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Gluten and gluten-dependent diseases

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Abstract

Gluten is a mixture of many individual, related proteins that create a storage material in wheat. They are mainly monomeric gliadins and polymeric glutenins forming complexes with each other, stabilized by disulfide bridges, therefore the cysteine that forms them plays a very important role for the structure and functionality of gluten. The article compares the attributes of selected wheats, such as the content of individual nutrients, soil and climate requirements, and properties used in food production. The presence of gluten in food is a problem in terms of its impact on the human body. Focusing research on modifying the wheat genome is expected to lead to obtaining a wheat variant with non-toxic properties for people suffering from celiac disease and various forms of gluten protein intolerance. Specific sequences found in wheat proteins bind to IgE antibodies, causing a variety of disease symptoms. The article discusses the diagnostic criteria for celiac disease and wheat allergy, as well as the impact of gluten withdrawal on the clinical manifestation of celiac disease.

Key words: gluten, celiac disease, NCGS

Introduction and purpose

Common wheat (*Triticum aestivum*) is the most widely grown grain in the world, accounting for 20% of the calories consumed by humans and an important source of protein, vitamins and minerals [1]. In a form converted into flour, it can be found in almost every food product [2]. Research on wheat mainly focuses on the composition of proteins that occur in grains and has a significant impact on the technological quality of wheat [3]. The baking value of wheat mainly depends on the proteins that are part of a complex called gluten which is also the main storage protein in wheat grains. Storage proteins in cereal grains are responsible for the formation of a large, flexible and polymeric network (gluten) in the dough, which is of great importance in the context of the baking quality of the flour [4, 5]. Gluten is a complex mixture of hundreds of related but distinct proteins, mainly gliadins and glutenins. Disulfide isomerase plays a huge role in the maturation of gluten proteins. It is responsible for the formation of covalent bonds between individual gluten proteins [5]. Gluten is primarily consisting of monomeric gliadins and polymeric glutenins. Their proportions depend mainly on the wheat genotype and environmental conditions. *T.aestivum* is a hexaploid species (AABBDD). The Glu-1A, Glu-1B and Glu-1D genes are responsible for the biosynthesis of high-molecular glutenin subunits. For the vast majority of consumers, gluten does not have any harmful properties, but in some people it may cause adverse reactions. Increasingly, gluten-dependent diseases are detected, such as celiac disease, food allergy to gluten, Dühring's disease (dermatitis herpetriformis); gluten ataxia or non-celiac gluten hypersensitivity [6–9].

Description of the state of knowledge

Structure of gluten

In 1924, Osborne [10] divided the proteins of kernels, including wheat, due to their solubility, i.e. into water-soluble and dilute solutions of neutral salts of albumin and globulin, and into prolamines and glutenins, which are soluble in 70% ethanol or acids (fig 1). Albumin and globulins in wheat grain perform many physiological functions and some of them are classified as spare proteins. However, the functions of prolamines and glutenins are not fully known, apart from their role as typical backup proteins, due to their amino acid reserve. Prolamines and glutenins are the main components of gluten [10].

