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The Facts of Celiac Disease; A Comprehensive Review

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Abstract Celiac disease (CD) is the most common permanent T-cell mediated gluten intolerance, caused by the dietary gluten in individuals who are genetically susceptible to the disease. CD characterized by small intestine mucosal lesions, subtotal, or total intestinal villi atrophy and nutrient malabsorptions. Sometimes the diagnosis of CD is so challenging and needs a combination of clinical, serological, histopathological and genetic evaluations. The well-known cornerstone treatment of CD is gluten-free diet (GFD) and there is need to regular monitoring of patients after starting the GFD. The main aim of this review was to discussing the definition and pathogenesis of CD, together with the diagnostics, treatment and follow-up strategies in this disease.

Keywords: *celiac disease, glutens, t-lymphocytes, diet, gluten-free, diagnosis*

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1. Introduction

Celiac disease (CD) is a chronic inflammatory disorder related to the gastrointestinal tract with the autoimmune features that are developed in genetically susceptible individuals by consuming the gluten protein of the wheat and similar proteins in the barley and rye [1]. CD is a common autoimmune disorder, which is prevailed among 1% of people in different parts of the world [2]. In fact, the interplay between innate and adaptive immune responses play a crucial role in the pathogenesis of CD [3]. This disorder affects the small intestine and in particular the duodenum, causing atrophy of the absorbent apparatus and malabsorption of nutrients including iron, B12 and folic acid [2,4,5,6]. The intestinal mucosal changes in CD are different from mild (slight increase of inflammatory infiltrate in both the epithelium and lamina propria) to severe lesions (villous flattening and crypt hyperplasia) [7]. Most CD patients present with highly variable clinical manifestations including intestinal and extra-intestinal symptoms, or it can even be without any symptoms [8]. This review focused on celiac disease pathogenesis, it's diagnostics, follow-up and therapeutic approaches.

2. Clinical features of CD

The clinical manifestations of CD are extensive and different, therefore it can be presented with a range of intestinal (Chronic diarrhea, bloating, dyspepsia, and abdominal pain) and extra intestinal (Iron deficiency anemia, osteoporosis, dermatitis herpetiformis, neurologic abnormalities, increased liver enzyme levels, arthritis and weight loss) symptoms [6,9,10]. Although more than 80% of patients with celiac disease in general population screenings are clinically silent, they have no symptoms or their symptoms are very minor or they may have an atypical presentation. Moreover, the risk of developing the enteropathy-associated T-cell lymphoma (EATL) and small bowel adenocarcinoma is increased in undiagnosed cases with CD [7].

3. Pathogenesis of CD

The pathogenesis of CD depends on the interaction of triple factors (genetic background, gluten, and environmental influences) as follow:

a. Genetic background: The susceptibility to celiac disease is significantly related to the human leukocyte antigen (HLA) class II genes (HLA-DQ2 and HLA-DQ8). It is also estimated that various non-HLA genes contribute to develop the CD in different populations [7]. However, HLA-DQ2 and/or DQ8 genes are required for developing the celiac disease and there are in nearly all CD patients. Macrophages, dendritic cells, and B-cells express these HLA class II molecules which are important components of antigen-presenting cells [7,9,11].

b. Gluten: Gluten proteins are rich in proline and glutamine residues, and they are highly resistant to breakdown by pepsin, pancreatic proteases, and intestinal brush border membrane peptidases. Because gastric and pancreatic endoproteases cannot cleave proline or glutamine residue and the long remaining peptides do not break down in the brush border membrane by dipeptidyl peptidase IV and dipeptidyl carboxypeptidase I, gluten comparatively breaks down into the gliadin fragments. These fragments remain for longer time in the lumen, and

they enter into the lamina propria (LP) area by increasing the permeability of the epithelial cells [9,12,13] and this is the first stage of the start of celiac disease, which will be explained in more detail in the following part.

c. Environment: Both of the above-mentioned factors play a significant role in the development of CD, but these are not enough to cause the disease [14]. For example, 30%–35% of the general population has HLA-DQ2 or HLA-DQ8 and only 2%–5% of gene carriers develop celiac disease [7,10]. This explains that various environmental factors can also play a role in the pathogenesis of celiac disease. In particular, the factors that affect the intestinal environment such as infection, alterations in the intestinal microbiota, duration of breast-feeding and increased consumption of gluten in early years of life [9,15,16].

4. Diagnosis of CD

Serological evaluation and antibody testing is the initial step in diagnosing patients with CD. This diagnostic process should be undertaken while patients are on a normal gluten-containing diet. Serologic evaluation can be performed with disease-specific antibodies such as anti-tissue transglutaminase antibody (Anti-TG2), Endomysial antibody (EMA) and antibody against gliadin peptides (AGA) [17].

IgA class antibodies have been shown to have a significantly higher sensitivity and specificity as compared to its IgG subclasses. Therefore, IgA anti-TG2 is recommended to be used as effective first-line screening test for detecting CD in these patients [18].

