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Celiac Disease Review: Background and Emphasis on the Important Role of Health Education in the Prevention and Control of Symptom

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Abstract **Review Article**

Celiac disease is related to dietary gluten found in wheat, rye, and barley, CD is an immune-mediated enteropathy and it is one of the most prevalent lifelong food-related illnesses globally. In addition, CD is also thought to be a systemic ailment marked by a variety of gluten-related signs and symptoms as well as disease-specific antibodies. When gluten is consumed, it produces toxic gluten peptides that can trigger both innate and adaptive immune responses in people who are predisposed to them. The transglutaminase enzyme plays a role in the development of the situation by deaminating gluten to produce glutamic acid. Furthermore, the peptidase enzyme finds it difficult to break down the prolamin component of gluten, which is high in proline and glutamine. This leads to incomplete protein digestion and the creation of peptides that trigger the immunological response. Moreover, CD causes remarkable damage to the small intestinal mucosa in the jejunum, resulting in inflammation of the villi and villous atrophy, which hinders the absorption of nutrients. Combining small intestine mucosal histology under a gluten-containing diet with CD serology allows for the diagnosis of the condition. A stringent lifelong gluten-free diet is now the only effective treatment for CD; nevertheless, the diet is demanding, and avoiding gluten is challenging. Further research is needed to improve and develop the diagnosis and treatment of CD via healthcare professional education programs.

Keywords: Celiac disease, gluten peptides, small intestinal mucosa, and gluten-free diet.

INTRODUCTION

The term Celiac disease (CD) originates from the Greek word (koiliakós, meaning "abdominal") and was first used in the 19th century by Aretaios of Cappadocia, a renowned ancient Greek physician who provided early detailed descriptions of CD and various other medical conditions (Adams, 1856).

CD is a hereditary autoimmune condition that predominantly impacts the small intestine upon gluten consumption; gluten is frequently present in foods such as barley, wheat, and rye. Gliadin, a major constituent of gluten, contributes to increased intestinal permeability. The transglutaminase enzyme converts gluten into glutamic acid through deamination, which acts a function in the circumstance's development (Abadie *et al.,* 2011). Additionally, the prolamin component of gluten, rich in proline and glutamine, is not easily broken down by the peptidase enzyme, resulting in partial protein digestion and the construction of peptides that initiate the immune response (Lundin & Wijmenga, 2015).

CD damages the small intestine mucosa, remarkably in the jejunum, causing villi's inflammation, known as villous atrophy, which impairs nutrient absorption (Lindfors *et al.,* 2019). It is projected to impact roughly 1 in 100 individuals worldwide. While CD was initially observed in children, it can occur at any age. CD is frequently observed in conjunction with additional autoimmune disorders, involving type 1 diabetes and Hashimoto's thyroiditis (Ciccocioppo *et al.,* 2015).

CD cases are predominantly correlated with particular HLA DQ haplotypes situated on the chromosome VI short arm. A total of eight distinct varieties of HLA DQ genes exist (DQ2-DQ9); in most cases, cases with CD possess either the DQ2 or DQ8 type (Ciccocioppo *et al.,* 2015).

CD differs from gluten intolerance and wheat allergy, although they may share some symptoms such as fatigue and abdominal pain. However, neither gluten intolerance nor wheat allergy are autoimmune diseases or cause damage to the small intestine (Ciccocioppo *et al.,* 2015).

Causes and Predisposing Factors for Celiac Disease

The cause of CD remains unknown. However, it is generally hereditary, commonly linked to the DQ8 and HLA DQ2 genes' genetic predisposition. However, there are other, as yet to be known genes that act a function in this disease's development (Gopalakrishnan *et al.,* 2012). The CD is featured via an aberrant immune response to gliadin, a component of the gluten protein. The immune system's improper activation provokes GIT inflammation in the gastrointestinal tract, which in turn destroys the villi—fingers-like projections lining the small intestine and aids in nutrients absorption from food into the bloodstream (Ritchey *et al.,* 2018).

Prevalence of Celiac Disease

CD, established as celiac disease, is a widespread autoimmune disorder impacting approximately 0.5–1% of the general population, excluding in regions with low frequencies of CD-predisposing genes and minimal gluten intake, such as Japan and sub-Saharan Africa (Ciccocioppo *et al.,* 2015; Dieterich *et al.,* 1997; Green *et al.,* 2015; Hadithi *et al.,* 2007; Jores *et al.,* 2007; Singh *et al.,* 2016; Villanacci *et al.,* 2011). Most cases of CD go undetected due to diverse symptoms and limited disease consciousness, highlighting the need for serological screening. Notably, CD prevalence is on the rise in Western countries, with a fivefold increase observed in the US between 1975 and 2000, the reasons for which remain unidentified (Goel *et al.,* 2017). In addition to first-degree CD relatives (10–15%), the incidence of CD is greater in other high-risk populations, such as those with type 1 diabetes, Down syndrome, or IgA deficiency (Adams, 1856).