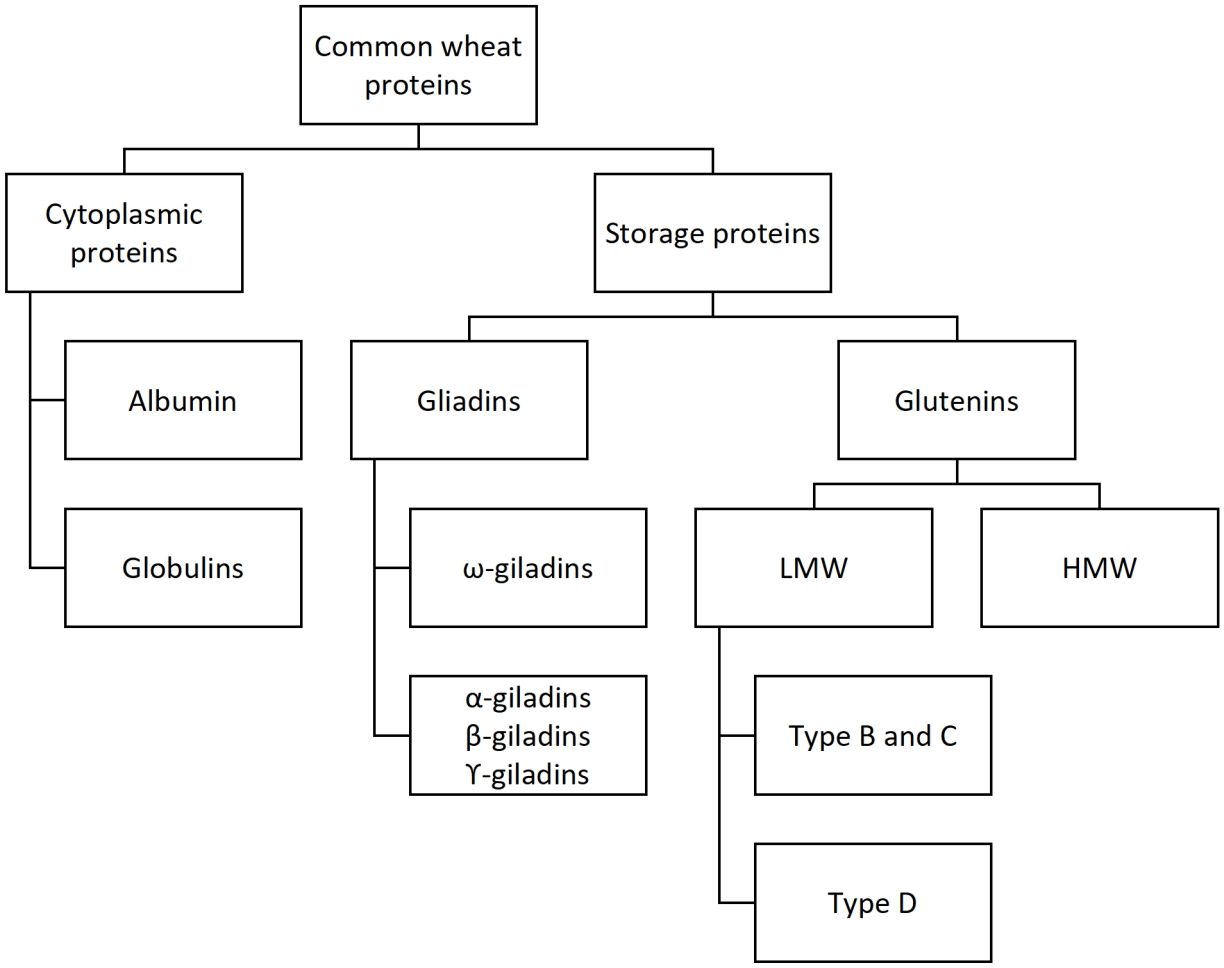

Figure 1. Classification of gluten proteins.

Gluten is a complex of at least 50 proteins. Wheat storage proteins form a network called gluten in the kernels, which determines the quality of the dough, giving it adequate water absorption capacity, cohesiveness, stickiness and elasticity [5]. Gluten proteins are mainly: monomeric gliadins and polymeric glutenins. These proteins react with each other in the endosperm cells of the endosperm to form polymers of considerable size, stabilized by intramolecular and intermolecular disulfide bonds [10–12]. Gluten protein fractions are also divided according to the amount of cysteine present. The fraction α-, β-, γ- and LMW-GS (Low Molecular Weight Glutenin Subunits) are considered to be rich in sulfur, while ω-gliadins are among the fractions poor in sulfur. HMW-GS (High Molecular-Weight Glutenin Subunits) has an average content of this element [10]. Cysteine is one of the smaller amino acids in gluten proteins (E2%), however, it is extremely important for the structure and functionality of gluten. Most cysteines are present in an oxidized state and form intra-chain disulfide bonds within the protein or inter-chain disulfide bonds between proteins [5].

The covalent structure of the gluten network is imposed by non-covalent bonds (hydrogen bonds, ionic bonds, hydrophobic bonds). Although this class of chemical bonds is less energetic than covalent bonds, they are clearly related to gluten protein aggregation and dough structure [5].

Gliadins

Most gliadins exist as chemically similar monomers with a size of 30-40 kDa. They were initially divided into four groups on the basis of mobility at low pH in α-, β-, γ-, ω-gliadin gel electrophoresis in order of decreasing mobility. Within each type, the structural differences are slight due to the substitution, deletion and insertion of single amino acid residues [5]. They are monomeric proteins that contain significant amounts of proline and glutamine in the amino acid composition and do not have inter-chain disulfide bridges [13].

