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Celiac disease: An immune reaction to gladin (Gluten Protien)

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Abstract
Celiac disease is a chronic digestive disorder of intestine resulting from an immune reaction to gladin, a gluten protein found in wheat, barley, rye, and sometimes in oats, or it is also found in many foods as well as in cosmetics and alcohol like lip balm, lipsticks and antiaging creams. Celiac disease is an autoimmune disorder; autoimmune disorders occur when the immune system malfunctions and attacks the body's own tissues and organs. The disease can cause long-term digestive problems and keep you away from getting nutrients you need.
Celiac disease can develop at any age after an individual starts eating foods containing gluten. The classic symptoms of the condition result from inflammation affecting the gastrointestinal tract. This inflammation damages the villi, which are small, finger-like projections that line the small intestine and provide a greatly increased surface area to absorb nutrients. In celiac disease, the villi become shortened and eventually flatten out. Intestinal damage causes diarrhoea and poor absorption of nutrients, which may lead to weight loss. Abdominal pain, swelling (distention), and food intolerances are common in celiac disease. Inflammation associated with celiac disease may lead to an increased risk of developing certain gastrointestinal cancers such as cancers of the small intestine or oesophagus.
Inflammation and poor nutrient absorption may lead to problems affecting many other organs and systems of the body in affected individuals. These health problems may include iron deficiency that results in a low number of red blood cells (Anemia), vitamin deficiencies, low bone mineral density (osteoporosis), itchy skin rashes (dermatitis herpetiformis), defects in the enamel of the teeth, chronic fatigue, joint pain, poor growth, delayed puberty, infertility, or repeated miscarriages. Researchers now believe that non-classic celiac disease is actually more common than the classic form.

Keywords: celiac disease, inflammation, autoimmune disorders, distension, gladin protein, intestinal damage, dermatitis herpetiformis, osteoporosis, anemia

Introduction
Celiac disease is a serious autoimmune disease that occurs in genetically predisposed people where the ingestion of gluten leads to damage in the small intestine. It is estimated to affect 1 in 100 people worldwide. Two and one-half million Americans are undiagnosed and are at risk for long-term health complications. Celiac disease is hereditary, meaning that it runs in families. People with a first-degree relative with celiac disease (parent, child, sibling) have a 1 in 10 risk of developing celiac disease. Celiac disease can develop at any age after people start eating foods or medicines that contain gluten. Left untreated, celiac disease can lead to additional serious health problems [2].
In a new study, researchers conducted a meta-analysis and review of studies from all over the world to estimate the global prevalence of celiac disease and identify possible variations in prevalence between different regions and populations. Prevalence refers to the proportion of individuals who have a condition at or during a particular time period. A meta-analysis is a statistical method used to combine research study data to summarize the results of multiple studies. The authors reviewed 96 studies published between January 1991 through March 2016 from Asia, Europe, Africa, South America, North America, and Australia. Celiac disease diagnosis was based on a positive celiac-specific blood test, a small intestinal biopsy revealing abnormalities, or a combination of both. The results of the meta-analysis found the current worldwide prevalence of celiac disease to be 1.4% based on blood tests and 0.7% based on biopsy results. The prevalence of celiac disease was 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania. The prevalence was higher in female than male individuals, and was significantly greater in children than adults. In conclusion, the prevalence of celiac disease varies with sex, age, and location [5].
A major milestone in the history of celiac disease was the identification of tissue transglutaminase asthe autoantigen, thereby confirming the autoimmune nature of this disorder. A genetic background (HLA-DQ2/DQ8positivity and non-HLA genes) is a mandatory determinant of the development of the disease, which occurs with the contribution of environmental factors (e.g., viral infections and dysbiosis of gut microbiota). Its prevalence in the general population is of approximately 1%, with female predominance. The disease can occur at any age, with a variety of symptoms/manifestations. This multifaceted clinical presentation leads to several phenotypes, i.e., gastrointestinal, extraintestinal, subclinical, potential, seronegative, non-responsive, and refractory. Although small intestinal biopsy remains the diagnostic ‘gold standard’, highly sensitive and specific serological tests, such as tissue transglutaminase, endomysial and deamidated gliadin peptide antibodies, have become gradually more important in the diagnostic work-up of celiac disease. Currently, the only treatment for celiac disease is a life-long,

strict gluten-free diet leading to improvement in quality of life, ameliorating symptoms, and preventing the occurrence of refractory celiac disease, ulcerative jejunoileitis, and small intestinal adenocarcinoma and lymphoma [8].