Diagnosis

Globally, the incidence of CD is rising as a consequence of developments in diagnostic instruments. In the past, the primary criteria for diagnosing CD were clinical symptoms and malabsorptive findings. In 1955, histopathologic and intestinal biopsy results were implemented, which substantially altered the method of diagnosing CD. Precise and targeted serum studies of autoantibodies, including anti-reticulin antibodies, endomysial antibodies, anti-deaminated gliadin peptides, and anti-tissue transglutaminase antibodies, were first developed in the 1980s (Villanacci *et al.,* 2011).

According to the American Gastroenterological Association Institute, the initial diagnostic technique for CD involves the identification and measurement of immunoglobulin A (IgA) antibodies towards tissue transglutaminase (tTG) (Goel *et al.,* 2017).

In individuals with untreated underlying celiac disease, tTG antibodies have shown to be extremely sensitive (85-95%) and specific (95-99%). Nevertheless, Silvester *et al.,*'s meta-analysis revealed fluctuations in the sensitivity and specificity of this serologic assay, mainly attributed to the gluten exposure's level prior to sample gathering (Siegel *et al.,* 2006).

Anti-endomysial antibodies (EmA) are an additional specific serological test utilized to diagnose celiac disease. These antibodies exhibit a sensitivity varying from 95% to 100% and a specificity of 99–100%. Anti-EmA has been applied to patients undergoing intestinal biopsies to a significant degree. This EmA serology test's statistical significance is even compared by some authors to that of an intestinal biopsy (Drake, 2005; Fasano *et al.,* 2000).

Conversely, serological markers such as IgA and IgG antibodies that target gliadin, the protein constituent of gluten, have also been correlated to the diagnosis of CD (Vilensky *et al.,* 2015). However, their specificity is comparatively lower than that of the aforementioned markers. In 1977, the first indirect immunofluorescence assay (IFA) serology test for antibodies (IgG and IgA) versus reticulin was documented. Antibodies directed versus the endomysium's reticular fibers are detected by this test. Although endomysium comprises five distinct reticular fibers (R1–R5), CD is exclusively associated with R1. Nevertheless, the diagnostic utility of IgG and IgA reticulin antibodies is restricted due to the test's reliance on rodent substrates and the relatively low number of studies that employ them in comparison to alternative serological tests (White *et al.,* 2015).

The ongoing discussion revolves around the necessity of an intestinal biopsy as a confirmatory diagnostic technique. As per the European Society for Hepatology, Pediatric Gastroenterology, and Nutrition (ESPGHAN 2020), persons with greatly increased levels of serum transglutaminase 2 (TG2) IgA (>10 times the upper limit of normal) may not need to undergo a biopsy to be diagnosed with CD. However, the United States has not adopted this strategy and it has not been included in the Central Europe Guideline (Goel *et al.,* 2017). While the management of this condition is multidisciplinary, the guidance emphasizes the pivotal role of dietitians as discussed in numerous guidelines (Paterson *et al.,* 2007).

Pathology of CD

CD is classified as a unique autoimmune disorder due to the well-defined essential genetic constituents (HLA-DQ8 and HLA-DQ2), the implicated autoantigen (tissue transglutaminase (tTG)), and the environmental stimulus (gluten). A major challenge in CD research has been the absence of a dependable and reproducible animal model, however the Irish setter dog may be an exception as it can potentially acquire a gluten-related illness (Siegel *et al.,* 2006). However, emerging technologies in the fields of human gastrointestinal biology and immunology are generating

unparalleled prospects for substantial progress in research.

The increase in celiac disease cases has led to questioning the preceding belief that gluten is the sole factor in triggering the disease in genetically susceptible individuals, similar to other autoimmune conditions. Lifestyle changes, enhanced hygiene, and decreased exposure to numerous microorganisms are thought to contribute to the steep rise in autoimmune illnesses in industrialized countries over the last 40 years. This supports the hygiene hypothesis, suggesting that the decrease in pathogen exposure due to environmental and lifestyle changes may contribute to the cumulative occurrence of autoimmune disorders. With new findings on the gut microbiome's impact (White *et al.,* 2015) in influencing the equilibrium between immune response and tolerance that can lead to autoimmunity, this theory is currently under examination. Whether autoimmune illnesses arise from an excess or deficit of microbe exposure, it is commonly recognized that adaptive immunity and the imbalance between T helper 1 and 2 cell responses are key factors in the development of autoimmune processes. Additional factors that appear to have a significant impact on the development of autoimmune reactions in celiac disease include impaired intestinal barrier function, an inadequate adaptive immune response, a pro-inflammatory innate immune response triggered by gluten, and an imbalanced gut microbiome. These factors, along with genetic predisposition and exposure to gluten, contribute to the etiology of the disease (figure1).

