Wheat and gluten: Technological and health aspects

Katharina Anne Scherf, Peter Köhler, Freising

Summary
Among the gluten-containing cereals only wheat contains gluten that converts flour into a cohesive, viscoelastic dough after mixing with water. Due to its high gas holding capacity, wheat dough is the basis for bread with high volume and typical crumb structure as well as for a variety of different baked goods. On the other hand, in some individuals, the consumption of wheat and gluten-containing cereals, such as rye and barley, triggers hypersensitivity reactions; these include wheat allergy, coeliac disease or non-coeliac gluten sensitivity (NCGS). The only effective therapy for these individuals is to avoid exposure by strictly following a gluten-free diet. The great majority of the population (90–95%) do not exhibit hypersensitivities and have no scientific reason to avoid products from gluten-containing cereals.

Keywords: gluten, baking properties, non-coeliac gluten sensitivity, wheat allergy, coeliac disease

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Cereals and cereal proteins

Cereals are among the most important raw materials in the world and are grown on about 60% of agricultural land. In 2014, more than 2.5 billion tons of cereals were harvested, the main ones being maize (986 million tons), wheat (727 million tons) and rice (714 million tons) [11]. Cereal products are among the most important staple foods, particularly bread. With a mean content of only 10%, proteins are not the main ingredient of bread. Nevertheless, cereal proteins provide about 30% of human protein requirements, due to the high levels of consumption.

According to the extraction scheme developed by Osborne [2], cereal proteins can be classified into the fractions of albumins, globulins, prolamins and glutelins, depending on their solubility in water, dilute salt solutions, 70% ethanol and dilute acetic acid or alkali. The albumins and globulins are metabolic proteins, with functions during grain development. Prolamins and glutelins are storage proteins, which make up about 70–80% of grain protein and are storage proteins, which make up about 70–80% of grain protein and which occur in the starchy endosperm of different cereal grains. Prolamins mostly occur as monomers, whereas most of the glutelins are polymers linked through intermolecular disulphide bonds which can be converted to monomeric subunits by reduction. Like the prolamins, glutelin subunits are soluble in aqueous alcohols. Common names for these storage proteins are gliadins (prolamins) and glutelins (glutelins) from wheat, hordeins from barley, secalins from rye and avenins (only prolamins) from oats. Both the prolamin and glutelin fractions contain numerous protein components; these can be classified as high molecular weight (HMW), medium molecular weight (MMW) and low molecular weight (LMW) groups on the basis of their homologous amino acid sequences and similar molecular weights. Within the groups, closely related proteins are subclassified into individual types (Table 1) [3].

Gluten

The term “gluten” means different things, depending on the context. The classical definition of gluten is related to the baking quality of wheat flour. Gluten is also referred to as wheat glue and is a rubber-like proteinaceous mass, which remains after rinsing wheat dough with water or salt solutions (“wet gluten”) [3]. In the starch industry, the term gluten means something a little different. During the production of wheat starch, gluten is a by-product after starch has been separated and is used in dried and powdered form (so-called “vital gluten”) as a flour improver, food texturiser or in animal feed. The by-product formed in the preparation of maize starch is also known as maize gluten (“corn gluten meal”), which gives the false impression that maize also contains gluten.

The term “gluten” is defined in the Codex Alimentarius – in the context of hypersensitivity to cereal food proteins. According to this, “gluten is defined as a protein fraction from wheat, rye, barley, oats or their crossbred varieties and derivatives thereof, to which some persons are intolerant and that is insoluble in water and 0.5 mol/l NaCl” [4]. As oats is concerned, a footnote is added that permits special national regulations, as pure oats are tolerated by most, but not all, individuals with coeliac disease.

Wheat gluten and baking quality

Wheat has a special position among the cereals, as, after kneading with water, only wheat flour forms a dough with unique techno-functional properties. This is due to the so-called wheat gluten, which is made up of the gliadin and glutenin fractions. Gluten confers high water absorption to the flour and makes the dough cohesive and viscous with high capacity for gas retention. This gives bread of high volume and with the typical crumb structure. Wheat gluten is a decisive ingredient for high quality bread, cakes and pastries. Flours from all other