Aims and Objective

1. Explain the growing significance of celiac disease and intestinal damage in public health.
2. Focus on effective prevention and risk reduction strategies and promote school, family, community into promotional programme.
3. Describe the epidemiological disease of Celiac Disease.
4. Understand the pathophysiology of Celiac Disease.
5. Understand the screenings and confirmatory tests for Celiac Disease.

Material and Method

This study is carried out by literature search and critical review of the obtained facts. The various medical research databases like PubMed, Google scholar and another national research databases. The terms entered for search are autoimmune disorder "Celiac Disease" (CD), "Gluten Allergy" (GA). Manual search was made by going through the reference list of retrieved articles to identify relevant additional study.

Epidemiology of Celiac Disease

Celiac disease is a common disorder in the US and in Europe. A relatively uniform prevalence has been found in many countries, with pooled global seroprevalence and biopsy-confirmed prevalence of 1.4% and 0.7%, respectively, according to well-designed studies. However, although seroprevalence is about the same, biopsy-confirmed celiac disease is slightly less common in South America, the Middle East, Turkey, and sub-Saharan Africa [3]. With the exception of Malaysia and Vietnam, population-based studies from the Far East, including China, Japan, and Southeast Asia, are lacking. In North America, after several decades of rising prevalence, the prevalence of celiac disease appears stable in recent years [4].

Women are slightly more likely to be affected by celiac disease. In clinical practice they make up almost two-thirds of diagnosed patients. The first peak period of presentation is in childhood around age 6 to 7 years, but celiac disease can arise as soon as gluten is introduced. A second, larger peak occurs in the fourth and fifth decades. Although the most common age at diagnosis in the US is about 40 years, celiac disease may be diagnosed at any age [7].

Silent celiac disease is serologic and histologic evidence of celiac disease, but without any evident symptoms, signs, or deficiency states. The proportion of celiac disease that is truly silent is not well known, but it is thought to account for at least 20% of patients. Refractory celiac disease is a specific diagnosis within the category of nonresponsive celiac disease, defined as the persistence of clinical symptoms and histologic abnormalities after at least 6 months on a strict gluten-free diet and in the absence of other evident causes or of overt lymphoma. The incidence of refractory celiac disease in patients with celiac disease is not well known but is felt to be approximately 1% [10].

A multicentre study reported a prevalence of 1 out of 133 (0.75%) in healthy people in the United States, and similar frequency is confirmed by studies on European and Australian populations [12]. The overall prevalence of celiac disease ranges from 4.5% among high-risk subjects to 0.75% in not-at-risk subjects. High-risk subjects include the relatives of patients with celiac disease, children or adults with celiac disease-associated symptoms (i.e., diarrhoea, abdominal pain and constipation) and children or adult subjects with celiac disease-associated disorders (i.e., Diabetes Mellitus type-1, Down syndrome, Anemia, infertility, osteoporosis) [13]. It has been shown that celiac disease is not exclusive of industrialized countries, but includes North Africa, Middle East and India with an incidence overlapping those of European countries [18-20]. However, given the worldwide distribution of the causal factors this heterogeneous diffusion is not surprising. It has been shown that the Saharawi, an Algerian population has the highest prevalence of celiac disease (nearly, 6%) among all of the worldwide populations [14].

Pathophysiology of Celiac Disease

In CD there is unique insight into what drives the disease once it has been initiated. In the affected individual, 4 well-defined components interact: gluten, tissue transglutaminase (TG2), HLA-DQ2/8 and T cells. Upon ingestion gluten is degraded into relatively large fragments due to the activity of the enzyme pepsin in the stomach. Such fragments may be further trimmed by enzymes in the small intestine but because of the proline-rich nature of gluten relatively large fragments persist [15]. Some of these can bind with low affinity to the disease predisposing HLA-DQ2 or HLA-DQ8 molecules and T cells reactive to such DQ-peptide complexes have been found in patients with CD, although in low frequencies. Nevertheless, such T-cell responses, probably in conjunction with the induction of innate responses, could lead to tissue damage [16]. This would lead to the release of the enzyme TG2, which in the calcium-rich extracellular environment can modify gluten peptides.

The modification, termed deamidation, involves the conversion of the neutral amino acid glutamine into the negatively charged glutamic acid. As a result of this introduction of a negative charge such deamidated gluten peptides bind with much higher affinity to HLA-DQ2 or HLA-DQ8 because these HLA molecules prefer to bind peptides in which one or more negatively charged residues are present [17, 18]. Moreover, a large number of gluten peptides can be modified in this fashion, thus broadening and amplifying the gluten specific T-cell response in the lamina propria (Fig. 1). This response is characterized by the secretion of proinflammatory cytokines that drive the local inflammation, in particular IFNγ More important, these results explain the well-established fact that CD almost exclusively develops in HLA-DQ2 and/or -DQ8 positive individuals [19, 20].

