

Celiac Disease and Role of a Gluten-Free Diet

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Abstract

Celiac disease, also known as gluten-sensitive enteropathy and nontropical sprue, is a prevalent autoimmune disorder that is triggered by the ingestion of wheat gluten and related proteins of rye and barley in genetically susceptible individuals. The immune response in celiac disease involves the adaptive, as well as the innate, and is characterized by the presence of anti-gluten and anti-transglutaminase 2 antibodies, lymphocytic infiltration in the epithelial membrane and the lamina propria, and expression of multiple cytokines and other signaling proteins. The disease leads to inflammation, villous atrophy, and crypt hyperplasia in the small intestine. In addition to the intestinal symptoms, celiac disease is associated with various extra-intestinal complications, including bone and skin disease, anemia, endocrine disorders, and neurologic deficits. Screening studies have revealed that celiac disease is most common in asymptomatic adults in the United States. Although considerable scientific progress has been made in understanding celiac disease and in preventing or curing its manifestations, a strict gluten-free diet is the only treatment for celiac disease to date. Early diagnosis and treatment, together with regular follow-up visits with a dietitian, are necessary to ensure nutritional adequacy and to prevent malnutrition while adhering to the gluten-free diet for life. This review focuses in detail on the gluten-free diet and the importance of intense expert dietary counseling for all patients with celiac disease.

Keywords: *Celiac disease; Diet; Gluten-free; prolamin*

Introduction

Celiac disease is a chronic inflammatory disorder in genetically susceptible subjects, characterized by damage of the small intestinal mucosa caused by gluten [1]. Approximately 1% of the world population is afflicted with celiac disease [2,3]. The distribution of celiac disease also extends beyond persons primarily of European ancestry, with significant prevalence identified in such disparate populations as the Middle East, Asia, South America, and North Africa [4]. One proposed reason for this trend is that, with a globalizing world market, developing nations that traditionally relied on gluten-free grains, such as rice and maize, are increasingly incorporating wheat-based foods into their diets [5]. As more mass screening studies are performed in different populations, more cases of previously undiagnosed celiac disease are identified. Particularly on a global scale, there is evidence that celiac disease is a missed diagnosis in many children in whom infection and malnutrition

are quite common and the presumed cause for diarrheal illness [6]. The only currently available treatment for celiac disease is complete elimination of gluten and related proteins from diet, where by food products containing wheat, rye, and barley are avoided. Improvement of symptoms is generally seen within days to weeks after the initiation of gluten-free diet, while full mucosal recovery usually takes longer [7].

In the past years interest in foods that may help to gluten-free diets was considered [8]. Gluten is a complex mixture of proteins comprising the gliadins and glutenins in wheat and equivalent proteins in barley and rye, representing 80% of total grain proteins. However, gluten proteins also have negative impacts on human health, in relation to allergies and intolerances. Gluten is defined differently depending on the discipline (biochemistry, food technology, nutrition). In the gluten-free intolerance context the most appropriate definition is that provided by the European Commission where “gluten means a protein fraction from wheat, rye, barley, oats or their crossbred varieties and derivatives thereof, to which some persons are intolerant and which is insoluble in water and 0.5 M sodium chloride solution” [9]. Intake of diets free of protamine group proteins or gluten-free diets is the only coeliac curing method all the time [10].

Wheat (gliadins), barley (hordeins), rye (secalins) and, for some people, oats (avenin) should be eliminated in gluten-free diets [11]. There is a doubt about oat elimination from gluten-free diets and grains like corn and rice could be ingested by coeliac patients [12]. Gluten is the most essential protein in wheat flour products, which plays a significant role in the texture and appearance of final products such as bread [13]. It has also a great role in bread-making process because of its share in visco-elasticity, mixing resistance, dough spread-ability, and gas holding capacity and good body structure in the final product. For this reason, gluten substitution in bread is one of the most controversial challenges that grain technologists are facing with [14]. Simulation of visco-elastic properties of gluten in wheat dough is done by using various flours and starches (e.g., rice, corn, cassava and soy) and also gums, enzymes, soy proteins and egg-white. Cato et al. studied the effect of carboxymethylcellulose (CMC), hydroxypropyl methylcellulose (HPMC) and guar gums in glu-ten-free bread made by rice flour and potato starch [15]. Curic et al. studied the effect of soy flour on the protein fortification, mechanical properties, plasticity and mixing resistance of glu-ten-free bread [16]. Mezaize et al. examined the effect of guar gum and CMC instead of gluten in French bread and reported that breads containing 20 g kg⁻¹ guar gum have favorite properties such as increased volume, softer crumb and favorable color [17]. Anton and Artfield investigated the effect of different hydrocolloids as binding agents and gluten alternative in bread made from corn starch [18]. The common point between the above authors was that among xanthan, carob, guar gum and tragacanth, xanthan showed the best quality in bread making. Different methods including the use of enzymes have been applied to propose the similar network to gluten with regard to gas holding capacity and quality develop-ment of the final product. For instance, Moore et al. studied the effect of different values of TGase on protein network formation in gluten-free breads [19].