On the other hand, it is important to keep in mind that IgA deficiency is prevalent among CD patients and it may cause false-negative results of IgA antibody testing in these patients' population. In this scenario, it is recommended to measure total serum IgA levels along with IgA anti-TG2, and also IgG-based serologic tests including IgG anti-gliadin antibody and IgG anti-TG2 antibody should be used for disease evaluating [18,19].

IgA anti-EMA antibody testing is a qualitative test that can be used as a confirmatory test along with anti-TG2 antibodies for a more accurate diagnosis [17,20].

On the other hand, EMA and TG2 antibodies tests seem to be less sensitive in in children <2 years of age. Therefore, antibodies against gliadin are useful for their assessment [17,20,21].

It should be noted that seronegativity in individuals consuming gluten does not rule out the possibility of CD and final confirmation of celiac disease is only possible after a small bowel biopsy examination [22].

4.1. Small Intestinal Biopsy

The histological judgment of small intestinal biopsy is commonly regarded as the gold standard for diagnosis of CD which is routinely performed after seropositive results of CD patients. In addition, patients with normal serological markers but with celiac disease symptoms should also undergo endoscopic evaluation for definitive diagnosis of the disease [23].

The hallmarks of CD in microscopic assessment of the biopsies include: increased intraepithelial lymphocytes (IELs), crypt hyperplasia, and villous atrophy [22].

4.2. Genetic Testing

HLA-DQ tests are useful in excluding CD in cases where the diagnosis is unclear; for example, when there is a discrepancy between serology and histopathology results, genetic tests should be performed [17].

Since nearly all patients with CD are positive for HLA-DQ2/ DQ8, if a patient is negative for these alleles, CD can be excluded lifelong. However, positive DQ2/DQ8 cannot be used to confirm a diagnosis of CD, because Approximately, 40 % of all individuals are positive for HLA-DQ2/ 8 and only 2% to 5% of this population develop CD [17].

5. Treatment of CD

Following a strict gluten-free diet (GFD) lifelong is the current essential treatment of celiac disease which requires complete elimination of all foods containing the gluten protein from the diet, and is difficult to maintain [5].

Due to advanced understanding of CD pathogenesis, a number of novel and experimental therapeutic trials for the treatment of CD are ongoing. These therapeutic strategies aimed at inducing tolerance to ingested gluten. Of particular interest are: development of gluten products with low immunogenicity, oral enzyme therapy, probiotics, tight junction regulatory peptides, tissue transglutaminase enzyme and proinflammatory cytokines blockage and more [5,11,22].

6. Intestinal Permeability to Gliadin Peptides

6.1. Paracellular Transport

The small intestine includes a paracellular barrier which is collected from the tight junction (TJ) and the adherens junction (AJ). There is an endogenous protein called ‘Zonulin’ that can regulate the reversible permeability of tight junctions and allow an increased passage of the macromolecular proteins such as gliadin into lamina propria. When gliadine peptides enter into the small intestinal lumen and bind to the CXCR3 receptor, zonulin will be released by intestinal epithelial cells (IECs) and lamina propria macrophages and bind to IECs, thereby leading to a signal cascade that can break up the paracellular tight junctions and increase the intestinal permeability, and as a result, gliadin peptides can enter into the lamina propria [14,24,25,26,27].

6.2. Transcellular Transport

In addition to the enhanced paracellular intestinal permeability, there is also a transcellular transition for gliadin peptides. The hypothesis of this process is that the secretory IgA (sIgA) released by the plasma cells in the

pathogenic pathway of celiac disease, binds to the transferrin receptor (CD71), a protein that is up regulated in the intestinal epithelium of celiac patients. As a result, partially degraded gliadin moves through epithelial cells [24,28].

Moreover, the small intestinal permeability can be increased by other pro-inflammatory mediators such as interferon γ (IFN-γ) and tumor necrosis factor α (TNFα) which are released from gluten-activated CD4+ T-cells. In addition, some genomic studies have reported that MAGI2, MYO9B, and PARD3 genes control the intestinal permeability in celiac disease patients [14,24,29,30].

It should be noted that in healthy individuals, gliadin peptides enter into the enterocytes through endocytosis and they are totally degraded by the lysosomal system. Therefore, gluten does not enter into the lamina propria, and unlike celiac patients, it does not cause the immune responses in normal individuals [31,32].

7. Immune Responses to Gluten in CD

Immune responses develop in CD patients after incomplete digested gliadin peptides enter into the lamina propria [9,13]. As it will be explained in more detail in the following section, similar to many other autoimmune diseases, innate and adaptive immune responses contribute to the pathogenesis of celiac disease [33].

