Celiac Disease - A Chronic Enteropathy, Its Management with an Emphasis on Probiotics

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Chapter 2

1. Introduction

Celiac Disease (CD) is a form of chronic enteropathy affecting the small intestine in genetically predisposed individuals expressing HLA DQ 2 and DQ 8 molecules. The disease is precipitated by the ingestion of gluten and related cereal proteins derived from barley and rye containing foods [1]. Often CD referred to gluten sensitive enteropathy, celiac sprue and non tropical sprue. This disease was first described in the 2nd century AD by Aretaeus Cappadocia who used the Greek term ‘koeliakos’ meaning ‘sufferings of the bowel’ [2]. Later in 1880, British physician Samuel Gee, clinically described CD “as a kind of chronic indigestion which has met with persons of all ages, yet it is especially apt to affect children between one and five years old, correctly surmised that errors in diet may perhaps be a cause, but could not pinpoint the true nature of the disease” [3]. Later on, much progress has been made by several scientists to determine the cause and treatment measures of the disease. Although documentation on CD dates back to 2nd century, the exact cause for the CD i.e. the link to gluten ingestion and the onset of CD had observed by a Dutch pediatrician, Dicke in 1940. Dicke observed that children suffering from CD had shown improvement in their intestinal health during food shortages at the time of Second World War. Interestingly, he noticed the relapse of CD symptoms in those children after restoration of cereals in their diet [4]. Earlier, CD was considered as a very rare malabsorption syndrome of children but now it has been recognized as a common condition that may be diagnosed at any age. With all these observations, ironically, in last few decades, the emergence of CD has been linked to the revolutionary discovery of seeds which led to the
domestication of crops, the scientific revolution in agriculture, and large scale production of grains in Man’s quest to feed the world [5].

2. Causes and prevalence

Trigger from ingested gluten and related cereal proteins, presence of HLA DQ 2/DQ 8 molecules, and generation of circulatory autoantibodies to tissues transglutaminase (tTG) are essential factors for the precipitation of celiac disease [6]. Unless a person has alleles for encoding HLA DQ 2/DQ 8 molecules, CD generally does not develop [1]. Interestingly, 90 to 95% of the people express HLA DQ 2 and only 5 to 10% express HLA DQ 8 [7]. There are clear geographical differences in the prevalence of CD between and within countries. According to the World Gastroenterology Organization data, worldwide CD prevalence in healthy adult population varies between roughly 1 in 100 and 1 in 300 with 2:1 female to male ratio. In Middle East, North Africa and in India, the prevalence of CD has been found to be same as western population. In these regions, the prevalence is 3 to 20% at risk population and 3 to 5% in people with type I diabetes. However, in USA, the prevalence of CD in first and second degree relatives of CD patients was found to be 4.5% and 2.5% respectively. Whereas in Europe, prevalence of CD is between 0.5% and 1% [8,9].

3. Pathogenesis

Wheat gluten is rich in glutamine and proline residues. Since human digestive enzymes lack post prolyl activity, gluten undergoes partial digestion yielding peptides rich in proline and glutamine residues. These peptides deposit on intestinal epithelial surface and binds to CXCR3 chemokine receptor. Binding of peptides to CXCR3 leads to MyD88 dependent zonulin release pathway that disrupts intestinal tight junction barrier leading to the increased intestinal permeability. Thereafter, either by transcytosis or by permeability through disrupted barrier, gluten peptides reach lamina propria and undergo tTG mediated selective deamidation at glutamine residue [6,10]. The deamidation of glutamine to glutamic acid increases the number of negative charges in the gliadin peptide enhancing its affinity to bind HLA DQ 2 / DQ 8 molecules on antigen presenting cells [11]. In addition to deamidation, affinity between deamidated peptides and peptide binding pocket of HLA DQ molecules is also important. The peptide binding pocket of DQ2 prefers bulky hydrophobic polar residues at p1 anchor site, aliphatic residues at p4, whereas β71 Lys residue influentially allows negatively charged amino acid residue to p6/p7, while bulky hydrophobic negatively charged residues are preferred at p9 anchoring sites. Whereas in case of HLA DQ 8 binding pocket, negatively charged amino acid residues are preferred at P1, aliphatic amino acids at P4, P6/P7 and negative or polar at P9 anchor sites in the groove [12].

Further, presentation of HLA DQ2/DQ 8 molecules bound deamidated peptides to CD4 TH cells activates both cellular as well as humoral mediated immune response. In humoral me-
diated immune response, the activated B cells produce antibodies against gluten peptides, tTG, and cytokines namely interferon-\(\gamma\), interleukin (IL)–1\(\beta\), tumor necrosis factor–\(\alpha\), IL-6 and IL-8 at higher levels. These cytokines make the enteric lymphocytes as cytotoxic cells and results in inflammation [13,14]. All these immune compounds produced in response to gluten results in the extensive tissue damage causing increased intestinal permeability, dysfunction of intestinal tight junction barrier, infiltration of intra epithelial lymphocytes (Figure 1). The symptoms are characterized by severe immune mediated damage to the small bowel with altered histology such as partial and subtotal villous atrophy with hyperplasic crypts, increased intra epithelial lymphocytes and mononuclear infiltration in the lamina propria, chronic diarrhea, abdominal bloating and distention, weight loss, iron deficient anemia, malnutrition, vitamin deficiency, abnormal fat excretion, delayed puberty and also metabolic bone disease [15].