In 2011 in London a panel of 15 experts announced a new classification of gluten-related disorders that was then published in February 2012 (Figure 1) [20]. Catassi et al. expressed the opinion that the term “gluten-related disorders” is the umbrella-term to be used for describing all the conditions related to ingestion of gluten-containing food [21]. The classification covers a wide range of disorders including allergies (food allergy, anaphylaxis, wheat-dependent exercise induced anaphylaxis, baker's asthma, contact dermatitis), autoimmune diseases (celiac disease, dermatitis herpetiformis, gluten ataxia) and the diseases that are likely to be immune mediated (gluten sensitivity). At the Second Expert Meeting on GS that was held in

Munich in 2012, it was noted that besides the IgE-mediated WA the non-IgE-mediated WA existed as well [21]. This form of WA may be difficult to distinguish from NCGS [21]. Groups of gluten-related disorders are manifested not only by disturbances in the gastrointestinal tract, but also by dermatological, haematological, endocrinological, rheumatological, gynaeco-logical, dental and neurological symptoms. After the administration of a GFD the symptoms disappear. However, when the diet is abandoned, all the symptoms recur [20]. What is critical for making right diagnostic decisions is to carefully define the symptoms and choose such serological tests and histological imaging of duodenal mucosa that make it possible to distinguish between different gluten-dependent disorders with their varying courses, diet protocols, prognoses and complications [22,23].

This review will be focused on cereal-based commodities available for developing gluten-free blends and the biochemical tools for mimicking gluten network viscoelastic properties.

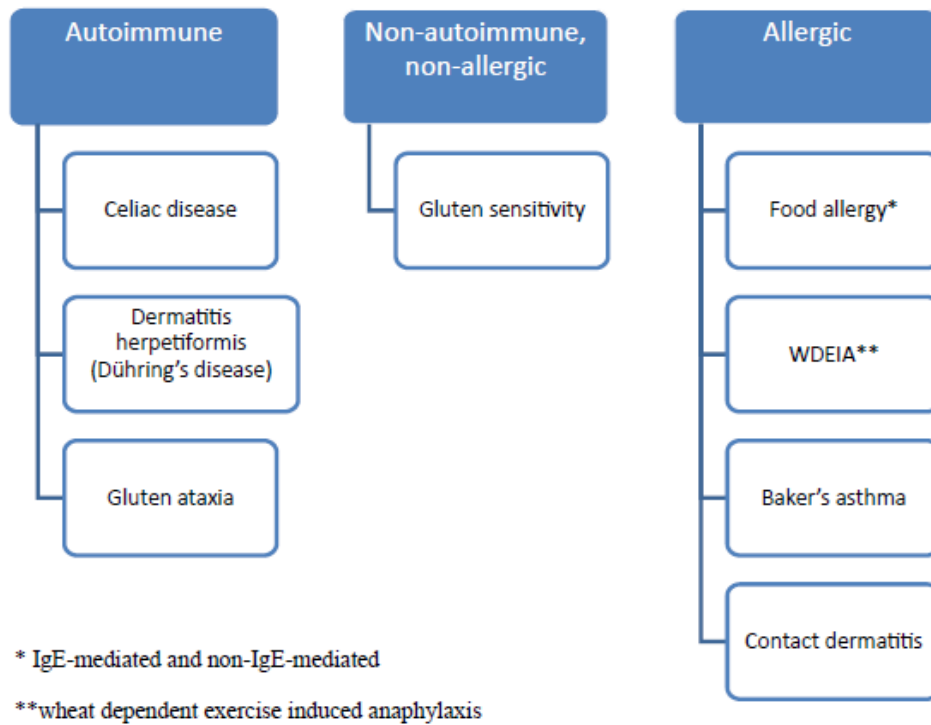


Figure 1: Classification of gluten-related disorders [20].