<table>
<thead>
<tr>
<th>Group</th>
<th>Wheat</th>
<th>Barley</th>
<th>Rye</th>
<th>Oats</th>
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<tbody>
<tr>
<td>HMW</td>
<td>HMW-Glutensins (p) 11%</td>
<td>D-Hordeins (p) 5%</td>
<td>HMW-Secalins (p) 9%</td>
<td>-</td>
</tr>
<tr>
<td>MMW</td>
<td>ω1,2-Gliadins (m) 4%</td>
<td>C-Hordeins (m) 36%</td>
<td>ω-Secalins (m) 18%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>ω5-Gliadins (m) 3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LMW</td>
<td>LMW-Glutensins (p) 22%</td>
<td>B-Hordeins (p) 27%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>γ-Gliadins (m) 27%</td>
<td>γ-Hordeins (m) 32%</td>
<td>γ-75k-Secalins (p) 48%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>α-Gliadins (m) 33%</td>
<td>-</td>
<td>γ-40k-Secalins (m) 25%</td>
<td>Avenins (m) 100%</td>
</tr>
</tbody>
</table>

Tab. 1: Classification of storage proteins from wheat, barley and rye with the corresponding percentages of the total storage protein [3]

HMW = high molecular weight, LMW = low molecular weight, m = monomer, MMW = medium molecular weight, p = polymer
cereal species give bread of lower volume, as the gas bubbles are either unstable and collapse, or cannot expand enough.

Composition, structure and function of the gluten proteins

Wheat gluten proteins consist of hundreds of protein components, some are present as monomers and some as more or less high molecular weight aggregates (Table 1). They are poorly soluble in water or aqueous salt solutions. Although some of the monomeric components have been well characterised, little is known about their aggregation or the interactions between the protein components. It is nevertheless well established that the gluten proteins have a decisive influence on the baking quality of wheat. Wheat gluten is made up of two functionally distinct groups of storage proteins: the monomeric gliadins and the polymeric glutenins. Gliadins are present at higher levels (gliadin/glutenin ratio: 1.5–2.7:1), soluble in aqueous alcohols and their molecular weights are between 28,000 and 55,000 [6]. Glutenins consist of aggregated proteins, linked by disulphide bonds. Their molecular weights range from 500,000 to more than 10 million [7]. This means that they are among the largest proteins occurring in nature [8]. In contrast to the gliadins, only a very small fraction with the lowest molecular weight is soluble in aqueous alcohols.

The molecular weight distribution of the glutenins is regarded as one of the most important factors that influence dough and baking properties. The largest polymers are called glutenin macropolymer (GMP) or gel protein [9]. The content of GMP in wheat flour (20–40 mg/g) is highly correlated with dough consistency and baking volume (Figure 2) [6, 10]. It is known that the glutenins are made up of protein subunits linked by disulphide bonds. Thus, when glutenins are treated

\[ r = 0.80 \]
\[ p < 0.01 \]

Fig. 1: Breads from different cereals and pseudocereals, prepared using a standard recipe with yeast and a straight dough procedure. 1: wheat, 2: rye, 3: barley, 4: oats, 5: rice, 6: maize, 7: buckwheat, 8: millet

A material is viscoelastic when it exhibits both viscous and elastic properties.

1 Deformation and flow properties of a substance

<table>
<thead>
<tr>
<th>GMP-content [mg/g flour]</th>
<th>Specific loaf volume [mL/g dough]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0</td>
<td>2.1</td>
</tr>
<tr>
<td>10.0</td>
<td>2.2</td>
</tr>
<tr>
<td>12.0</td>
<td>2.3</td>
</tr>
<tr>
<td>14.0</td>
<td>2.4</td>
</tr>
<tr>
<td>16.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Fig. 2: Dependence of specific bread volume on the content of glutenin macropolymer (GMP) in flours from various wheat cultivars (modified from [10]) statistical test procedure: Pearson correlation

GMP = glutenin macropolymer, p = significance, r = correlation coefficient
with reducing agents (e.g. dithiothreitol, 2-mercaptoethanol), they form monomeric components (sub-units), which are soluble in aqueous alcohols. The structure of the polymers formed from the glutenin sub-units (= glutenins) is only partially known and is currently shown in models [3, 11].

The technological function of gluten is essentially determined by two parameters: the gliadin/glutenin ratio and the quantity of GMP. The reason for the importance of the gliadin/glutenin ratio is that gliadins and glutenins have different roles in dough. As glutenins are high molecular weight polymers, they form a three-dimensional network, which is responsible for the gluten’s resistance to extension and elasticity [12, 13]. Gliadins are regarded as “softeners” in dough, responsible for viscosity and extensibility [14, 15]. It is, therefore, obvious that optimal baking quality is based on a balanced ratio between viscosity and elasticity and, thus, between gliadins and glutenins (Figure 3).