α-, γ-gliadins have internal disulfide bonds in their structure, ω-gliadins do not. Modern methods such as two-dimensional electrophoresis or reversed-phase high-performance liquid chromatography (RP-HPLC) allow the gliadin fraction to be separated into more than one hundred components. Based on the analysis of complete or partial amino acid sequences, amino acid composition and Molecular Weight (MW), they can be divided into four different types: ω5-, ω1,2-, α / β- and γ-gliadin [5].

Glutenins

The glutenin fraction contains aggregated proteins linked by inter-chain disulfide bonds; they vary in size from about 500,000 to over 10 million Da. Thus, some glutenins are among the largest proteins in nature [5]. We divide glutenins according to their molecular weight into high molecular weight (HMW) and low molecular weight (LMW). This fraction contains complex proteins with non-protein components in their structure [10].

Health effect of gluten

The influence of gluten proteins on the human body is an increasingly frequent point of interest for researchers. Prolamines found in cereal grains cause allergenic reactions when introduced into the body. This causes physiologists and geneticists to focus research on modifying the wheat genome. The purpose of such modifications is to obtain a wheat variety with non-toxic properties for people suffering from a disease called celiac disease [14]. Short, highly specific sequences found in wheat proteins contribute to allergenic reactions. They bind to IgE antibodies causing disease symptoms. Gluten protein intolerance occurs not only in adults, but also in children and can manifest itself in various forms, such as: celiac disease, non-celiac gluten sensitivity - NCGS, food allergy to gluten, Dühring's disease (dermatitis herpetiformis) or gluten ataxia [6–9].

Celiac disease

Celiac disease is a congenital disease in which, due to the immunotoxic effect of gluten proteins, intolerance to products consisting of wheat flour occurs. This action results in an abnormal immune response. It is the disease best known among the prolamine-induced diseases of cereals, it is more common among women than men in a ratio of 3 to 1. The clinical picture of celiac disease is very diverse.

Children with celiac disease are characterized by short stature, lack of development, delayed puberty, chronic diarrhea, fatty diarrhea, abdominal distension and anemia. In adults, symptomatic or classic cases of the disease may manifest as malabsorption, weakness, flatulence, chronic diarrhea and abdominal pain. Interestingly, many patients experience little or no gastrointestinal symptoms, while parenteral symptoms such as infertility, Duhring's disease, osteoporosis, anemia, and neurological problems can be observed. For this reason, it seems appropriate to treat celiac disease as a multi-system disorder, not mainly gastrointestinal [15]. Diagnosis of celiac disease can only be carried out by a gastroenterologist while consuming gluten by the patient. A serological examination of the antibodies specific for celiac disease is performed:

- against tissue transglutaminase (IgA and IgG tTG);
- against smooth muscle endomysium (EmA IgA and IgG);
- against deamidated gliadin peptides (DGP), anti-gliadin (AgA) in IgA and IgG class.

Obtaining a positive serological result is a prerequisite for further tests. Further diagnostics include a biopsy of the small intestine and assessment of changes in the mucosa by taking samples from various parts of the intestine, most often from the duodenum, for histopathological examination. Treatment for celiac disease is to completely eliminate gluten from the diet [16].

Non-celiac gluten sensitivity – NCGS

In recent years, there has been an increasing number of patients worldwide suffering from a new type of food hypersensitivity called gluten hypersensitivity (NCGS). It is more common in adolescents and adults, especially females, with a large number of cases diagnosed in old age. Currently, it is estimated to cover 6% of the population. Gluten sensitivity is characterized by the presence of many gastrointestinal symptoms, such as flatulence, diarrhea, abdominal pain, and parenteral symptoms, including confusion, headaches, joint and muscle pains, anxiety and depression. Symptoms begin shortly after consuming gluten and improve or disappear after switching to a gluten-free diet.

