Celiac Diseases

Subjects: Pathology

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Celiac Disease (CD) is an immune-mediated disease triggered by the ingestion of gluten from wheat and other cereals, such as barley and rye. The gluten intake exerts toxic effects through several pathways involving gut barrier integrity, intestinal microbiota composition and immune system stimulation. Immunity against peptides generated by an incomplete gluten digestion is mediated by pro-inflammatory cytokines produced by both innate and adaptive system response in individuals unable to adequately digest them. A lifelong adherence to a gluten-free (GF) diet is currently the only treatment for CD. However, despite the great benefit of the GF diet for CD patients, the adherence to a GF diet determines nutritional deficiencies as well as the risk of an excessive intake of fats and carbohydrates. Therefore, it is necessary to integrate micronutrients and fibers, which are lacking in gluten free foods, as well as follow controlled dietary regimes. In this regard, it is very important to adjust and improve the formulations of GF products, in order to ensure the consumer a diet that is as balanced and tastier as possible.

Celiac disease autoimmune disease gluten gliadin glute-free diet

1. Introduction

Gluten is a complex molecule present in several grains, including wheat, rye an barley[1], consisting of glutenin polymers and gliadin monomers. Both glutenin and gliadin contain high percentage of prolines (20%) and glutamines (40%) protecting them from complete degradation in the gastrointestinal tract and resulting in their incomplete digestion[2].These undigested peptides have been demonstrated to play biological activities in gastrointestinal tracts, including increased gut permeability and cytotoxic and immunomodulatory effects[3].

Gluten ingestion is responsible for the development of Celiac Disease (CD), an autoimmune enteropathy activated in the lamina propria of the gut of genetically predisposed individuals[4] by gliadin peptides and resulting in the recruitment of infiltrating T lymphocytes producing Interferon-gamma (IFN-γ) and Interleukin-15 (IL-15). A typical feature observed in CD patients is malabsorption. This is a critical condition in CD pathogenesis resulting from the T-cell mediated damage of the intestinal mucosa and it is histologically represented by villous atrophy, crypt hyperplasia, and the infiltration of lymphoid cells both in the epithelium and in the lamina propria[5].The pathogenesis of CD is related to both genetic and environmental factors. Among genetic factors, major histocompatibility complex (MHC) class II, HLA DQ2 and DQ8, confer the greatest susceptibility to the disease, with a reported gene dosage effect according to which homozygous allotypes are associated to an increased risk[6][7]. In addition, among environmental factors, gastrointestinal dysbiosis seems to be associated to CD onset,

consisting of an increased number of *Proteobacteria* and *Bacteroidetes* and a reduced number of *Firmicutes,* especially in the active phase of the disease[8].

The gluten intake exerts toxic effects through several pathways involving gut barrier integrity, intestinal microbiota composition and immune system stimulation. Experimental evidences showed that gliadin peptides are capable to trigger an adaptive immune response in CD patients, as demonstrated by the higher production of pro-inflammatory Th1/Th17 derived cytokines from intestinal biopsies of active CD patients when stimulated in vitro with gliadin[9]. In addition, peripheral blood mononuclear cells of CD patients produce Interleukin-1 β (IL-1β) and Interleukin-18 (IL-18) following their stimulation with gliadin[10]. Interleukin-15 (IL-15) is also up-regulated in the epithelium and the lamina propria of CD patients in the active phase[11]. To explain the toxic effect of gluten, it was hypothesized that, after gluten oral introduction, partially digested gliadin peptides, interacting with the small intestinal mucosa, may first activate an innate immune response. This is evidenced by the production of IL-8 by epithelial and lamina propria dendritic cells. IL-8, in turn, recruits neutrophils in situ amplifying the inflammatory process, whereas IL-15 induces enterocytes apoptosis[12]. Then, gliadin peptides, through the interaction with CXCR3 receptors present on the apical side of the epithelium, seem to trigger the release of zonulin, the regulator of the intestinal tight junctions, leading to an increase in intestinal permeability and consequent antigen trafficking that may cause autoimmune disorders[13][14]. As a consequence of the increased intestinal permeability, gliadin peptides may translocate into the lamina propria where they undergo to deamidation by transglutaminase 2[15]. This event has been shown to favor gliadin interaction with macrophages and dendritic cells of the submucosa[16], triggering an adaptive immune response with the production of increased pro-inflammatory cytokines such as IFN-γ, tumor necrosis factor-alpha (TNF-α) and IL-17[16], which damage the intestinal mucosa compromising its permeability[17].