7.1. Adaptive Immune Response

Transglutaminase 2 (TG2) enzymes can modify the gliadin peptides to deamidated form in LP. In fact, glutamine residues in the α2-gliadin peptide p56-88, generally named 33-mer, and its shorter version p56-68, in particular in Gln-X-Pro-Z (X can be each amino acid but Z must be hydrophobic) sequences are converted to negatively charged glutamate residues in deamidation process [5,7,34]. Then antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B-cells, uptake these deamidated gliadin peptides, break them down into smaller peptides and present these particles to gliadin-specific CD4+ T-cells by their HLA class II including DQ2 and/or DQ8 heterodimers [7,9]. The HLA-DQ2 and HLA-DQ8 molecules have positively charged pockets that have a preference for the negatively deamidated charged gliadin peptides [5,35]. After taking these gliadine fragments from APCs, the gliadin-specific CD4+ T-cells polarize along the T helper 1 (Th1)-type pathway and produce large amounts of IFNγ, the main cytokine of Th1 response, in combination with other cytokines such as Interleukin-4 (IL-4), IL-5, IL-10, TNF-α and Transforming growth factor β (TGF-β) [9,36,37,38]. Among these cytokines both TNF-α and IFN-γ stimulate the expression and activation of matrix metalloproteinases (MMPs) such as MMP-1, MMP-3 and MMP-12 in intestinal myofibroblasts. This activation results in degradation and proteolysis of the extracellular matrix that leads to architectural remodeling observed in celiac disease [7,39,40]. There is also increased humoral activity in CD. The density of the plasma cells as well as immunoglobulin secretion such as immunoglobulin class A (IgA) antibodies targeted against transglutaminase 2 increase in the active celiac lamina propria. These antibodies are used to diagnose the celiac disease and as previously noted, secretory IgA (sIgA) can play a role in the transcellular transitions of the gliadin peptides through binding to the transferrin receptor (CD71) [41-44].

7.2. Innate Immune Response

The α9-gliadin peptide 31-49 (p31-49) or its shorter version, p31-43, may activate the intestinal innate immune responses that produce the potent pro-inflammatory cytokines such as interleukin-15 (IL-15) commonly by monocytes/macrophages, dendritic and epithelial cells [24,31,37,45]. IL-15 causes differentiation of intraepithelial lymphocytes (IELs) into cytotoxic CD8+ T-cells that express the natural killer cell marker (NK-G2D). IL-15 also increases the expression of the NK-G2D ligand on epithelial cells, called MICA and MICB. In other hand, IELs in CD patients express CD94/ NKG2C compared to the normal IELs that is also an NK receptor. The ligand of this receptor is HLA-E protein, which is up regulated in epithelial cells in response to IFN-γ during the pathogenesis of celiac disease. The interaction of NKG2D with MICA/B and of CD94/NKG2C with HLA-E activates the IELs and they destroy the epithelial cells of the intestines in patients with celiac disease [24,46,47,48]. Therefore, Interleukin-15 is regarded to be an important cytokine to cause the pathological changes in the intestine of celiac disease patients and also plays an important role in the interaction between innate and adaptive immunity [37,45]

IL-21 is another cytokine produced by CD4+ T-cells in the intestinal mucosa of celiac disease patients which often operates in relation to IL-15 and also stimulates the innate immune system [7].

The final result of these immune responses and inflammatory cascades is damage to the intestinal mucosa [9].

8. Monitoring and Follow-up of CD

CD is a lifelong systemic disease that requires regular follow-up visits; thus, the follow-up is a critical aspect of treating the CD patients. The typical follow-up schedule includes a first visit in 3–6 months, then annually from date of diagnosis. It has been shown that CD patients have improved quality of life after treating with a gluten-free diet for at least 1 year [49].

In fact, management of CD needs assessment of changes in clinical symptoms, repeating serological tests and screening for other potential complications. Duodenal mucosal assessment is also recommended after the first year of a GFD as well as when patients have continued symptoms despite a GFD [49,50].

9. Conclusion

In conclusion, celiac disease is a T-cell mediated disorder triggered by gluten exposure which affects about 1% of the population. In particular, the collaboration between innate and adaptive immunity, which are formed

against dietary gluten, results in epithelial apoptosis, mucosal destruction and intestinal inflammation in CD. The clinical manifestations of CD are different, and it can be presented with a range of intestinal and extra intestinal symptoms. Serological markers evaluation followed by small bowel investigation are necessary for diagnosis of CD. Genetic testing can also be useful to rule out the condition. Once the diagnosis is confirmed, strict adherence to a gluten-free diet considered the only effective treatment for the individuals with celiac disease. Future perspectives on the treatment of this disease include therapeutic strategies that aimed at inducing tolerance to ingested gluten in different ways. Regular follow-up also requisite to increase compliance and minimize the potential complications of the disease.

List of Abbreviations

AGA: Antibody against gliadin peptides
AJ: Adherens Junction
APC: Antigen Presenting Cell
CD: Celiac Disease
EMA: Endomysial Antibody
GFD: Gluten Free Diet
HLA: Human Leukocyte Antigen
IEC: Intestinal Epithelial Cell
IFN: Interferon
IL: Interleukin
LP: Lamina Propria
MMP: Matrix Metallo Proteinase
TG2: Transglutaminase 2
TGF: Transforming Growth Factor
Th: T helper
TJ: Tight Junction

Statement of Competing Interests

The authors have no competing interests.

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