Due to the lack of specific biomarkers, the diagnosis of gluten hypersensitivity is based mainly on a thorough assessment of clinical symptoms, excluding wheat allergy (no elevated IgE concentration) and celiac disease (negative antibody result, no intestinal villus atrophy). In order to rule out wheat allergy, the concentration of IgE antibodies should be determined and allergic skin tests should be performed. In turn, the exclusion of celiac disease should be based on specific serological tests confirming the absence of IgA, tTGA, IgA, EmA and the absence of total IgG deficiency. [17, 18]. The only serological marker observed in 50% of patients with gluten sensitivity is a positive AGA antibody ("old type" anti-gliadin antibody)[19]. The exclusion of celiac disease is also confirmed by intestinal biopsy (no atrophy of the intestinal villi; Marsh 0 or I scale) and negative tests for the presence of HLA-DQ2 and -DQ8 genotypes occurring in 99% of patients with celiac disease. These genotypes are only observed in 46% of patients with gluten sensitivity [20]. After ruling out celiac disease and wheat allergy, patients should follow a gluten-free diet, which usually leads to a significant improvement in both gastrointestinal complaints and parenteral symptoms. The reintroduction of gluten into the diet and the accompanying recurrence of symptoms provide additional confirmation of gluten sensitivity.

Although a placebo effect on gluten withdrawal cannot be excluded, the efficacy of this diagnostic method has been confirmed in two double-blind, placebo-controlled studies. Besierski et al. Observed the return of clinical symptoms in 68% of patients receiving gluten, compared with 40% of patients receiving placebo [21]. Similar research results were confirmed by Carrocio et al., who observed a significant deterioration of intestinal and parenteral symptoms in the group of patients receiving gluten compared to the group of patients receiving placebo. [19].

On the contrary to the well-established celiac disease, the pathogenetic mechanism of NCGS has still not been clearly defined. The available evidence suggests that several mechanisms play an important role in the development of NCGS, such as activation of the innate immune response [22], changing the barrier function of the intestinal mucosa [18], eating foods that contain amylase inhibitors [23], and the presence of multi-component food hypersensitivity associated with a diet rich in FOODMAPs or food additives, stimulating the occurrence of gastrointestinal symptoms and stimulating the intestinal nervous system [24]. Treatment of gluten sensitivity is mainly based on changing eating habits and introducing a gluten-free diet [25]. Understanding the causes of the disorder is essential for the successful treatment of patients, setting therapeutic goals, and fully understanding the potential ramifications for the body. One of the significant limitations is the difficulty in proper patient selection due to the lack of clearly defined diagnostic criteria and the use of various triggers of gastrointestinal symptoms in research, including gluten or wheat, which, in addition to gluten, contains other components that may affect the test result [26, 27].

Diseases caused by the presence of gluten proteins make it necessary to avoid them in food products. Willingness to a healthy lifestyle influences the public's interest in products with high nutritional value. Proteins in spelt *(Triticum spelta*) are composed of amino acids with a better composition than in common wheat (*Triticum aestivum*), but it is richer in nutrients and better digested [31]. Spelt wheat, also like common wheat, belongs to the hexaploids, however, unlike the common wheat, it has lower soil and climate requirements. [28]. In addition, it has more gluten protein, which is different from the gluten found in common wheat flour. Spelt dough is less durable but more stretchy [29]. The main difference in the composition of *Triticum spelta* grains from *Triticum aestivum* is the greater amount of gliadins in relation to the amount of glutenins. However, according to the World Health Organization and the Food and Agriculture Organization of the United Nations (WHO; FAO), spelt is not recommended for people who do not tolerate gluten, although there are publications in which people with celiac disease can consume products derived from this flour. Without affecting the occurrence of any allergenic reactions [30–32]. Among the studies on the toxic effects of gluten on the body, studies by Obłutowicz and others [33] showed that the development of IgE-dependent allergy was influenced by the ω-5 and α-gliadin protein fractions with the mass of 43 kDa and the low-molecular-weight LMW-GS proteins with the mass of 45 kDa.

Summary

Gluten is a very important protein complex that is of great importance for the quality of the baked cereal dough containing this huge protein polymer. Worldwide, the demand for wheat is growing, and the number of its crops increases every year. Still, more and more people are showing symptoms of gluten allergy or intolerance. In recent times, breeders have been using genetic engineering techniques to grow wheat that will have a high yield, good baking quality and will be non-toxic to people suffering from gluten-related diseases. Organic products with a better composition of protein fractions present in grains and those that can be consumed by people suffering from diseases caused by the body's intolerance to gluten proteins are becoming more and more popular. One of the subspecies of hexaploid wheat - spelt, may be a hope for these people. There have been assumptions in the literature for years that spelt bread is tolerated by people suffering from various types of allergies, in particular allergies to wheat-based food products. For now, however, the only solution for people suffering from gluten-related diseases is to completely eliminate gluten from the diet.

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