Research & Reviews in BioSciences

Research & Reviews in BioSciences
ISSN: 0974-7532

**Research** | Vol11 Iss 2

# Celiac Disease and Role of a Gluten-Free Diet

**Esmaeil Ataye Salehi[1*] and Maryam Sardarodiyan[2]**

[1]Department of Food Science and Technology, Quchan Branch, Islamic Azad University, Quchan, Iran

[2]Young Researchers and Elite Club, Quchan Branch, Islamic Azad University, Quchan, IRAN

[*]**Corresponding author:** College of Pharmacy, Pharmaceutical Chemistry Department, Jazan University, Alrawda Dist, Jazan, 82726, Saudi Arabia. Tel: 966 567736698; E-Mail: Barrati99@Hotmail.Com

**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

**Citation:** Esmaeil Ataye Salehi (2016) Celiac Disease and Role of a Gluten-Free Diet, Research & Reviews in BioSciences, 11.

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]. Curić 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.

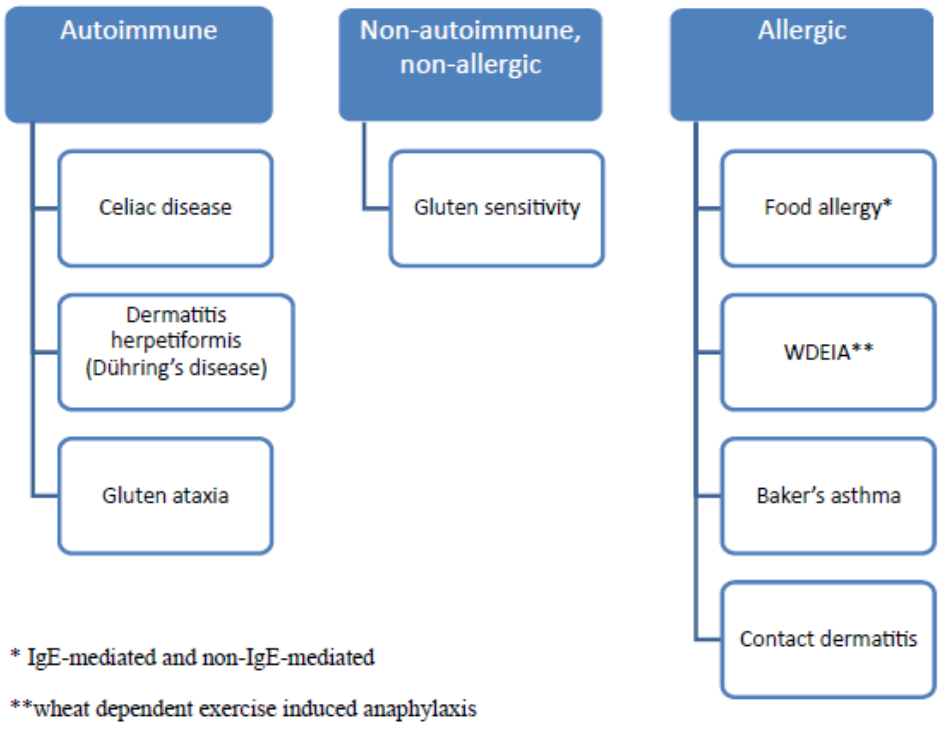



**Figure 1:** Classification of gluten-related disorders [20].

## 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.

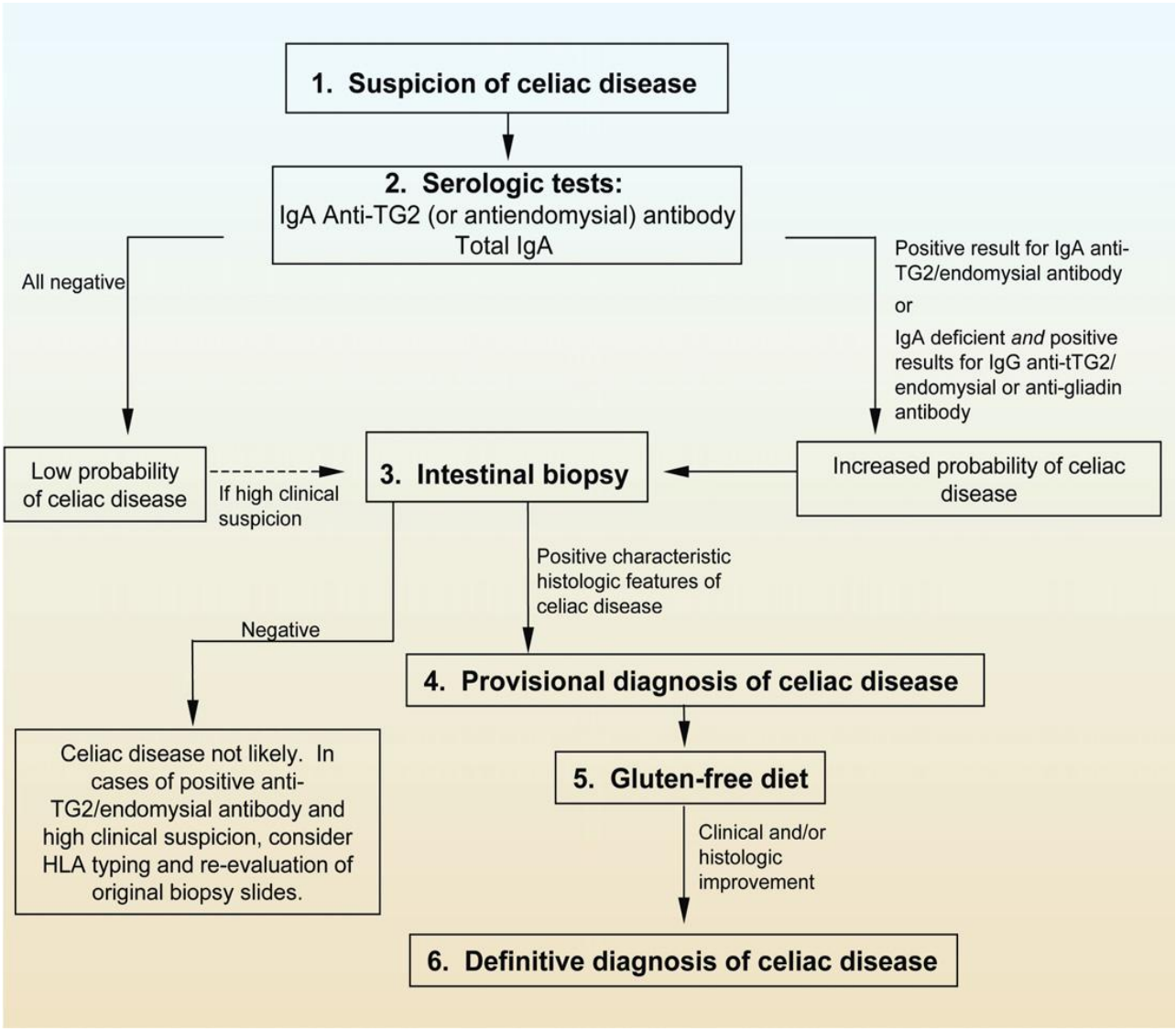



**Figure 2:** Proposed plan for evaluation of patients suspected of having celiac disease [26].

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).