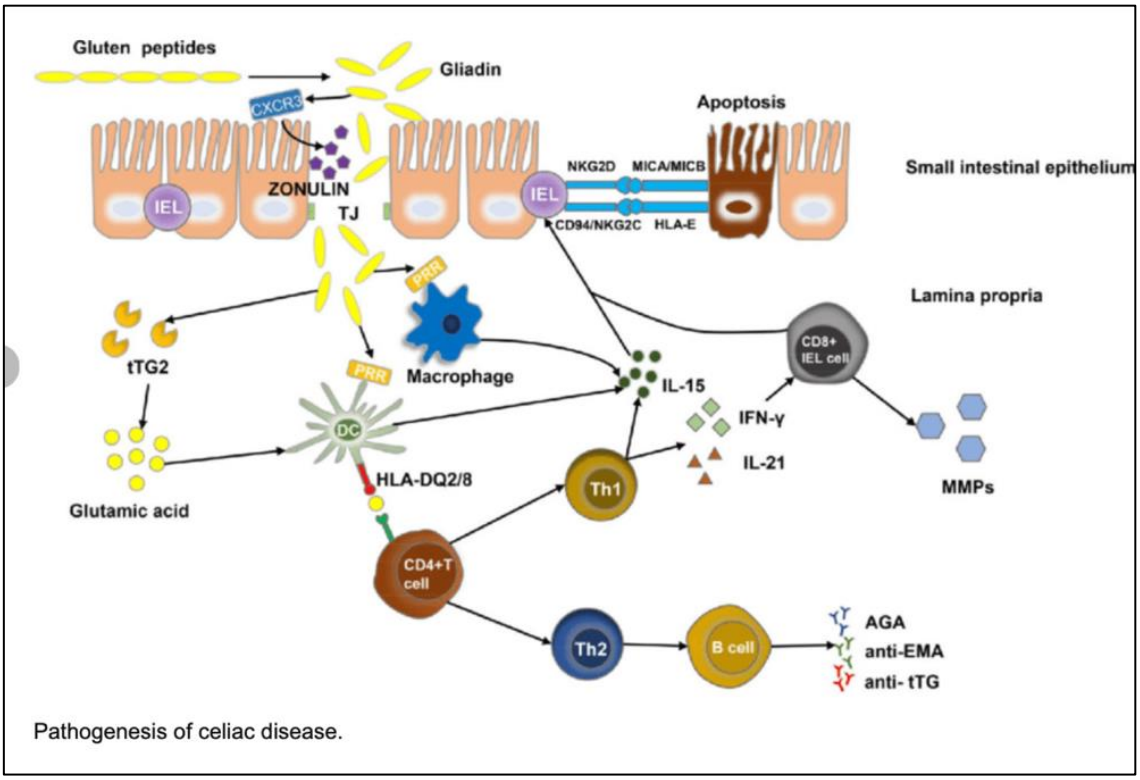

Figure1.shows pathogenesis of CD and itis relation with gluten

Genetics

With new findings on the gut microbiome's influence (White *et al.,* 2015) in influencing the equilibrium between immune response and tolerance that can lead to autoimmunity, this theory is currently under examination. Irrespective of whether autoimmune disorders stem from an excess or deficiency of microorganism exposure, the importance of adaptive immunity and the dysregulation of T helper 1 and 2 cell responses in the progression of autoimmune diseases is extensively recognized. Furthermore, autoimmune reactions in celiac disease seem to be influenced by various factors, including aberrant adaptive immune response, compromised intestinal barrier function, an unbalanced gut microbiome, and pro-inflammatory innate immune response induced by gluten, in addition to genetic predisposition and gluten exposure (Korkmaz *et al.,* 2015; Vriezinga *et al.,* 2018).

Gluten as an environmental cause of CD

Grain gluten content, which was initiated 10,000 years ago throughout the transition from a nomadic to an agricultural lifestyle, is a comparatively recent development in the human diet. Multiple non-digestible immune-stimulating peptides comprise gluten, which is additionally one of the few proteins to withstand digestion when consumed in large quantities over an extended period of time. These characteristics could potentially lead to the immune system developing a reaction to this food antigen, particularly throughout an

enteric infection. Gliadins, essential constituents of gluten, are complex proteins that contain high levels of glutamines and prolines, and are not completely digested by intestinal enzymes (Gopalakrishnan *et al.,* 2012).

The final result of this incomplete digestion is the production of peptides that can trigger host reactions, such as increased gut permeability and both innate and adaptive immune responses, which closely match the responses caused by exposure to potentially dangerous microbes (Fasano *et al.,* 2000; Leffler *et al.,* 2012; Ritchey *et al.,* 2018).