The dominant role of HLA-DQ2 is further illustrated by the fact that individuals homozygous for HLA-DQ2 have an at least 5-fold higher risk to develop CD compared with individuals heterozygous for HLA-DQ2. We observed that the HLA-DQ2 gene dose has a strong quantitative effect on the magnitude of gluten-specific T-cell responses which correlated with the level of gluten peptide binding to antigen-presenting cells, providing a functional explanation for the HLA-DQ2 gene dose effect [15, 16].

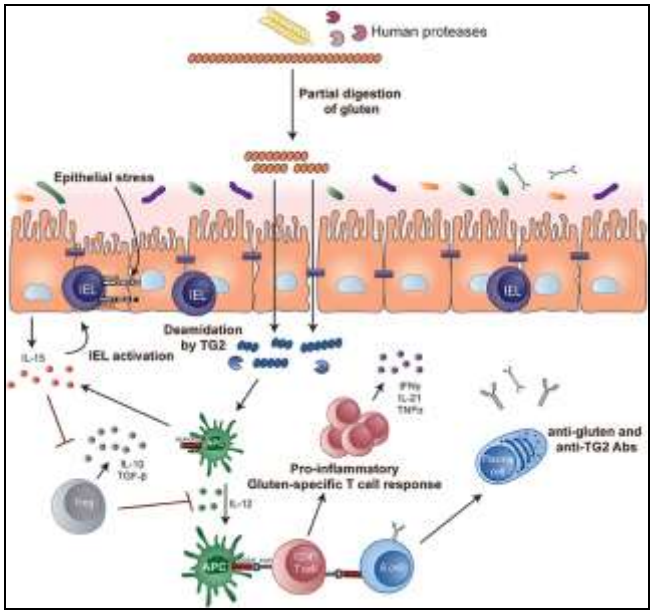

Fig 1: Pathophysiology of Celiac Disease

Gluten as an Environmental Trigger of Celiac Disease

Introduced 10,000 years ago during the transition from a nomadic lifestyle to agricultural settlements, gluten-containing grains are a recent addition to the human diet. Moreover, gluten is one of the few digestion-resistant proteins consumed chronically in significant quantities and is constituted by several non-digestible immunogenic peptides. These two characteristics could help in breaking the tolerance to this food antigen, when the immune system is activated, as can happen during an enteric infection. Gliadins, key components of gluten, are complex proteins unusually rich in prolines and glutamines and are not completely digestible by intestinal enzymes. The final product of this partial digestion is a mix of peptides that can trigger host responses (increased gut permeability and innate and adaptive immune response) that closely resemble those instigated by the exposure to potentially harmful microorganisms [23, 25].

Clinical Presentation

Table 1: Clinical Presentation of Celiac Disease

Symptoms	Extraintestinal manifestations	Associated conditions
Gastro-Intestinal		
▪ Diarrhoea ▪ Abdominal Pain ▪ Bloating ▪ Constipation	▪ Arthritis ▪ Aphthous stomatitis ▪ Dermatitis Herpetiformis ▪ Osteoporosis/Osteopenia ▪ Elevation in transaminases ▪ Infertility ▪ Recurrent abortions ▪ Neurologic ▪ Ataxia ▪ Epilepsy ▪ Anxiety ▪ Depression	▪ Type 1 diabetes ▪ Turner syndrome ▪ Autoimmune Thyroid disease ▪ Down syndrome ▪ IgA deficiency ▪ IgA nephropathy
Nutritional Deficiency		
▪ Anemia: ▪ Iron Deficiency ▪ Folate Deficiency		
Vitamin D deficiency		
▪ Rickets ▪ Hypocalcaemia		
Vitamin K Deficiency		
▪ Coagulation		
Growth Factor		

The clinical presentation of celiac disease is remarkably varied and depends on age the classic presentation with failure to thrive, malnutrition, diarrhoea, abdominal pain and distension within the first couple of years of life represents the tip of what is commonly referred to as the "celiac disease iceberg". In contrast to the dramatic presentation noted typically in younger children, many patients with celiac disease present at a later age with subtle symptoms and the diagnosis of celiac disease may be delayed. Gastrointestinal symptoms may include abdominal pain, diarrhoea or constipation, bloating, and excessive gas.