**Figure 1:** Illustrating mechanism of celiac disease pathogenesis. The gluten peptides escaping digestion cross the intestinal epithelial layer either by transcytosis or by increased permeability and reaches lamina propria. tTG deamidates gluten peptides and increases its affinity to bind HLA DQ2/DQ 8 on antigen presenting cells. Further activation of gluten specific CD4 TH cells results in the activation of both humoral as well as cell mediated immune response producing various immune compounds that lead to tissue damage which includes increased permeability, dysfunction of intestinal tight junction, infiltration of IELs, flattening of villi, inflammation and malabsorption as in late phase of pathogenesis of CD [12].

### 4. Association of CD with other diseases

Further, CD has been known to associate with several conditions particularly autoimmune diseases such as type I diabetes, Addison, Sjogren’s syndrome, and glomerulonephritis [16,17,18]. In addition, liver disease and hypertrans aminasaemia are also associated with CD. Furthermore, it has been also found that there is an increased risk of neuro psychiatric diseases like peripheral neuropathy, mood disorders, psychosis and epilepsy in CD [18]. Malnutrition as a result of CD often leads to osteoporosis and depression. Sometimes, thyroid diseases and similar conditions that yield high “immune pressure” are also found to be associated with CD. Interestingly, CD is commonly diagnosed in patients suffering iron deficiency anemia particu-
larly premenopausal women [19].

5. Treatment

Several non-dietary strategies such as decreasing the intestinal tight junction permeability using tight junction regulators like Larazotide acetate, inhibition of tTG activity, use of corticosteroids like budesonide, and changing the structure of gliadin using sequestering polymers have been suggested to treat CD [20-23]. These novel strategies provide promise of alternative, adjunctive treatment options but also raise important questions regarding safety, efficacy and monitoring of long term treatment effect. Moreover, the responses of CD individuals to these strategies are found to be not so satisfactory [12]. In contrast to these non-dietary strategies, gluten free dietary therapies are found to be safe without much side effects and remains mainstay of CD treatment. Dietary therapy involves life time elimination of wheat, rye and barley from the diet. Gluten content of food can be reduced by breeding less immunogenic varieties of wheat and also by biotechnological approaches using microbial proteases to hydrolyze immunogenic gluten peptides in the diet [24,25] (figure 2).

To detoxify gluten using microorganisms, generally two strategies are in practice and are as follows: a) medical approach and b) food technological approach. In medical approach, gluten detoxification will take place in gastro intestinal tract after ingestion of gluten food by resident microbiota or by regular oral administration of probiotics. Whereas in food technological approach, gluten detoxification takes place prior to ingestion i.e. during food processing by microbial fermentation [26]. Often purified microbial enzymes are used during fermentation process to enhance gluten hydrolysis in order to remove celiac immune peptides. Currently, prolyl endopeptidase from Flavobacterium meningosepticum, Myxococcus Xanthus, Sphingomonas capsulate and Lactobacillus helveticus, Aspergillus nigerare in use for gluten detoxification commercially. In addition, sourdough fermentation by combination of lactic acid bacteria mainly Lactobacillus alimentarius, L. brevis, L. sanfranciscensis and L.hilgardii is also in practice for the development of gluten free wheat foods [24,25].

![Possible approaches to reduce gluten in diet](image)
In addition to gluten hydrolysis, probiotics also confer several health benefits to celiac patients. To consider, malabsorption is one of the common symptoms in CD due to improper digestion. Probiotics are equipped with an array of hydrolytic enzymes that help in digestion of ingested food and thereby facilitate its absorption [27]. Further, probiotics also strengthen intestinal tight junction barrier and decrease permeability which further prevents diarrhea [28]. Noticeably, the lactic acid bacteria are proven to produce several amino acids, vitamins and other micro nutrients which help in fighting several deficiencies. Furthermore, probiotics also confer anti inflammatory effect by producing several anti-inflammatory cytokines and anti oxidants. In addition, the short chain fatty acids like acetic acid, butyric acid, propionic acid which are produced during fermentation of probiotics or sugars in the intestine nourishes colonocytes and help in healing mucosal injuries caused as a result of hyper immune response [29]. Recently, beneficial bacteria or probiotics are known to influence the gut brain axis communication and thereby play an important role in behavior, cognitive functions, decision making and signal transmission. Probiotics also reduce the burden of depression and other mood disorders by producing “happy hormones” like serotonin and GABA [30]. In this way, probiotics are beneficial in management as well as in treatment of celiac disease.

6. References