Diagnosis

Accurate diagnosis of celiac disease is achieved by following the current diagnostic guidelines and keeping in mind that intestinal biopsy remains the only widely accepted diagnostic gold standard. We will discuss the diagnosis of celiac disease, based on the recommendations of the European Society for Paediatric Gastroenterology and Nutrition (ESPGAN) [24], and

the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) [25], which is also summarized by the algorithm in Figure 2.

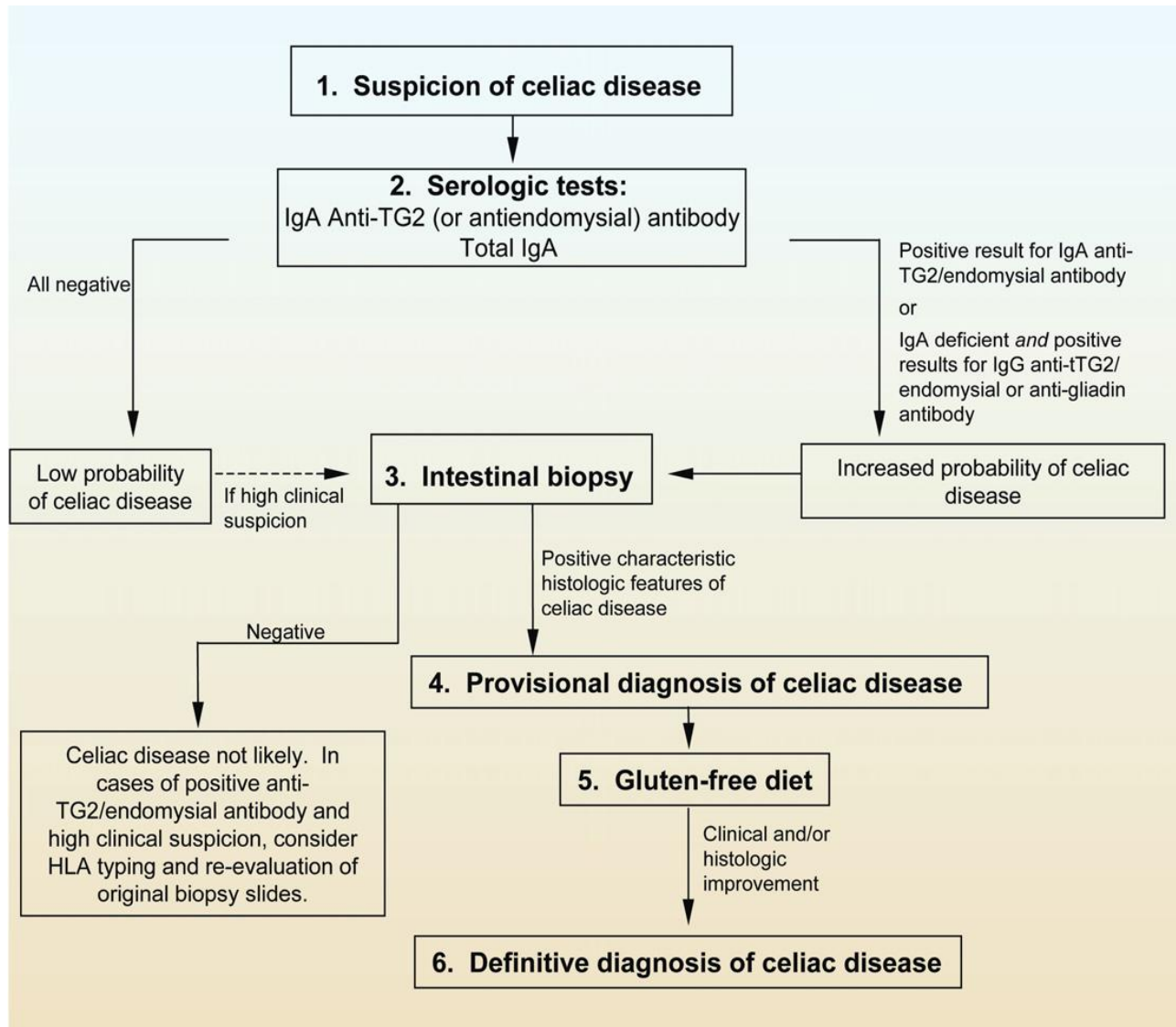


Figure 2: Proposed plan for evaluation of patients suspected of having celiac disease [26].