Gluten transportation from the inner cavity of the intestine to the lamina propria can occur via paracellular and transcellular pathways. Research conducted by our team and others has revealed that gliadin can promptly and temporarily elevate the permeability of intercellular tight junctions in intestinal epithelial cells (Gopalakrishnan *et al.,* 2012) (Fig. 1). The observed impact has been correlated with the zonulin's liberation, a molecules' collection that promotes enhanced paracellular permeability through the disruption of tight junctions *et al.,* 2007). Irrespective of disease status, gliadin augments zonulin-mediated enhancement of paracellular permeability in the gut (Collin et al., 1992; Crabbé & Heremans, 1967; Goel *et al.,* 2017; Kelly *et al.,* 2013; Leffler *et al.,* 2015; Lundin & Wijmenga, 2015; Malamut *et al.,* 2009). In addition, experiments on the duodenal tissues of C57BL/6 mice revealed that gliadin increased GI mucosa permeability in a manner dependent on myeloid differentiation primary response 88 (Ohlund *et al.,* 2010).

Additionally, we have identified two alpha-gliadin patterns that, through their interaction with chemokine receptor 3, can impact the functionality of the intestinal barrier. The zonulin release that results from this process induces the degradation of the interepithelial tight junction complex (Myléus *et al.,* 2012). In addition, genetic investigations have confirmed the participation of the paracellular pathway in the transportation of gluten into the lamina propria through the identification of a correlation between specific tight junction genes and CD (Canova *et al.,* 2014; Fasano *et al.,* 2000; Mårild *et al.,* 2013). Compelling evidence suggests that if gluten sensitivity has developed, gluten can pass through the intestinal barrier utilizing the transcellular pathway (McLean *et al.,* 2015; Virta *et al.,* 2009).

CD71, the transferrin receptor, is typically localized on the basolateral aspect of CD71, the transferrin receptor that is normally located on the enterocytes' basolateral side, exhibits upregulation on the intestinal mucosa's luminal side throughout the acute phase of CD. As a consequence, the customary pathway for trafficking gliadin peptides and secretory IgA is inverted, leading to their translocation from the apical to the cells' basal region. IgA-gliadin complexes are transported in a retrograde manner, allowing dangerous gliadin peptides to enter the intestinal lamina propria. This process also prevents the breakdown of gliadin fragments by lysosomes, which in turn contributes to the persistence of intestinal inflammation. Afterwards, these gluten immunogenic peptides (GIP) that are resistant can pass through the weakened epithelial barrier, enter the bloodstream, and eventually be excreted through urine (Catassi *et al.,* 2007).

The innate immune response

The initiation of celiac disease is significantly influenced by natural immunity. Cytokines involving interleukin (IL)-15 and interferon α have the capability to stimulate the innate immune response through their effects on dendritic cell and intraepithelial lymphocyte functionality. Recent research has revealed that certain gliadin peptides have the potential to induce epithelial cell proliferation and enterocyte growth in a manner dependent on IL-15. This may result in structural alterations, modifications in vesicular trafficking, signaling, and proliferation, as well as the activation of stress and innate immunity. In addition, it has been observed that alpha-amylase/trypsin inhibitors, which are responsible for conferring resistance to pests in wheat, exert an impact on the innate immune response in individuals with celiac disease. This is achieved through their interaction with the Toll-like receptor 4–MD2–CD14 complex, which induces proinflammatory cytokines to be released from cells of celiac disease patients and the upregulation of maturation markers (Lionetti *et al.,* 2014). The combination of mucosal events, epithelial barrier function's disruption due to gliadin-induced zonulin release, allowing toxic peptides access to the lamina propria, and the great levels of neutrophil-activating chemokine IL-8 produced by gliadin, collectively contribute to the initiation of CD enteropathy. Additionally, recent research from our group indicates that gliadin directly attracts neutrophils via interacting with the fMet-Leu-Phe receptor 1 (Lee *et al.,* 2009; Wessels *et al.,* 2018).

The adaptive immune response

The celiac disease's significant development is primarily driven by the flawed adaptive immune response, which count on the specific interaction between certain gluten peptides and HLA-DQ2/8-restricted T cells of the main histocompatibility complex class II (Vriezinga *et al.,* 2018). This interaction is influenced by the gluten peptides' post-translational deamidation via transglutaminase 2 (TG2) and is affected via the innate immune system's initial impact, particularly through the upregulation of IL-15, which supports the CD4+ T cells' adaptive immune response (Esch *et al.,* 2011; Roos *et al.,* 2011). HLA class II-expressing dendritic cells, B cells, macrophages, and enterocytes are capable of presenting gluten to CD4+ T

cells, thereby inducing their migration within the lamina propria (Rubio-Tapia *et al.,* 2010).

The proliferation and stimulation of CD4+ T cells occur as a consequence of their interaction with gluten in the lamina propria. Stromal cells generate proinflammatory cytokines, metalloproteases, and keratinocyte growth factor as a consequence; these factors contribute to the development of cryptal hyperplasia and villous blunting. Intraepithelial lymphocytes induce cellular demise in intestinal epithelium. Furthermore, a membrane-bound IL-15 overexpression on enterocytes is linked to active celiac disease (CD), which induces an upregulation of the natural killer (NK) receptors CD94 and NKG2D on CD3+ iIELs. It has been suggested that CD crypt hyperplasia may result from an imbalance within the tissue (Vriezinga *et al.,* 2014).