Avoidance of foods containing gluten may also occur and a careful diet history is necessary to identify this symptom. Vitamin deficiencies due to fat malabsorption can also occur. With longer-standing disease, patients may present with profound vitamin D deficiency resulting in rickets or hypocalcaemia and tetany or coagulopathy secondary to vitamin K deficiency. Anemia secondary to iron and/or folate deficiency is also observed [26, 27, 28].

Children and adolescents often present with short stature and constitutional delay of puberty. Two to 8% of children and adolescents presenting for evaluation of short stature have evidence of celiac disease [29]. Once endocrine causes of short stature have been excluded, rates of celiac disease increase two- to four-fold depending upon the population and referral base studies [30]. Access to previous growth points may be useful in the differentiation between constitutional delay of puberty and an underlying pathological cause of short stature such as celiac disease. Children presenting with celiac disease often will experience a decline in both height and weight growth velocity resulting in a decrease in the growth percentiles. In contrast, children presenting with constitutional delay of puberty often have low-normal growth velocity and will have no change in their growth percentiles. In the setting of declining growth percentiles or where the data are not available, the diagnosis of celiac disease should be entertained and testing with autoantibodies performed [31].

Adults have diarrhoea as a major symptom of celiac disease in approximately 50% of cases [32]. They may also be diagnosed in the setting of Anemia or osteoporosis. Adults may be symptomatic for years prior to their diagnosis or have short stature (suggesting long-standing celiac disease). They are often initially misdiagnosed with irritable bowel syndrome and may have had multiple procedures and/or hospital admissions that can ultimately be traced to their

undiagnosed celiac disease [32].
Patients identified by screening due to genetic risk factors are often asymptomatic or mildly symptomatic for celiac disease. This is the population of individuals with celiac disease that is rapidly growing due to increased screening efforts [33].

Risk Factors
Celiac disease tends to be more common in people who have:
A family member with celiac disease or dermatitis herpetiformis
- Type 1 diabetes
- Down syndrome or Turner syndrome
- Autoimmune thyroid disease
- Microscopic colitis (lymphocytic or collagenous colitis)
- Addison's disease

Complications
Untreated, celiac disease can cause:
Malnutrition. This occurs if your small intestine can't absorb enough nutrients. Malnutrition can lead to Anemia and weight loss. In children, malnutrition can cause slow growth and short stature.
Bone weakening. Malabsorption of calcium and vitamin D can lead to a softening of the bone (osteomalacia or rickets) in children and a loss of bone density (osteopenia or osteoporosis) in adults.
Infertility and miscarriage. Malabsorption of calcium and vitamin D can contribute to reproductive issues.
Lactose intolerance. Damage to your small intestine might cause you abdominal pain and diarrhoea after eating or drinking dairy products that contain lactose. Once your intestine has healed, you might be able to tolerate dairy products again.
Cancer. People with celiac disease who don't maintain a gluten-free diet have a greater risk of developing several forms of cancer, including intestinal lymphoma and small bowel cancer.
Nervous system problems. Some people with celiac disease can develop problems such as seizures or a disease of the nerves to the hands and feet (peripheral neuropathy).

Diagnostic Criteria
The diagnosis of celiac disease is made using a combination of serologic tests, small bowel biopsy, and response to a gluten-free diet several serologic antibody tests can be used as initial tests in patients with clinically suspected celiac disease. (Table-2) Because of their low sensitivity and specificity, antigliadin antibodies are no longer recommended for initial testing [34, 35, 36]. The test for endomysial antibodies has higher sensitivity and specificity, but is also more expensive. Tissue transglutaminase (tTG) testing is of similarly high sensitivity and specificity, but is not as costly. Thus, IgA tTG is currently the test of choice for serologic diagnosis and monitoring of celiac disease [41, 42]. (Fig-2)

Genetic Testing
More than 99% of patients with celiac disease have human leukocyte antigen DQ2, DQ8, or both. Celiac disease is unlikely if neither of these haplotypes are present, with a negative predictive value approaching 100%.Genetic testing is used rarely, but occasionally may be useful in excluding disease when other testing results are unclear. The human leukocyte antigen DQ2 and DQ8 alleles are present in 25% to 30% of the general population without celiac disease, but only about 4% of these persons develop celiac disease. Therefore, this testing should not be used to randomly assess genetic susceptibility to the disease.

Endoscopy
Doctor may ask a gastroenterologist to perform an endoscopy to confirm your diagnosis if a blood test shows you may have celiac disease. You'll swallow a small, flexible tube containing a tiny camera. A specialist (usually a pathologist) will view this tissue under a microscope to see whether it has been damaged by celiac disease.