As mentioned previously, celiac disease is a polygenic disorder having the most important genetic susceptibility determinant located in the class II MHC locus, with HLA-DQ2 and/or HLA-DQ8 being necessary but not sufficient for disease development. These susceptibility alleles only explain 35% of genetic risk, however, and several other genes contribute to celiac disease pathogenesis [27]. Two GWAS and ImmunoChip analyses performed on celiac disease patients have revealed 39 regions of genetic susceptibility to the disease [27, 28]. Many of the genes identified in these studies have been implicated in numerous other immune-modulated diseases (Figure 3).

protein, fibre, and folate (Table 1); whereas teff, quinoa, amaranth and buckwheat show a favourable fatty acid composition and they are high in protein [31]. Immunochemical, molecular and *in vitro* and *in vivo* studies support the conclusion that sorghum does not contain peptides that are toxic for coeliac patients. The analysis of aqueous/alcohol-soluble prolamins (kafirins) from different sorghum varieties provides molecular evidence for the absence of toxic gliadin-like peptides in sorghum [32]. A similar study carried out with amaranth revealed that all of the amaranth samples studied showed similar binding affinities for both specific anti-gliadin antibodies and human IgAs, and the molecular characterization of amaranth proteins suggests that it is safe for coeliacs to consume [33]. Teff, a low risk cereal for coeliacs that is grown in Ethiopia and other countries, has an excellent amino acid composition (including all 8 essential amino acids for humans), very high fibre content and high nutrient content in general, being suitable for gluten-free applications [34].

Table 1: Proximate composition of some gluten free kernels compared to wheat [35].

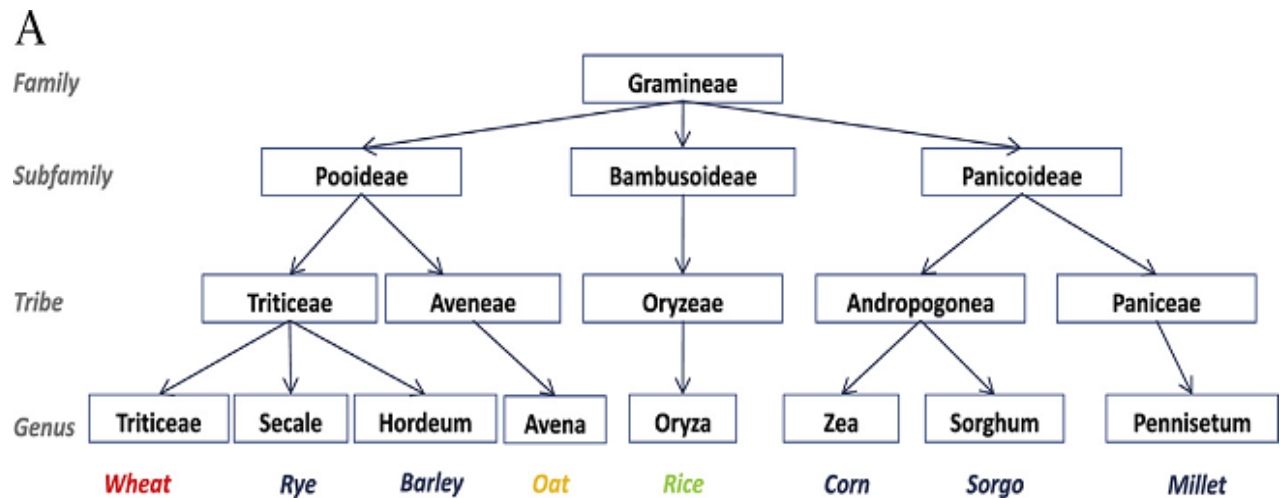
	Wheat	Rice	Corn	Quinoa	Amaranth	Teff	Buckwheat	Sorghum
Carbohydrates (%)	7.90	77.20	74.30	64.20	65.70	73.10	71.50	74.6
Dietary Fibre (%)	12.20	3.50	7.30	7.00	6.70	8.00	10.00	6.3
Proteins (%)	11.30	7.90	9.40	14.10	13.60	13.30	13.20	11.3
Fats (%)	1.70	2.90	4.70	6.10	7.00	2.40	3.40	3.3
Calcium (mg)	32	23	7	47	159	180	18	28
Iron (mg)	4.6	1.5	2.7	4.6	7.6	7.6	2.2	4.4
Magnesium (mg)	93	143	127	197	248	184	231	
Folate (µg)	38	20	19	184	82		30	

The Oats controversy: selection of oat varieties with no toxicity in coeliac disease

There is an on-going debate concerning the presence or absence of proteins in oats that could be toxic for coeliac patients. Traditionally, treatment with a gluten free diet GFD has excluded not only wheat, barley, and rye, but also oats. Oats, like rice, differs from other cereals in having a low prolamins content. The percentages of proline and glutamine (amino acids abundant in toxic regions) in avenins are lower than in prolamins from toxic cereals (Figure 4). However, there is still some debate about the safety of oats [36].