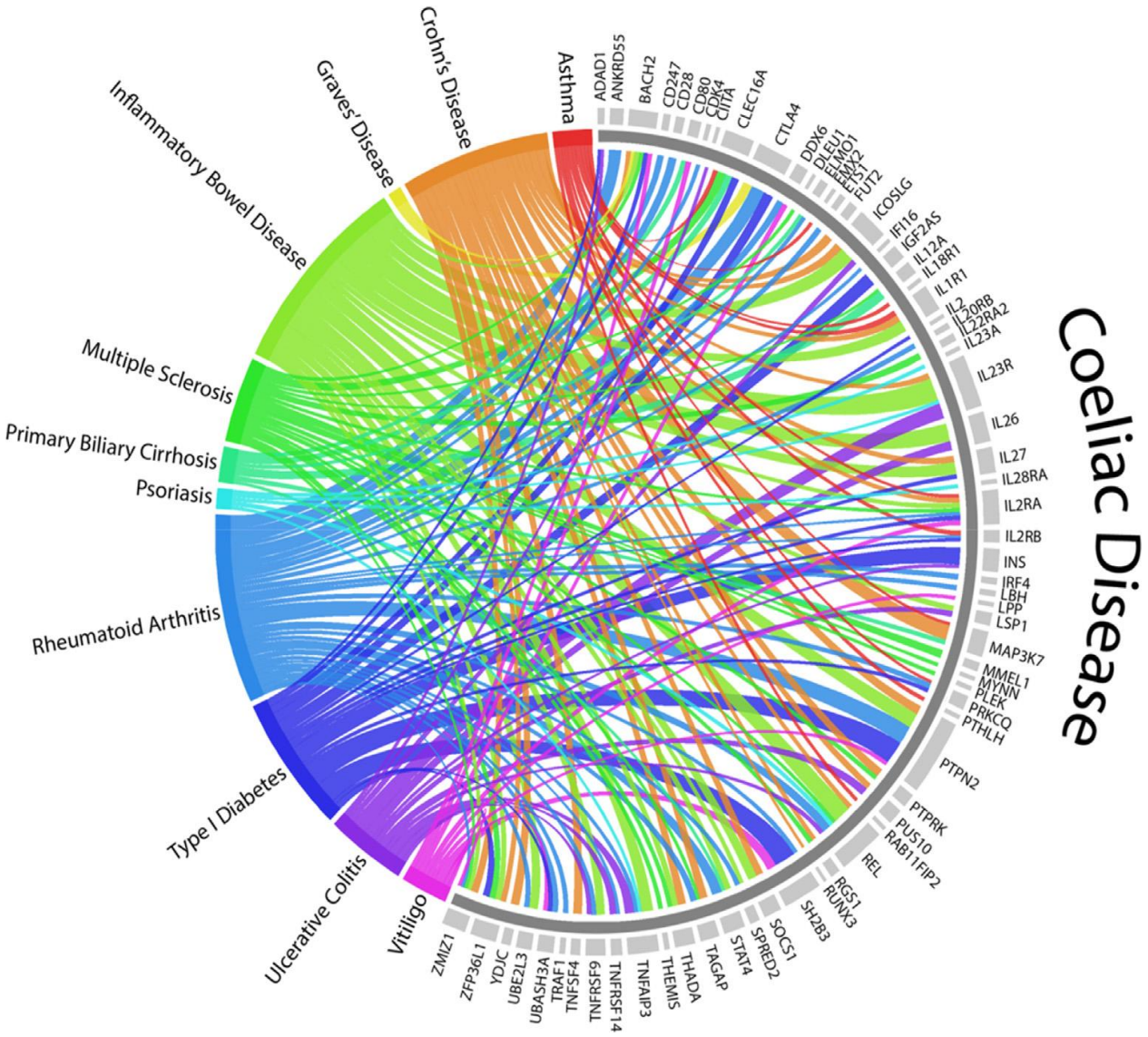



**Figure 3:** Non-HLA susceptibility regions shared between celiac disease and select immune-modulated diseases [29]. A genome-wide significance threshold was set at $P=5\times10^{-8}$. FUT2 was included despite not being identified in a celiac disease-specific GWAS.

## Gluten Free Cereals

### Cereals reported to be gluten free

Cereals that are always considered gluten free are rice (Oryza sativa L.), maize (Zea mays L.) and sorghum (Sorghum bicolor (L.) Moench), which are distant relatives of wheat and are known to be safe for coeliacs. In addition, a number of species of millets, the Ethiopian cereal teff, and a range of pseudocereals are also available for providing gluten free flours, even increasing the nutritional pattern of those products in the case of pseudocereals [30]. Nevertheless, rice and corn are low in

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/alcoholsoluble 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 antigliadin 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 Ethiopa 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 | |

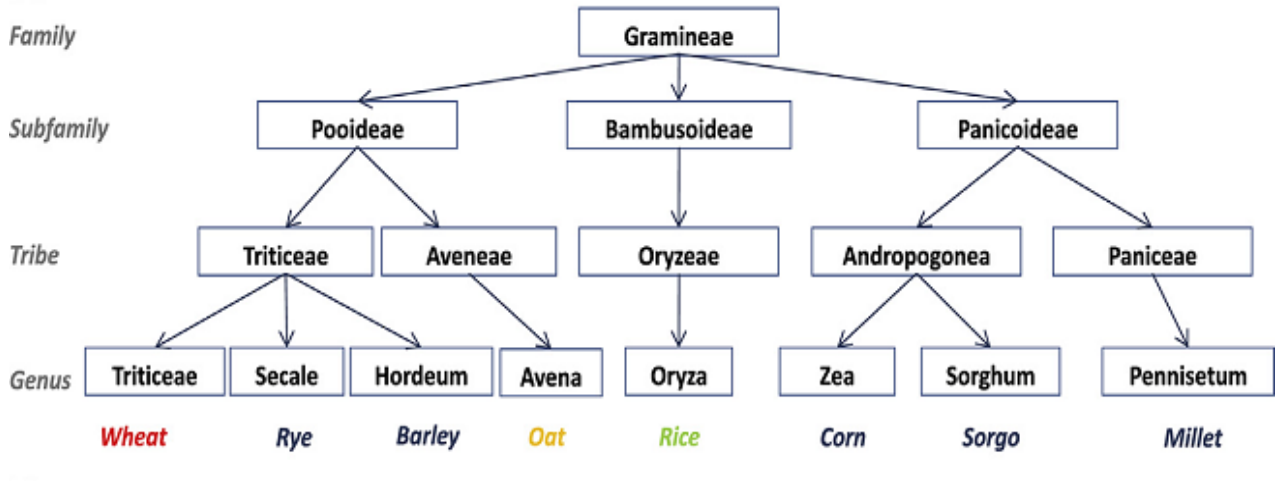
**The Oats controversy: selection of oat varieties with no toxicity in coeliac disease**

