa; due to lack of awareness, low suspicion of the disease, the scarce commercially available alternatives and the economic status. Gluten is a protein with low nutritional value, hence it can be replaced by other nutritional proteins. However, patients who adhere to gluten-free diets tend to consume less of some nutrients, such as fibers, calcium, iron, and folate. Although no gluten consumption represents the best management for celiac disease, traces of gluten contamination is hard to evade. The gluten threshold which causes damage to the celiac intestinal mucosa over is 10 to 50 mg per day. The Food and Drug Administration (FDA) has issued new rules for defining gluten thresholds and gluten-free foods. The new rules establish some uniformity in labeling [13, 17].

During the maintenance of a gluten-free diet, symptoms subside, serum celiac antibodies slowly disappear, and the intestinal damage typically starts healing within 6 to 24 months after introduction of the diet. However, even with the best gluten-free compliance practices, some patients who are symptom free and negative for serologic testing continue to have intestinal damage. It is essential to give patients and their families' extensive nutritional counseling as well as support in their attempts to maintain the diet [20].

New Therapies and Future Hopes

Given the high prevalence of celiac disease and the difficulty in maintaining a gluten free diet, there should be new therapies on the horizon for treating this condition.

The key barrier to endogenous and exogenous stimuli is the intestinal epithelium. Immunogenic antigens pass through the mucosal barrier during a normal physiological state by two main methods: transcellular and paracellular, the second being directly involved in regulation of tight junctions. Recent

understanding into the complicated mechanism that controls intestinal epithelial paracellular pathways have led to the finding of Zonulin, a protein extensively studied in a variation of clinical settings including celiac disease [21-23].

As reported in some recent studies, Larazotide acetate which is an 8-mer peptide and Tight Junction (TG) regulator that panels cellular changes induced by gliadin and cytokines, inhibits gliadin 13-mer peptide translocation; which is highly correlated with celiac disease. Other studies have shown that Larazotide inhibits gliadin-induced macrophage buildup in the small intestine and hence preserves the TG structure [23, 24]

Three phase II human clinical trials have made larazotide a suitable and potential candidate for treating celiac disease. All randomized, placebo-controlled trials have appeared to be safe, well tolerated and effective in decreasing gastrointestinal symptoms after gluten ingestion. The most recent preliminary results from one of the three phase II b trials have shown that of larazotide acetate can sustain a clinical improvement in the gastrointestinal and non-gastrointestinal symptoms in patients with celiac disease on a gluten-free diet for more than 12 months, as compared with placebo effects (Clinical Trials registration number NCT01396213). All of these increasing evidence suggests that larazotide acetate can actually be a safe and efficient drug for the treatment of celiac disease [24].

Regulation of Immune Reaction

Further studies have proposed that current changes in lifestyle and health practices. Absence of the normal microbial flora that was once plentiful might have played a major role in raising the incidence of celiac disease. Therefore, focusing on the environmental factors can present possible therapeutic replacements that can reestablish immune tolerance in celiac disease. The induction of tolerance through vaccination has been broadly considered for the treatment of autoimmune diseases including celiac disease [25] Nexvax 2, a gluten-specific therapeutic vaccine, is a combination of three peptides (gliadin, hordein, secalin) commonly recognized by T-cells in HLA-DQ2 patients, which will eventually lead to

reprogramming gluten-specific T cells. One of the phase I clinical trials showed that Nexvax 2 is considered safe and tolerable in patients with celiac disease and who follow a gluten free diet after giving them weekly injections for three weeks. (Clinical Trials registration number NCT00879749). Nexvax 2 induces a biological reaction, but further research will be needed to study the efficacy of vaccination in restoring immune tolerance to gluten.

During the course of celiac disease, the pro-inflammatory response results produces cytokines, such as TNF- α , IFN- γ and IL-15, which suggests that a possible approach with monoclonal antibody-based therapies [26]. Monoclonal antibodies against TNF- α (infliximab) have been widely studied in inflammatory bowel disease, infliximab was successfully used in the treatment of a few refractory celiac disease [27]. Additionally, humanized IL-15-specific antibody is a hopeful treatment for Type 2 refractory celiac disease [28]. IL-15 Monoclonal antibodies can target and block effectively the signaling pathway by which IL-15 transmits anti-apoptotic signals (Jak3/STAT5) to NK and CD8+ T lymphocytes [28, 29]. A phase I clinical trial, currently going on, will assess the safety and efficacy of the humanized Hu-MiK-Beta-1 monoclonal antibody in patients with refractory celiac disease, as a substitute treatment (Clinical Trials registration number NCT01893775).

Other Less well-known therapies include celiac-specific HLA inhibition, CCR-9 blockade by CCX282-B agent and lymphocyte recruitment blockade. Most of these treatments have been widely studied in connection with Crohn's disease and seemed to be effective [30-32] CCX282-B is the only agent that has been assessed in a phase II clinical trial of small-intestinal biopsies from patients with celiac disease before and after gluten exposure. No complications occurred during the study and no serious changes in clinical parameters (Clinical Trials registration number NCT00540657).

Novel Therapies for Celiac Disease: A Role for Stem Cells?

Stem Cells (SC) might be used as novel treatments for many diseases including celiac disease. The development in SC

biology has led to the principle of regenerative medicine which is based on the potentials of SC in facilitating the repair of injured tissues. These therapies require a profound understanding of the mechanisms underlying SC regulation in normal and pathological conditions [33].

A possible cure for celiac disease lies in the discovery of epithelial mitogens that stimulates mucosa growth. Lately, R-spondin-1 has been shown to stimulate crypt cell growth, speed up mucosal regeneration and reestablish intestinal structure in experimental colitis in mice. During celiac disease, the infusion of such mitogens might accelerate intestinal healing [34].

Another SC potential therapy is based on the transplantation of multipotent bone marrow derived SC aids in intestinal repair. In the last two decades, bone marrow (BM)-derived SC therapy has become a choice for patients with severe autoimmune diseases which were considered resistant to conventional therapies. Such a therapy has been recently applied in gastroenterology for the treatment of certain cases of complicated celiac disease [35]. Hoekstra et al. stated a patient with aplastic anemia and celiac disease, allotransplant of SCs made improvements in celiac disease state even after the return to a free diet [36]. Recently, Ciccocioppo et al. presented that in 2 patients affected with celiac disease and β -thalassemia major who underwent successful myeloablative allogeneic HSC transplantation for the latter condition, the introduction of a gluten-containing diet did not cause the recurrence of clinical, serological and histological markers of celiac disease in up to 5 years of follow-up [37].

The molecular mechanisms involved in the beneficial effects of HSC transplantation in Celiac disease remain a mystery. A hypothesis has been proposed to explain these effects, which states that the immune system depletion of harmful T cells followed by SC transplantation provides a rearrangement in the patient immune system. Furthermore, SCs might contribute to differentiation into epithelial cells and myofibroblasts and tissue repair by stimulating angiogenesis [38].

Conclusion

Celiac disease is an exceptional autoimmune disorder. In spite of being well studied and characterized, there are still mysterious mechanisms and processes that need to be addressed in the course of the disease, and there are still a majority of patients who are misdiagnosed or under diagnosed. The key knowledge of gluten as the main trigger for celiac disease has led to the improvement of diagnostic tools and alternative therapeutic approaches. Nowadays, innovative therapies such as stem cell transplantation have shown to be potentially effective and safe, but true effectiveness and long-term benefits are still a long way ahead. Further research in the diagnosis, management, and treatment of celiac disease will lead to better improvements in the lives of many patients worldwide.

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