The composition (qualitative and quantitative) of the glutenins is also important for the properties of the gluten and the baking quality of flour and also reflects the content of GMP. One important factor is the presence or absence of specific sub-units, their concentrations and their mutual relationships. For example, each wheat cultivar contains 3–5 HMW glutenin subunits (=GSs) [16] and 7–16 LMW-GS [17]. As more than 20 different HMW-GS are known and more than 40 different LMW-GS, a large number of combinations and concentrations would be conceivable and this is one reason for the enormous difference in baking quality between different wheat cultivars. Much less is known about how the different types of GS are linked within the glutenins. Studies on the size of glutenin aggregates have shown that polymers only have a positive influence on elasticity and baking properties when they are above a specific size [5, 18]. The formation of these high molecular weight polymers (= GMP) depends on the available GS. For example, the presence of specific combinations and concentrations of HMW-GS leads to high levels of GMP. The explanation for this is thought to be that HMW-GS of the x-type and LMW-GS act as so-called “chain extenders”, i.e. they contain two or more free cysteine residues, which favour polymerisation. In contrast, so-called “chain terminators” reduce GMP content. These are high or low molecular weight proteins with only a single free cysteine residue, which hinder or prevent polymerisation.

**Hypersensitivities to gluten and wheat**

About 10,000 years ago, gluten-containing cereals were introduced into human nutrition when diploid einkorn wheat1 was grown for the first time [19]. The immune system was then faced with the challenge of developing tolerance to gluten, which had previously only been a rare source of protein. However, in a part of the population, this immune tolerance to gluten is either only partially present due to genetic predisposition or is lost in the course of life, due to interactions with external cofactors, such as infections [20]. Hypersensitivities can be differentiated by their different pathological mechanisms [21]. During the adaptive immune response in wheat allergies, B cells produce immunoglobulin (Ig) E antibodies and these trigger the release of inflammatory substances (e.g. histamine) from basophilic granulocytes and mast cells. In coeliac disease, dermatitis herpetiformis Duhring4 and gluten-induced ataxia5, the IgA and IgG antibodies of the adaptive immune response are characteristic and are directed against the external antigen gluten, as well as the endogenous tissue transglutaminase (TG2) and the endomysium (autoimmune reactivity). However, some gluten

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1 Einkorn (a primitive cereal) is a diploid form of wheat (which is actually hexaploid).
2 See article in “Ernährungslehre & Praxis” in this issue on p. 529.
3 Dermatitis herpetiformis Duhring is a skin disease from the group of the blister forming autoimmune dermatoses and is closely linked to coeliac disease.
4 Disorder affecting movement
peptides can also directly stimulate an innate immune response. If neither allergic nor autoimmune mechanisms are involved, the gluten-dependent symptoms are caused by NCGS (non-coeliac gluten sensitivity), in which the innate immune system is thought to play an essential role (Table 2) [22, 23]. Values on the prevalence of wheat allergies are in the range of 0.5–4% of the population. The prevalence of NCGS lies within the broad range of 0.6–6%. About 1% of the population is affected by coeliac disease. According to Codex Standard 1-1985 [24], wheat and other gluten-containing cereals (rye, barley, oats) are among the eight most important food ingredients that trigger hypersensitivity reactions and which therefore must be declared on packaged food. In the European Union, the Food Information Regulation (VO (EU) No. 1169/2011) came into force on 14 December 2014. Since then, the 14 most frequent triggers of allergies and food intolerance – including gluten-containing cereals – must be labelled on packed and loose products [25], in order to make it easier for the customer to select suitable foods.

Wheat allergies

Wheat allergies are caused by specific hypersensitivity to many different wheat proteins, including gluten proteins. Wheat allergies can be classified as follows, depending on the path of exposure to the allergens and the underlying pathological mechanism:
- respiratory tract allergy (baker’s asthma, allergic rhinitis),
- food allergy,
- wheat-dependent exercise-induced anaphylaxis (WDEIA) and
- contact urticaria or dermatitis.
Sensitisation to wheat proteins can take place through skin exposure or oral ingestion. Diagnosis is performed through the skin prick test, the analysis of specific IgE serum antibodies or functional assays, such as oral provocation tests or in vitro basophil activation tests (BAT). Although functional assays are regarded as the gold standard for diagnosis and can provide clarity if the results from skin prick tests and IgE serum antibodies are unclear, they are much more labour- and time-intensive and expose the patient to the risk of a severe allergic reaction [26]. Therapy of wheat allergy depends on its form and is based on either avoiding exposure to flour and flour dust or of abstaining from foods containing wheat. In acute cases, antihistamines or corticosteroids can help.