The damage resulting from the autoimmune attack on the mucosal cells, and the inability of the stem cells to repair it, has been recently explained in a more detailed and evidence-based manner. Our research has shown that active celiac disease leads to the expansion of immature progenitor cells and a decrease in the Hedgehog signaling pathway within the hyperplastic crypts. These findings present understanding into the molecular processes underlying celiac disease's tissue changes and help to explain why mouse models for celiac disease do not consistently exhibit the same intestinal damage seen in humans. This provides support for the hypothesis that the development of celiac disease cannot be solely attributed to the rapid destruction of enterocytes by T cells of the immune system. Rather, it suggests that a fundamental defect within the stem cell compartment of cases at risk for celiac disease is a critical component of CD enteropathy (De Marchi *et al.,* 2013; Korkmaz *et al.,* 2015; Wolf & Ley, 2019).

Symptoms of Celiac Disease

CD symptoms can differ broadly from one case to another. Indigestion is a well-known complication that affect children than the adults due to the inflammation of the GIT, particularly in the intestinal villi, and it is typically accompanied by some symptoms such as bloating, persistent diarrhea, constipation, gas. This can lead to more serious complications in children due to their inability to absorb nutrients such as severe weight loss, permanent tooth enamel damage, delayed puberty, and subsequently mood change due to such delayed growth (Paterson *et al.,* 2007).

This intestinal damage may further lead to some food intolerances such as lactose intolerance, which gives rise to more symptoms, such as loose, bulky, greasy, and foul-smelling stools, vomiting or nausea, and abdominal pain. It also increases the risk of developing gastrointestinal cancers, like esophageal or small intestine cancers (Laurikka *et al.,* 2018).

Extra-intestinal symptoms include osteoporosis, arthritis, and joint pain; anemia due to iron deficiency; vitamin deficiencies; bleeding; infertility and recurrent abortions; chronic fatigue syndrome; and skin rashes like dermatitis herpetiformis and mouth sores may also arise (Ford *et al.,* 2009).

Children are usually diagnosed between the ages of six months to two years old upon their first exposure to gluten in their diet. Some patients may have been misdiagnosed with other digestive issues such as lactose intolerance or inflammatory bowel disease (IBD) as the symptoms may manifest slowly and irregularly (Kozman *et al.,* 2020).

Complications

Health of Cardiovascular

Coeliac disease, like many other autoimmune conditions, may potentially raise the risk of cardiovascular diseases. This could be due to chronic inflammation causing an hastening of atherosclerosis (Korkmaz *et al.,* 2015). The scientific evidence that is available, however, is limited and lacking consistency. Although the developing coronary heart disease and cerebrovascular disease's likelihood seems to be comparatively low, cardiovascular event-related mortality may remain elevated in comparison to the overall population. Furthermore, while the findings are equivocal, coeliac disease may also be correlated with non-ischemic conditions like idiopathic dilated cardiomyopathy. Given the contradictory scientific evidence, screening for cardiovascular diseases on the basis of celiac disease alone is not endorsed. It is critical to consider that the existence of other conditions, such as type 1 diabetes, may influence the risk (Heikkilä *et al.,* 2015).

Health of Mental

Determining the correlation between coeliac disease and mental health poses difficulties, given that chronic symptoms can manifest as detrimental effects on mood. However, it seems that there is a higher incidence of numerous psychiatric conditions, including anxiety, food disorders, and depression, among untreated patients (Wolf & Ley, 2019). While the precise biological mechanisms underlying this association remain unknown, hypotheses include alterations in white matter tracts and disruptions in the gut-brain axis as potential contributors. Individuals with embryonic diseases undergoing treatment have also been linked to a higher prevalence of psychiatric comorbidities. The current absence of long-term follow-up studies has resulted in an uncertain understanding of the fundamental causes and consequences of a gluten-free diet on psychological symptoms and quality of life. When diagnosing celiac disease, it is imperative to take into account the psychological well-being of individuals and the occurrence of psychiatric symptoms. The provision of

low-threshold psychiatric consultation should occur no later than when symptoms continue to remain despite effective treatment or when concomitant psychiatric disease is suspected (De Marchi *et al.,* 2013).

Malabsorption

Despite the healthy diet, this disease can lead to malabsorption, and consequently lead to malnutrition. Deficits in vital minerals and vitamins, involving folic acid, vitamin B12, iron, and vitamin D, may consequently arise. These deficiencies can lead to anemia, weight loss, and hinder the normal growth and development of children. Increased bleeding tendency may also occur due to low vitamin K levels in the blood (Crowe, 2011).

Calcium Loss and Bone Density

Constant loss of stool fat results in significant loss of vitamin D and calcium which leads to soft bones known as osteomalacia in adults, similar to rickets in children. Another complication is osteoporosis, a disorder that causes brittle, easily broken bones. Furthermore, oxalate urolithiasis, a form of kidney stone, can result from decreased calcium absorption (Fasano *et al.*, 2000).