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 prolamin 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].

A




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%)<br>Pro (25%) | Gln (30%)<br>Pro (10%) | Gln (22%)<br>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 prolamin-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 ($NaN_3$) 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.

## References

1. Catassi C, Fasano A (2008) Celiac disease. In: Arendt, E., Dal Bello, F. (Eds.), Gluten free Cereal Products and Beverages. Academic Press (Elsevier) London, UK, 1-27.

2. Lionetti E, Catassi C (2011) New clues in celiac disease epidemiology, pathogenesis, clinical manifestations, and treatment. International Reviews of Immunology 30: 219-231.

3. Reilly NR, Green PH (2012) Epidemiology and clinical presentations of celiac disease. Semin Immunopathol 34: 473-478.

4. Green PH, Cellier C (2007) Celiac disease. N Engl J Med 357: 1731-1743.

5. Kearney J1 (2010) Food consumption trends and drivers. Philos Trans R Soc Lond B Biol Sci 365: 2793-2807.

6. Byass P, Kahn K, Ivarsson A (2011) The global burden of childhood coeliac disease: a neglected component of diarrhoeal mortality? PLoS One 6: e22774.

7. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH (2003) Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. Gastrointest Endosc 57: 187-191.

8. Gallagher E, Gormley, TR, Arendt, EK (2004) Recent advances in the formulation of gluten-free cereal-based products. Trends Food Sci Technol 1: 143-152.

9. Commission of the European Communities (2009) Commision regulation (EC) no 41/2009 of 20 January 2009 concerning the composition and labelling of foodstuffs suitable for people intolerant to gluten. Official J. Eur. Union, 16/13e16/15.

10. Niewinski MM (2008) Advances in celiac disease and gluten-free diet. J Am Diet Assoc 108: 661-672.

11. Zannini E, Pontonio E, Waters DM, Arendt EK (2012) Applications of microbial fermentations for production of gluten-free products and perspectives. Appl Microbiol Biotechnol 93: 473-485.

12. Haboubi NY, Taylor S, Jones S (2006) Coeliac disease and oats: a systematic review. Postgrad Med J 82: 672-678.

13. Lazaridou Duta D, Papageorgiou M, Belc N, Biliaderis CG (2007) J Food Eng 79: 1033-1047.

14. Moore MM, Schober TJ, Dockery P, Arendt EK (2004) Cereal Chem 81: 567- 575.

15. Cato L, Gan J, Rafael L, Small D (2004) gluten-free breads using rice flour and hydrocolloid gums. Food Aust 56: 75-78.

16. Curic D, Novotni D, Tušak D, Bauman I, Gabric D (2007) Agric Conspec Sci 72: 227–232.

17. Mezaize S, Chevallier S, Le Bail A, de Lamballerie M (2009) Optimization of gluten-free formulations for French-style breads. J Food Sci 74: E140-146.

18. Anton AA, Artfield SD (2008) Hydrocolloids in gluten-free breads: a review. Int J Food Sci Nutr 59: 11-23.

19. Moore MM, Heinbockel M, Dockery P, Ulmer HM, Arendt EK (2006) Cereal Chem 83: 28-36.

20. Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH et al. (2012) Spectrum of gluten-related disorders: consensus on new nomenclature and classification. BMC Med 10: 13.

21. Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A et al. (2013) Non-Celiac Gluten sensitivity: the new frontier of gluten related disorders. Nutrients 5: 3839-3853.

22. Pietzak M (2012) Celiac disease, wheat allergy, and gluten sensitivity: when gluten free is not a fad. JPEN J Parenter Enteral Nutr 36: 68S-75S.