Baker’s asthma and allergic rhinitis

Baker’s asthma and allergic rhinitis were already described in Roman times and are among the most frequent occupational allergies. Up to 10–15% of millers, bakers and confectioners suffer an allergic reaction when they inhale flour and dust, so that they may even have to change their occupation if the symptoms are severe. α-Amylase inhibitors (chloroform-methanol soluble [CM] proteins) have been identified as the main allergens. Many other proteins may also trigger allergic reactions, including wheat germ agglutinin, peroxidase, lipid transfer proteins (LTPs), amylases, thioredoxin (Tri a 25) and gluten proteins [27].

Contact urticaria and dermatitis

Contact urticaria and dermatitis are allergic reactions, most often on the hands and face after contact with the allergen. As with baker’s asthma, employees in grain handling are most often affected by the different forms of these skin diseases. For example, allergens from wheat, rye, barley and other flours may also trigger allergic reactions, including wheat-containing cosmetics such as soaps, shampoos and creams may contain glu-

<table>
<thead>
<tr>
<th>Wheat Allergy</th>
<th>Coeliac Disease</th>
<th>NCGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>0.5–4%</td>
<td>≈ 1%</td>
</tr>
<tr>
<td>Genetics</td>
<td>-</td>
<td>HLA-DQ2/DQ8</td>
</tr>
<tr>
<td>Time till start of symptoms</td>
<td>minutes–hours</td>
<td>days–weeks</td>
</tr>
<tr>
<td>Symptoms</td>
<td>intra-/extraintestinal</td>
<td>intra-/extraintestinal</td>
</tr>
<tr>
<td>Triggering Proteins</td>
<td>gluten/other wheat proteins</td>
<td>gluten</td>
</tr>
<tr>
<td>Immune response</td>
<td>adaptive</td>
<td>adaptive/innate</td>
</tr>
<tr>
<td>Antibodies</td>
<td>IgE</td>
<td>IgA/IgG</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>none</td>
<td>yes</td>
</tr>
<tr>
<td>Intestinal damage</td>
<td>wheat-free diet</td>
<td>gluten-free diet</td>
</tr>
</tbody>
</table>

Tab. 2: Overview of the characteristics of gluten-dependent hypersensitivities

HLA = human leukocyte antigen; Ig = immunoglobulin; NCGS: non-coeliac gluten sensitivity
ten hydrolysates as foaming agent or emulsifier. They may also cause allergic reactions, such as angio-oedema of the eyelids. For all these skin diseases, exposure to allergens should be avoided with gloves, protective creams or by totally avoiding contact.

Food allergies

Aside from milk and eggs, wheat is one of the three most common food allergies that occur after ingesting allergenic products [28]. The prevalence of wheat allergies is higher in children than in adults, because the allergy often subsides when the child reaches school age. Most children with wheat allergy suffer from moderate to severe atopic dermatitis and wheat consumption can lead to typical IgE-mediated symptoms, such as urticaria, angio-oedema, bronchial obstruction, dizziness and pain in the lower abdomen, even extending to anaphylactic shock. In adults, food allergy to wheat occurs irregularly. The most frequent form is wheat-dependent, exercise-induced anaphylaxis (WDEIA). In contrast to coeliac disease and other food allergies, the dose needed to trigger the reaction is rather high – namely about 1 g wheat protein. All gluten proteins can trigger wheat allergies, as can many other wheat proteins, such as α-amylase inhibitors, germ agglutinin, peroxidase, LTPs, β-purothionin, puroindolines A and B and starch synthase.