Lactose Intolerance

Another complication that arises from the damage that gluten consumption causes to the intestinal lining is lactose intolerance. While it is recommended to refrain from the ingestion of gluten or lactose in the diet until the intestine is fully healed, some patients may still suffer from lactose intolerance. Ingestion of gluten can cause chronic inflammation, which raises the risk of developing intestinal lymphoma and colorectal cancer, among other cancers (Leffler *et al.*, 2012).

Neurological Complications

CD is also linked to behavioral abnormalities, attention-deficit/hyperactivity disorder (ADHD), depression, and epilepsy. Peripheral neuropathy, a kind of nerve damage, may result from it as well (Hvas *et al.*, 2015).

Immunological Disorders

They are more likely to have additional autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, Addison's disease, Down syndrome, Sjogren's syndrome, Hashimoto's thyroiditis, and type 1 diabetes mellitus. Another autoimmune skin condition that affects people with CD is called dermatitis herpetiformis which is characterized by itchy skin, brought on by the glutamine-transporting enzyme's activity. IgA immunoglobulin deficiency is one of the immunodeficiency disorders that is linked to this disease (Collin *et al.*, 1992).

Malignancies

An uncommon yet widely recognized complication of unresponsive (refractory) celiac disease is enteropathy-associated T-cell lymphoma (EATL), which affects an estimated 0.1%–3.2% of all celiac disease patients. ETL is a subtype of non-Hodgkin lymphoma. Additionally, intestinal adenocarcinoma and other non-Hodgkin lymphoma subtypes are associated with an elevated risk (Olivares *et al.*, 2018).

The correlation between coeliac disease and overall cancer threat stays a subject of contention, as has been duly recognized. Coeliac disease has been correlated with a range of cancer prevalence rates (Galipeau *et al.,* 2015), from 2.3% to 15.9%. Although the likelihood of developing breast cancer may be diminished, certain studies indicate an elevated risk for malignancies, especially during the initial few years following a diagnosis of coeliac disease. This may be attributed, at least in part, to the increased scrutiny that malignancy evaluations receive from newly diagnosed patients, particularly in cases where treatment response is suboptimal. On the other hand, the existence of cancer symptoms may necessitate comprehensive examinations, such as gastrointestinal endoscopies or serological testing for coeliac disease (Dydensborg Sander *et al.*, 2018).

Probably contributing to the variation in noted cancer risk correlated with celiac disease is the overrepresentation of clinically acknowledged forms of the disease with a greater risk of malignant problems, particularly in earlier studies. Advances in non-invasive diagnostics and proactive screening over the past few decades have led to earlier detection and reduced clinical symptoms. Simultaneously, the improved availability of gluten-free products has made adherence to strict dietary medication more manageable. These timely changes may account for some of the disparities observed in overall cancer risk across different studies (Kivelä *et al.,* 2017).

Prevention of CD

Primary Prevention

In theory, the condition could be prevented by restricting the consumption of gluten in the diets of neonates who have a genetic predisposition to CD. However, since the most influential genetic variables for CD, HLA DQ2 and/or HLA-DQ8, are found in around 40% of the Caucasian population, this approach is not practical. Furthermore, the overwhelming majority of these individuals do not develop CD, since its prevalence stands at a mere 1%. Another reason for not promoting the avoidance of gluten for a large percentage of the population is that gluten-containing cereals, such as wheat, barley, and rye, provide important nutrients and minerals (Dieterich *et al.,* 1997; Villanacci *et al.,* 2011), including dietary iron, fiber, folate, calcium, and vitamin B12.

A significant amount of our understanding of the potential link between newborn feeding habits and the development of CD was obtained from the analysis of "The Swedish Epidemic of CD" in the mid-1980s. The prevalence of CD in Swedish infants aged two and below experienced a fourfold rise between 1985 and 1987, followed by a sharp decline about 1995. The outbreak was associated with modified dietary regimens, which involved postponing the introduction of gluten-containing meals to newborns until they reached six months of age, along with changes in breastfeeding methods. In Sweden, the occurrence of CD decreased after the reintroduction of gluten at an earlier stage (before four months) (Goel *et al.,* 2017). The emergence of the epidemic was correlated with revised dietary guidelines, particularly the deferral of gluten-containing food introduction to neonates until they reach the age of six months, in addition to modifications in breastfeeding protocols. The incidence of CD declined in Sweden when gluten was reintroduced earlier than four months prior. Diverse conclusions have been reached in the retrospective investigations that have examined the hypothesis that delayed gluten introduction contributes to CD. Observational studies have demonstrated that introducing gluten to infants between 4 and 6 months of age may be a viable primary prevention strategy for CD. In conjunction with other early nutrition practices, these results indicate the existence of a "window of opportunity" for preventative measures (Collado *et al.*, 2008).