2. Clinical Manifestations

Clinical manifestations of CD are mainly gastrointestinal symptoms, such as intermittent or chronic diarrhea, bloating and abdominal distension, colitis, flatulence, abdominal cramps, in association with malabsorption and consequent iron deficiency and weight loss. Extraintestinal symptoms are chronic fatigue, foggy mind, aphtous stomatitis, reduced bone density, growth retardation in children and short stature[18]. Beyond gastrointestinal symptoms, celiac patients can be affected by neurological and psychiatric disorders, including epilepsy, schizophrenia and Autistic Spectrum Disorder ASD [4]. Although the correlation between CD and ASD is supported by different clinical studies, the exact mechanism, on the basis of this correlation, remains unknown. Data presented in the literature correlating CD with ASD highlight how cereal-derived peptides produced in celiac patients cross the blood–brain barrier and bind to endogenous opioid receptors. This effect could explain the defects in the brain maturation, attention, learning and public relations of autistic patients. Moreover, several clinical and in vitro studies supported the hypothesis that oxidative stress associated with gluten-related disorders can favor mitochondrial damage and neurological dysfunctions, which are involved in the pathogenesis of ASD[4].

3. Diagnosis

CD diagnosis is a multi-step process. First, patients are screened for serum IgA anti-tissue transglutaminase, if they have detectable IgA level[19], otherwise serum IgG anti-tissue transglutaminases are preferred. In addition, they can be screened for serum IgG anti-deamidated gliadin, an alternative test with an increased sensitivity and specificity[1], and anti-endomysium IgA, to confirm borderline results. Finally, a full-blown diagnosis requires small intestinal biopsy showing villous atrophy, an increased number of intraepithelial lymphocytes and elongated crypts[18].

4. Treatment

Currently, the only treatment of Celiac Disease is the complete elimination of gluten from diet, which leads to **symptoms disappearance.** The Gluten-free (GF) diet was introduced for the treatment for CD since 1941, as reported by the paediatrician Willem Karl Dicke[20]. However, despite the great benefit of GF diet for CD patients, its use has been debated. About 7–30% of CD patients do not fully improve after adopting a gluten-free (GF) diet. Therefore, alternative CD therapies are required, such as genetically modified gluten, inhibitors of zonulin and supplementary probiotics[5][21][22][23].

GF foods can be distinguished into those naturally GF, such as rice, corn, potatoes, some grains, seeds and legumes, and those that become GF after purification, a process that alters their macro-and micro-nutrient composition, as well as their nutritional values[24]. Gluten contained in wheat flours owns the unique ability to form aggregates, which are important for some products such as, bread, pasta and pretzels, whose production process requires a cohesive dough. Gluten is composed mostly of gliadin, the 70% ethanol-soluble protein fraction of wheat flour, and by glutenin and both contribute to the cohesiveness and to the elasticity of the dough[25]. Notably, wheat is not only a source of protein but also a food rich in micronutrients, including folate, iron, B vitamins (thiamine, riboflavin and niacin) and fibers. Therefore, a disadvantage in using a GF diet my result by the fact that often GF products have a lower amount of these components when compared to their gluten containing equivalents[26][27][28]. GF products have generally lower amounts of folate, iron, riboflavin, niacin and thiamine[29] and researchers in this field work to overcome these limits without altering their taste[30]. Furthermore, fibers are lost because they are mostly contained in the outer layer of grain which is eliminated during the refining process. Gluten replacing ingredients are starches, hydrocolloids, gluten-free flours of cereals/pseudocereals, proteins, enzymes and emulsifiers. These components are used in combination to improve rheological features of GF products, often leading to their substantial price increase[31]. Moreover, some GF products are foods richer in carbohydrates and lipids than their gluten containing equivalents[32], as for GF bread with a higher fat content and glycemic index and with a lower amount of proteins. The glycemic index of GF products changes according to the type and quality of contained ingredients and to the procedures used to obtain them[33].

Thus, the adherence to a GF diet is strictly necessary for celiac subjects. However, the use of a GF diet may imply disadvantages related to nutritional deficiencies and high carbohydrate and fat contents. Such a condition could be probably improved if manufacturers and health professional collaborated to continuously adjust and improve the

formulations and the processing techniques used in GF manufacturing, in order to ensure the consumer a diet that is as balanced and tastier as possible.

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