WDEIA

WDEIA is a rare, but potentially life-threatening form of wheat allergy. It only occurs when wheat consumption is combined with co-factors, such as physical exertion, acetyl salicylic acid, alcohol, stress or infections [29]. The typical symptoms include skin rashes, urticaria, drop in blood pressure and breathing problems, extending to anaphylactic shock, and mostly occur during exercise 1–4 hours after ingesting wheat. It is therefore recommended to avoid the combination of wheat consumption and exercise or, to be safe, to switch to a gluten-free diet [30]. The main allergens are α- and γ-gliadins and HMW glutenins, although other gluten proteins may be involved in triggering the reaction, such as α- and γ-gliadins, LMW glutenins or gluten hydrolysates.

Coeliac disease, dermatitis herpetiformis Duhring and gluten-induced ataxia

Coeliac disease

Coeliac disease is a chronic disease of the small intestine that occurs in genetically predisposed individuals and is due to lifelong intolerance to gluten in food [23]. Although Samuel Gutz already described the symptoms of coeliac disease in 1888, the link between coeliac disease and gluten – the external factor triggering the disease – was established by the Dutch paediatrician Willem Karel Dicke not until the 1940s. Almost 97% of coeliac disease patients are positive for the sequences HLA-DQ2 and -DQ8. These lie on human chromosome 6 and code for human leukocyte antigens (HLA). On the other hand, this genetic predisposition is also present in about 30% of the healthy population. For this reason, the absence of HLA-DQ2/8 is a relatively reliable exclusion criterion for coeliac disease, although its presence is not sufficient to trigger the disease. It is still unclear which other factors ultimately trigger the disease [31]. Possibilities include other genetic factors, virus infections, changes in intestinal bacterial flora, the hygiene hypothesis6 and the time when gluten was introduced to infant nutrition during breast feeding [3].

As a multifactorial clinical picture, coeliac disease may appear in symptomatic, asymptomatic, potential or refractory forms. The common feature of all these forms is the positive genetic predisposition (HLA-DQ2/8) and the occurrence of coeliac-specific IgA and IgG antibodies in blood. In the symptomatic form, the patient suffers typical intestinal symptoms (lower abdominal pain, chronic diarrhoea, impaired fat digestion, vomiting) and/or extraintestinal symptoms (anaemia, osteoporosis, joint pain, chronic exhaustion). The principle characteristics of coeliac disease include damage to the mucous membrane in the upper small intestine, with loss of intestinal villi, hyperplasia of the crypts and infiltration of lymphocytes. Villous atrophy is accompanied by a reduction in intestinal surface and this leads to impaired absorption of nutrients in the small intestine, with weight loss and signs of nutrient deficiencies. If the patient strictly complies with a gluten-free diet, these symptoms disappear in almost all cases and the mucous membrane in the small intestine is normalised, entailing only a slight risk of further complications. In a few rare cases, the small intestinal mucous membrane does not regenerate and the coeliac disease-specific intestinal symptoms remain or return, even though the gluten-free diet has been strictly adhered to for more than 12 months. Once unintentional ingestion of gluten and other intestinal diseases have been excluded, refractory coeliac disease is diagnosed.

Type 1 refractory coeliac disease is usually accompanied by intraepithelial lymphocytes of normal phenotype. It can mostly be treated with the glucocorticoids prednisolone or budesonide. If the phenotype of the intraepithelial lymphocytes is shown to be abnormal, the diagnosis of type 2 refractory coeliac disease is made. In the absence of an

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6 According to the hygiene hypothesis, a fairly sterile environment in childhood may inhibit the development of the immune system, as the immune system is confronted with too few genuine pathogens.
Asymptomatic coeliac disease exhibits specific damage to the small intestinal mucous membrane, but the typical symptoms are missing. In potential coeliac disease, the typical symptoms are absent. In contrast to other forms, the small intestinal mucous membrane is not damaged and exhibits normal villous structure. Patients with potential coeliac disease have a greater risk of developing coeliac disease later in life. Groups with particularly high risks include first degree relatives of patients with coeliac disease, people with genetically associated conditions such as Down’s, the Ul- rich-Turner and the Williams-Beuren syndromes, as well as patients with associated autoimmune diseases, such as type 1 diabetes mellitus, autoimmune hepatitis and autoimmune thyroiditis. As patients with asymptomatic or potential coeliac disease do not suffer from the typical symptoms of coeliac disease, a long time may pass until the correct diagnosis is made. Several specialists may have to be consulted; patients at risk may have to be actively screened for serum antibodies typical of coeliac disease [33]