Secondary Prevention

Secondary prevention of celiac disease emphasizes early diagnosis and treatment. Active case discovery entails the performance of diagnostic examinations on patients exhibiting symptoms consistent with CD. Numerous patients in the general population have been diagnosed at an early stage of the disease, which has resulted in substantial health improvements following treatment, strict adherence to the gluten-free diet, and a high quality of life in relation to celiac disease (Catassi *et al.,* 2007; Virta *et al.,* 2009). Unfortunately, this approach fails to fully tackle the issue of underdiagnosis of CD (Hujoel *et al.,* 2018; Rosén *et al.*, 2014), as it only detects a minority of undiagnosed patients. The fact that around fifty percent of children in screening-detected studies exhibit symptoms at the moment of diagnosis suggests that the approach should be reconsidered.

Celiac Disease Screening in High-risk Populations

Evidence-based guidelines advise high-risk populations, such as infants with type 1 diabetes mellitus and first-degree relatives of patients with celiac disease, to undergo screening for early detection of the condition. A multitude of studies have been conducted on these populations, emphasizing the considerable incidence of celiac disease among these demographic groups (Canova *et al.,* 2014).

First-degree Relatives of CD cases

Numerous research studies have demonstrated that there is an improved probability of celiac disease development among FDRs of those affected, as compared to the wide-ranging population. Prevalence rates for FDRs vary between 1.6% and 38%. Sing *et al.,* conducted a systematic review and meta-analysis which revealed that the combined occurrence of celiac disease in 10,252 FDRs was 7.5%. The susceptibility to celiac disease in FDRs is contingent upon both gender and HLA haplotype. Celiac disease exhibits a higher incidence among females, as indicated by a female-to-male ratio of 2-3:1. Furthermore, at the age of 3 years, children who are HLA-DQ2 homozygous face a substantially greater risk of developing the condition than those who are HLA-DQ2 heterozygous, with respective rates of 14.9% and 3.9% (Galipeau *et al.,* 2015; Olivares *et al.,* 2015).

Children with Circumstances/Diseases correlated with CD

The majority of studies document a prevalence ranging from 4% to 10% among patients diagnosed with type 1 diabetes mellitus (T1DM) who have celiac disease (CD). The absence of symptoms in numerous children with T1DM and CD necessitates serologic screening for the detection of the condition (Sevelsted *et al.,* 2015). In contrast, research suggests that a minority of minors (less than 30%) with both CD and T1DM adhere strictly to a gluten-free diet, in contrast to the 81% of patients with CD alone. Aside from managing diabetes, adhering to a strict gluten-free diet requires extra time, effort, and financial commitment. The available information is inconclusive regarding whether screening and perhaps treating those without symptoms would provide more benefits compared to the challenges of managing a population already suffering from a severe illness (Koletzko *et al.,* 2018).

Tertiary Prevention

Gluten-free Diet (GFD)

The objective of tertiary avoidance is to mitigate the consequences of established diseases using enhanced therapeutic interventions. One potential approach entails improving compliance with the GFD. It can be difficult to eliminate gluten from one's diet due to its prevalence in a vast array of foods. Nevertheless, gluten concealment in products has been prohibited in the European Union (EU) since the implementation of allergen labeling in 2005. The estimated threshold for gluten to induce an immune response is greater than 20 mg/kg (or parts per million = ppm). Gluten contamination below 20 ppm is deemed protected for daily consumption across a broad spectrum of foods (Mårild *et al.,* 2013).

Improving Oversight and Compliance with the Gluten-Free Diet (GFD)

Referring newly diagnosed patients to a dietician who specializes in CD is crucial, given the intricate nature of the GFD. The probability of patients receiving inaccurate information from sources such as the internet, health food stores, alternative health practitioners, family members, and friends is higher when there is a delay or lack in referrals. This frequently results in perplexity, exasperation, and insufficient understanding of CD and the GFD (Hujoel *et al.*, 2018). Cereals containing gluten, such as wheat, barley, and rye, are notable sources of vitamin B12, dietary iron, calcium, and folate. A GFD for the treatment of CD may result in nutritional deficiencies; therefore, the assistance of a dietitian is crucial in order to avert these deficiencies. Furthermore, it is imperative that individuals with CD consult a specialist in gluten-free products, including teff, amaranth, buckwheat, quinoa, and sorghum; doing so may augment their protein, iron, calcium, and fiber consumption (Öhlund *et al.*, 2010).

Validated Dietary Questionnaires

The efficacy of validated dietary questionnaires in assessing compliance with the gluten-free diet (GFD) among young adults and adolescents has been established. In order to assess adherence to a restricted food intake (GFD) in a more efficient manner, abbreviated questionnaires have been devised in lieu of the labor-intensive and time-consuming traditional dietary interviews. While certain questionnaires may lack sensitivity, others prove to be valuable tools for evaluating adherence to the prescribed diet. Utilizing electronic patient records and E-health tools, such as self-assessment and alternative follow-up methods, can help streamline the process of completing questionnaires prior to or throughout medical consultations for children and young adults with celiac disease (Mårild *et al.*, 2013).