23. Kabbani TA, Vanga RR, Leffler DA, Villafuerte-Galvez J, Pallav K et al. (2014) Celiac disease or non-celiac gluten sensitivity? An approach to clinical differential diagnosis. Am J Gastroenterol 109: 741-746.

24. [No authors listed] (1990) Revised criteria for diagnosis of coeliac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. Arch Dis Child 65: 909-911.

25. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A et al. (2005) Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 40: 1-19.

26. Briani C, Samaroo D, Alaedini A (2008) Celiac disease: from gluten to autoimmunity. Autoimmun Rev 7: 644-650.

27. Dubois PC, Trynka G, Franke L, Hunt KA, Romanos J, et al. (2010) Multiple common variants for celiac disease influencing immune gene expression. Nat Genet 42: 295-302.

28. van Heel DA, Franke L, Hunt KA, Gwilliam R, Zhernakova A, et al. (2007) A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet 39: 827-829.

29. Krzywinski M, Schein J, Birol I, Connors J, Gascoyne R et al. (2009) Circos: an information aesthetic for comparative genomics. Genome Res 19: 1639-45.

30. Alvarez-Jubete L, Arendt EK, Gallagher E, (2010) Nutritive value of pseudocereals and their increasing use as functional gluten-free ingredients. Trends Food Sci Technol 21: 106-113.

31. Hager AS, Wolter A, Jacob F, Zannini E, Arendt EK (2012) Nutritional properties and ultra-structure of commercial gluten free flours from different botanical sources compared to wheat flours. J Cereal Sci 56: 239-247.

32. Pontieri P, Mamone G, De Caro S, Tuinstra MR, Roemer E et al. (2013) Sorghum, a healthy and gluten-free food for celiac patients as demonstrated by genome, biochemical, and immunochemical analyses. J. Agric Food Chem 61: 2565-2571.

33. Ballabio C, Uberti F, Di Lorenzo C, Brandolini A, Penas E et al. (2011) Biochemical and immunochemical characterization of different varieties of amaranth (Amaranthus L. ssp.) as a safe ingredient for gluten-free products. J Agric Food Chem 59: 12969-12974.

34. Gebremariam MM, Zarnkow M, Becker T2 (2014) Teff (Eragrostis tef) as a raw material for malting, brewing and manufacturing of gluten-free foods and beverages: a review. J Food Sci Technol 51: 2881-2895.

35. Rosell CM, Barro F, Sousa C, Mena MC (2013) Cereals for developing gluten-free products and analytical tools for gluten detection. Journal of Cereal Science 59: 1-11.

36. Pulido O, Gillespie Z, Zarkadas M, Dubois S, Vavasour E et al. (2009) Introduction of oats in the diet of individuals with celiac disease: a systematic review. In: Taylor, Steve L. (Ed.), Advances in Food and Nutrition Research, (USA) 235-285.

37. Codex Alimentarius Commission (2008) Joint Food and Agriculture Organization of the United Nations/World health Organization food standards Program. Food for Special Dietary Use for Persons Intolerant to Gluten, CODEX STAN118-1979. Revised 2008.

38. Sollid LM, Qiao SW, Anderson RP, Gianfrani C, Koning F (2012) Nomenclature and listing of celiac disease relevant gluten T-cell epitopes restricted by HLA-DQ molecules. Immunogenetics 64: 455-460.

39. Camarca A, Del Mastro A, Gianfrani C (2012) Repertoire of gluten peptides active in celiac disease patients: perspectives for translational therapeutic applications. Endocr Metab Immune Disord Drug Targets 1: 207-219.

40. McCallum CM, Comai L, Greene EA, Henikoff S (2000) Targeting induced local lesions IN genomes (TILLING) for plant functional genomics. Plant Physiol 123: 439-442.

41. Comai L, Young K, Till BJ, Reynolds SH, Greene EA, et al. (2004) Efficient discovery of DNA polymorphisms in natural populations by Ecotilling. Plant J 37: 778-786.

42. Bovina R, Brunazzi A, Gasparini G, Sestili F, Palombieri S (2014) Development of a TILLING resource in durum wheat for reverse- and forward-genetic analyses. Crop Pasture Sci 112-124.

43. Slade AJ, McGuire C, Loeffler D, Mullenberg J, Skinner W et al. (2012) Development of high amylose wheat through TILLING. BMC Plant Biol 12: 69.