Diagnosis of coeliac disease includes the assessment of medical history and symptoms, detection of specific IgA and IgG antibodies in serum, taking biopsies from the small intestine and possibly checking the patient’s genetic predisposition with respect to HLA-DQ2/8. It is recommended that the first step should be to detect IgA anti-TG2 antibodies (TGA), as the specificity and sensitivity are both ca 95%. This can be confirmed by a test for IgA anti-endomysium antibodies and – particularly if there is selective IgA deficiency – with tests for IgG TGAs and IgG antibodies to deamidated gliadin peptides. Histological characterisation of at least four small intestinal biopsies is regarded as the gold standard for the diagnosis of coeliac disease [26]. The tests should be performed while the patient is still ingesting gluten. If the symptoms clearly improve after introduction of a gluten-free diet, this confirms both the success of the treatment and the correctness of the diagnosis.

Pathomechanism of coeliac disease

Both the adaptive and the innate immune response are involved in the complex pathomechanism of coeliac disease. The gluten ingested in food has very high contents of proline and glutamine. As a consequence, it is only partially hydrolysed by gastrointestinal enzymes and long peptides reach the epithelium of the small intestine. The gluten peptides pass the epithelial layer, either trans- or paracellularly, and pass to the enzyme tissue transglutaminase (TG2) in the lamina propria. The subsequent enzymatic de- or transamidation reactions give rise to deamidated gluten peptides or conjugates between TG2 and gluten peptides. Both these reactions enhance the immunostimulatory activity of the gluten peptides and their native, deamidated or TG2-conjugated forms now bind to HLA-DQ2/8 heterodimers on antigen-presenting cells and stimulate CD4+ T cells through the corresponding receptors. After their activation, gluten-reactive T cells secrete pro-inflammatory cytokines, such as interferon-γ, interleukins and tumour necrosis factor-α, which stimulate the release and activation of matrix metalloproteinases (MMPs). These break down extracellular matrix proteins and thus lead to the destruction of the epithelium. On the other hand, gluten-reactive T cells also interact with B cells. These can differentiate into plasma cells and produce IgA and IgG antibodies inducing an anti-inflammatory pathway. It is also known that gluten peptides stimulate the innate immune response and trigger the secretion of interleukin 15 by activating entero-cytes, macrophages and dendritic cells. As a result, lymphocytes are stimulated to express the receptor NKG2D and epithelial cells to express MICA (major histocompatibility complex class I chain-related molecule A), the ligand for NKG2D. Once MICA has bound to NKG2D, intraepithelial lymphocytes start to destroy epithelial cells [3]. This new knowledge of the pathomechanism of coeliac disease shows the way to possible new therapeutic approaches. One of the most promising is to break down gluten in the gastrointestinal tract with the help of gluten-degrading enzymes [34].

Asymptomatic coeliac disease, 40–58% of patients suffer fatal intestinal cancer within the following 5 years [32].

DH patients have additional antibodies to epidermal transglutaminase (TG3), which are useful in distinguishing between DH and other skin diseases [35]. Most DH patients show mild to moderate intestinal damage, although the main symptoms are intensely itching and burning blisters, erythema, eczema and wheals, mostly on the elbows, knees, shoulders and head. The acute symptoms can also be medically alleviated with dapsone7.

Gluten-induced ataxia

Gluten-induced ataxia (gluten ataxia) is a form of idiopathic sporadic ataxia, which is characterised

7 Dapsone is an anti-inflammatory drug with antibiotic activity.
by gluten-specific antibodies. The symptoms include nystagmus and other visual disorders, ataxia when walking or standing and atrophy of the cerebellum. About 40% of patients with gluten ataxia also exhibit changes in the small intestinal mucous membrane that are typical of coeliac disease. Antibodies against brain transglutaminase (TG6) can be detected in circulating blood, but accumulate in the cerebellum and brain stem. The white substance in the cerebellum is infiltrated with T lymphocytes and there is irreversible loss of Purkinje cells in the cerebellar cortex. For this reason, rapid diagnosis is essential, followed by therapy with a gluten-free diet [36].

Non-coeliac gluten sensitivity (NCGS)

NCGS is characterised by intestinal and extraintestinal symptoms linked to the consumption of gluten-containing foods and affects patients for whom wheat allergies, coeliac disease, irritable bowel syndrome and other types of food intolerances can be excluded. In some publications, this clinical picture is referred to as gluten sensitivity [22], wheat sensitivity or (non-allergy) non-coeliac wheat sensitivity [37, 38]. Symptoms are observed some hours or days after consumption of wheat (and possibly of other gluten-containing cereals). The clinical presentation includes intestinal symptoms, such as flatulence, lower abdominal pain and diarrhoea, as well as extraintestinal symptoms, such as exhaustion, impaired well-being, headache, anxiety attacks, a “foggy” feeling and pain in the joints and muscles.