According to the Codex Alimentarius Commission (2008), oats can be tolerated by most, but not all, people who are gluten-intolerant [37]. Therefore, the acceptance of oats that are not contaminated with wheat, rye, or barley in foods covered by this standard may be determined at the national level. Moreover, according to the Commission of the European Communities (2009), a major concern is the contamination of oats with wheat, rye, or barley that can occur during grain harvesting, transport, storage, and processing. Therefore, the risk of gluten contamination in products containing oats should be taken into consideration with regard to labelling of products. Some cross-reactivity with gliadin-specific antibody has been

attributed to wheat contamination in oat-based food [36]. However, other authors have reported clear evidence suggesting that avenins have the ability to induce the activation of mucosal T-cells, causing gut inflammation and villous atrophy [36].



B

Basic characteristics of prolamins	WHEAT	OAT	RICE
Number of genes	>100	8-25	34 (transcritos 21)
Molecular weight	20-40 kDa	19-31 kDa	10-16 kDa
Prevalence of amino acids	Gln (35%) Pro (25%)	Gln (30%) Pro (10%)	Gln (22%) Pro (<other cereals)
Percentage of prolamins based on the total seed proteins	40-50%	10-20%	25%

Figure 4: Taxonomy and basic characteristics of the prolamins of oats in relation with other cereals. A. Taxonomy of oats in relation with other cereals. B. Basic characteristics of the prolamins of wheat, oats, and rice [35].

Celiac Disease and the Identification of Toxic Motifs in Wheat

Identification of coeliac disease epitopes

Currently thirty-one, nine amino acid peptide sequences in the prolamins of wheat and related species have been defined as being coeliac toxic: these are often referred to as coeliac “epitopes”. However, mapping is incomplete and the number of distinct epitopes a matter of on-going discussion [38]. These epitopes are located in the repetitive domains of the prolamins, which are proline and glutamine-rich, and the high levels of proline in their sequences may reduce their susceptibility to protease activity in the GI tract. The prolamins-reactive T cells (T lymphocytes) of Celiac disease patients also recognise these epitopes to a greater extent when specific glutamine residues in their sequences have been deamidated to glutamic acid by a tissue transglutaminase (tTG2). This binding enables the formation of a stable peptide-MHC complex, which is important in the anti-prolamin T-cell response [38].

The majority of coeliac toxic peptides have been identified from in vitro studies using peptides cultured with T cell lines or T cell clones derived from the biopsied small intestinal mucosa of Celiac disease patients [39].

Reducing Celiac Toxicity by Molecular Breeding

In recent years, the identification of mutations at the gene sequence level has been facilitated by the development of PCR-based screening, a technology known as TILLING (Targeting Induced Local Lesions in Genomes) [40]. Seeds are treated with chemical agents such as sodium azide (NaN₃) or ethyl methane sulphonate (EMS) to induce point mutations which are randomly distributed over the entire genome. These will include mutations of several types: nonsense mutations which may cause loss of gene function, by truncation or loss of expression of corresponding protein; missense mutations which result in the change of an amino acid in the protein encoded by the mutated gene; and silent mutations which have no effect on the protein sequence or functionality. TILLING can also be used identify genetic variation in natural populations, an approach termed EcoTILLING [41]. Mutagenized populations and TILLING platforms are now widely available for wheat, including einkorn, durum and bread wheats [42], and this approach has been successfully applied for identifying mutations affecting starch synthesis and composition [43].

Conclusion

Celiac disease is recognized as a common multisystemic disorder that may be diagnosed at any age. At this time, the gluten-free diet remains the only available treatment. The gluten-free diet is a complex and challenging diet, but recent advances in the food industry are making it easier to follow. With more patients being diagnosed, there is a greater need for health care professionals who are knowledgeable about celiac disease and the gluten-free diet. Expert dietitians are responsible for nutrition assessment, treatment of nutritional deficiencies, and education of patients with celiac disease. Patients who understand the long-term consequences of celiac disease will make informed choices in managing their disease. Dietitians provide the tools that patients need to successfully understand the diet and integrate it into every aspect of their lives, leading to overall improvements in the physical and emotional challenges of the disease.

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