Measurement of Gluten Immunogenic Peptides (GIPs)

Current approaches to assessing adherence to a gluten-free diet (GFD) are laborious and inadequate in terms of sensitivity to identify inadvertent dietary errors that may result in harm to the intestinal mucosa. It is common practice to monitor serum TG2A levels when following up with patients on a GFD, as these levels tend to increase after gluten elimination. Nevertheless, research has shown that infants and women with celiac disease, despite following a GFD, exhibit a greater incidence of gastrointestinal symptoms and necessitate more frequent medical attention in comparison to individuals without the condition (Rosén *et al.*, 2014).

Treatment

After a biopsy confirms the diagnosis of CD, the patient is advised to adhere to a continuous gluten-free diet, which may initially seem difficult due to the presence of gluten in numerous foods. It is simple to adhere to a gluten-free diet with the guidance and support of knowledgeable CD patients and a certified nutritionist. For the most part, this dietary regimen alleviates symptoms, restores pre-existing intestinal injury, and averts additional harm (Hopman *et al.*, 2006). Almost immediately after beginning the diet, symptoms improve; however, it takes at least a year for antibody levels to return to normal after discontinuing gluten consumption. Your doctor will determine whether or not your intestinal injury is healing properly based on the rate at which your antibody levels decline (44). Although the symptoms may subside, research suggests that the intestinal lining of many adults may not completely heal, whereas in most children, the intestinal lining resolves entirely. The degree of amelioration observed in complications such as delayed development and discolored teeth may be contingent upon the patient's age at the moment of diagnosis. Although gluten-free diets are no longer advised for patients who do not exhibit any apparent symptoms. Notwithstanding these limitations, individuals diagnosed with CD are capable of incorporating a diverse array of foods into a well-balanced diet, including gluten-free pasta and bread. For example, potato, rice, soy, or legume flour may be substituted for wheat flour (Öhlund *et al.*, 2010).

Experimental Treatments

Prospects for CD therapy that are presently in the experimental phase, pending the results of clinical trials. One of the therapeutic methodologies involves the consumption of gluten-free and genetically modified cereals. However, the aforementioned cereals are of inferior quality due to the absence of gluten (Vriezinga *et al.*, 2018). In order to facilitate the patient's digestion of gluten-containing meals, gluten-digesting enzymes may be added to their regimen. This will significantly mitigate the inflammation that was initially initiated by the increased permeability of intestinal mucous membranes caused by prolamins penetrating the intestinal wall (Dennis & Case, 2004).

Important of health education in prevention and control the symptom of CD

Several prior investigations have examined the impact of health guidelines on celiac disease patients' knowledge, attitudes, and behaviors. The findings of these studies indicated that CD patients' knowledge increased subsequent to the implementation of the educational program, as opposed to their pre-program knowledge. This finding suggests that the program was successful in altering attitudes, behaviors, and knowledge regarding individuals with celiac disease (56). According to reports, the majority of parents have erroneous or contradictory information as a result of relying on weak sources of information on the Internet, which causes them to become confused and provide incorrect information about their diet, as well as restrict certain foods that are essential for good health; thus, dietary variety and nutritional quality are diminished (Korkmaz *et al.*, 2015).

In order to qualify as health care professionals, dietitians must possess a comprehensive academic and practical foundation in disease progression, prevention, treatment, and control. Additionally, determine the impact of CD and treatments on nutritional requirements from various vantage points, including food ingredient and preparation information, socioeconomic status (which influences an individual's food choices), and nutritional behaviors that persist throughout an individual's life (which are influenced by educational factors (Lee *et al.,* 2009; Vriezinga *et al.,* 2018). In addition, dietitians play a crucial role in supporting clients with self-awareness, acquiring knowledge, enhancing and refining decision-making, and modifying behavior. They accomplish this by simplifying complex scientific concepts for patients and providing comprehensive nutritional therapies (Roos *et al.,* 2011). Barzegar et al. discovered that the mean scores for treatment, epidemiology, and diagnosis for ninety CD patients improved significantly from 7.16, 2.72, and 6.81 prior to the training program to 8.98, 7.16, and 9.06 after the program. Moreover, an increase in professional knowledge was associated with an enhancement and positive effect on elderly CD patients, as per a study by (Rubio-Tapia *et al.,* 2010).

In general, education is of the utmost importance regarding dietary modifications, not only for individuals with CD and their immediate environment (including family members, caregivers, and school personnel), but also for healthcare practitioners (Esch *et al.,* 2011; Hopman *et al.,* 2006). In order to ensure optimal care for patients with CD, it is critical that both the patients and their families participate in decision-making processes. This will facilitate symptom amelioration and promote a more rapid adjustment to the new lifestyle. This was validated by Green, who discovered that physicians who had a greater understanding of the positive impact of knowledge on complications and gluten-free diet adherence were more likely to have compliant patients with CD. Conversely, physicians with inadequate knowledge regarding gluten-free diet compliance for CD patients resulted in the persistence of symptoms, the occurrence of complications, and other adverse health outcomes (de Lourdes Moreno *et al.,* 2017).

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