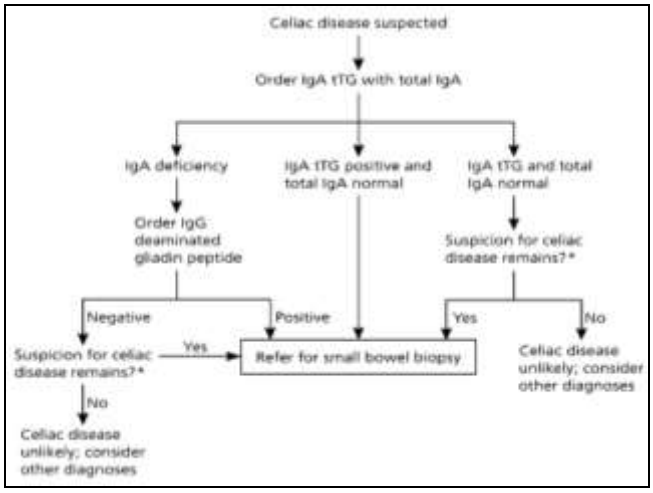

Fig 2: Algorithm for the diagnosis of celiac disease. (Ig = immunoglobulin; tTG = tissue transglutaminase.)

Serologic test	*Sensitivity (%)*	*Specificity (%)*	*LR+*	*LR–*
IgG deaminated gliadin peptide	80	98	40	0.20
IgA endomysial antibody	> 90	> 95	> 18	< 0.11
IgA deaminated gliadin peptide	88	95	17.6	0.13
IgA tissue transglutaminase*	95 to 98	94 to 95	17.5	0.04
IgA antigliadin antibody	80 to 90	85 to 95	8.5	0.17
IgG endomysial antibody	40	95	8	0.63
IgG tissue transglutaminase	40	95	8	0.63
IgG antigliadin antibody	80	80	4	0.25

Fig 2: Diagnostic Tests for Celiac Disease

Treatment and Prevention of Celiac Disease
Removing the antigenic substance responsible for the abnormal immune reaction typically reverses the manifestations of celiac disease. Therefore, treatment is a lifelong gluten-free diet. A gluten-free diet improves the quality of life in those with symptomatic celiac disease. Because dietary glutens are found in wheat, rye, and barley which make up the cornerstone of many (American diets), the diet is complex and can be difficult to follow. The dietary threshold to promote healing of intestinal inflammation in celiac disease has been found to be less than 50 mg of gluten per day.

People with celiac disease must avoid eating gluten-containing foods.
This means that they can't eat bread products made with

wheat, rye, or barley. Gluten is also found in many prepared foods such as pasta. Until recently, people with celiac disease were advised to avoid oats. We now know that oats themselves do not contain gluten, though they may be contaminated in processing.

People with celiac disease have to carefully check the labels on processed foods for gluten.
They shouldn't buy any processed food unless they know exactly what's in it. They should also be careful to check if the vitamins and medications they are taking contain any gluten. Fortunately, more and more gluten-free food options are becoming available.

Keeping the body hydrated is important.
Taking vitamin and mineral supplements may also be helpful to compensate for the problems of malabsorption. Once the person begins to follow the gluten-free diet, the bowel begins to heal and the problem of malabsorption may go away.

Findings
The systematic review search was conducted by formulating the terms separately and in integration with all synonyms, also according to the database. Likewise, a manual Google scholar search was undertaken using the keywords and search synonyms from already articles. Initial search recovers 450 articles over which 270 articles were selected manually.150 articles were rejected as a result of replication in the database. Replication was removed and reviewed 120 articles for acceptability.80 more studies were rejected because of unreachable of the full text.

Conclusion
The present review is timely and provides a thorough appraisal of various aspects characterizing celiac disease. Remaining challenges include obtaining a better understanding of still-unclear phenotypes such as slow-responsive, potential (minimal lesions) and seronegative celiac disease. The identification of alternative or complementary treatments to the gluten-free diet brings hope for patients unavoidably burdened by diet restrictions.
Over the decades since the initial description of Celiac Disease, there has been a major increase in the awareness of the disease among the general population. Although generally underdiagnosed, Celiac Disease appears to have an increasing prevalence worldwide. The introduction of wheat-based products into societies throughout the globe might contribute to the trend; however, other environmental factors that allow for patients with a predisposing genetic background to have the disease are only partially understood. Many patients with Celiac Disease present with nonclassical extraintestinal manifestations, such as Anemia and osteoporosis. Various serologic assays are available to help make the diagnosis with a high sensitivity and specificity; however, routine screening of asymptomatic patients is not yet recommended. The GFD is the mainstay of treatment for those given a diagnosis of Celiac Disease, although there is a significant amount of research into alternative targeted therapies.

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