As there is no sensitive and specific biomarker for NCGS, the diagnosis is based on a very thorough and standardised observation of the patient during a switch to a gluten-free diet, followed by a renewed challenge with gluten. Due to the very strong nocebo effect, the challenge is performed blinded once with gluten and – after a one week interval with a gluten-free diet – once with placebo [39]. The diagnosis of NCGS is regarded as positive if there is a difference of at least 30% on the symptom rating scale between the challenges with gluten and with placebo.

The therapy consists of adhering to a wheat- or gluten-free diet, although a low gluten diet may be sufficient in some cases. The individual steps in the pathomechanism of NCGS have not yet been fully studied, so that the triggering mechanism has not been unambiguously identified. There is evidence that NCGS is triggered by gluten and amylase trypsin inhibitors (ATIs) in gluten-containing cereals, as these activate the innate immune response. Thus both gluten and other wheat proteins may be responsible for triggering NCGS and it must be clarified whether other proteins or other components, such as FODMAPs (fermentable oligo-, di- and monosaccharides and polyols) in gluten-containing cereals play a role.

Gluten-free diet

A gluten-free diet is based on the strict elimination from the diet of cereals containing gluten (wheat, rye, barley, triticale, einkorn wheat, durum, emmer or khorasan wheat and their hybrids), as well as their products. In almost all patients, the small intestinal mucous membrane is regenerated within 6–12 months if maximally 20 mg gluten is ingested per day. According to the Codex Alimentarius Standard 118-1979 [4], products labelled as gluten-free by the manufacturer may contain a maximum of 20 mg gluten per kg.

It is a great challenge to comply with a gluten-free diet, in particular at the beginning, because gluten is widely used in the cosmetic, drug and food industries, where – also in modified forms – it is used as thickener, emulsifier, filler or bread improver. Patients and their families should seek detailed advice from doctors and dieticians, especially to avoid any dietary deficiencies (B vitamins, vitamin D, folate, calcium, iron, magnesium, dietary fibre). It is recommended to revise these instructions at least annually.

Instead of gluten-containing cereals, gluten-free products made from maize, rice, sorghum, teff, potatoes and pseudocereals, such as amaranth, buckwheat and quinoa serve as alternatives. The missing functionality of wheat gluten in bread and baked products must be compensated by adding proteins from e.g. milk, egg or soy, polysaccharides, e.g. hydroxypropylmethylcellulose, carboxymethylcellulose or xanthan, enzymes and/or using sourdough [39].

Although gluten-free baked products are still somewhat inferior to gluten-containing products with respect to aroma, flavour and texture, there have been substantial improvements in recent years due to intensive research and the use of new ingredients. The availability of tasty high-quality gluten-free products can greatly encourage the patients to accept a gluten-free diet and facilitate lifelong compliance.

Conclusions

The gluten proteins in wheat possess unique viscoelastic properties allowing the formation of dough with high water absorption and gas holding capacities. After baking, breads with high volume and the typical crumb structure are formed. Wheat gluten also offers the possibility to make a wide variety of other products, including biscuits, cakes, pizza and pasta, with good technological, functional and sensory properties (aroma, taste and texture).
In many parts of the world, wheat is a basic food. In particular, wholegrain flour provides important nutrients, dietary fibre and minerals, such as iron, zinc, magnesium and manganese, as well as B vitamins. On the other hand, some individuals develop hypersensitivities when they consume products containing wheat or gluten. Research is continuing to elucidate the underlying pathological mechanisms, in order to identify the genetic and environmental cofactors that are responsible for the loss of immune tolerance to the triggering proteins. After diagnosis of coeliac disease, wheat allergy or NCGS, it is essential for the patient to comply with a strict gluten-free diet, in order to prevent symptoms and long-term complications. However, there is no evidence that the great majority of the population (90–95%) suffer from gluten-dependent hypersensitivities and current scientific knowledge indicates that there is no reason for them to eliminate wheat, rye or barley from the diet.

Conflict of Interest
The authors declare no conflict of interest.

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