

PART I

FOOD ALLERGY AND THE CONSUMER

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IMMUNE-MEDIATED ADVERSE REACTIONS TO DIETARY PROTEINS

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1.1. INTRODUCTION

An adverse reaction to food is a general term applied to the clinically abnormal response to an ingested food, food ingredient, or food additive. Adverse reactions to food may or may not be mediated by the immune system [1–6]. Nonimmune-mediated adverse reactions to food mimicking food allergy are termed food intolerances and can be the result of toxicity, for example, histamine in scombroid fish poisoning or *nonallergic food hypersensitivity* (Fig. 1.1) [4–7]. In turn, *nonallergic food hypersensitivity* (Fig. 1.1) can result from (1) chemical/pharmacological action of food ingredients (e.g., caffeine in coffee, tyramine in aged cheese, sulfites in wine, phenylethylamine in chocolate, or the flavor enhancer monosodium glutamate [8–10]; (2) physiological factors associated with specific characteristics of the host (e.g., lactase deficiency leading to lactose intolerance and deficiency of glucose-6-phosphate dehydrogenase in favism) [5, 11–13]; or (3) others such as psychogenic causes (e.g., eating disorders may present clinical symptoms suggestive of an adverse reaction to food) [6, 14]. Conversely, an adverse reaction to food (Table 1.1) may be mediated by an immunologic response and should be distinguished from food intolerances that do not have an immune basis, but may be similar in clinical presentation [2, 7, 15–17].

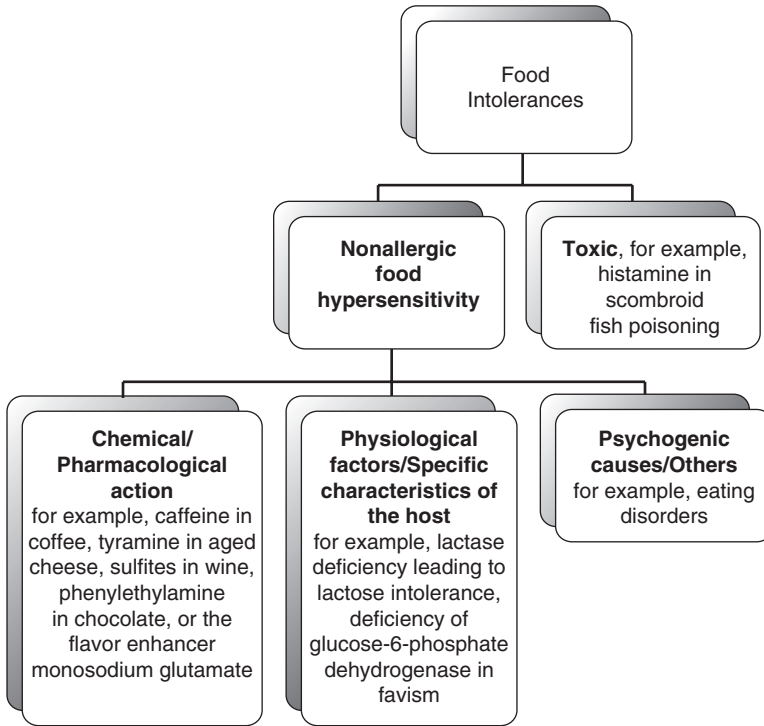


Fig. 1.1 Nonimmune-mediated adverse reaction to food “Food Intolerances.” See text and Glossary of Terms for further explanation and references.

Allergy is defined as a *hypersensitivity* reaction to intrinsically harmless antigens, most of which are environmental, and the process is initiated by specific immunologic mechanisms [3]. The term *food allergy* has been recommended when an adverse reaction to food is mediated by immunologic mechanisms [1, 3, 5, 18]. Food allergens are defined as the antigenic molecules giving rise to the immunologic response [3, 19–21]. Proteins are the food constituents responsible for eliciting immune-mediated adverse responses to food [3, 19–21]. Hence, the eliciting dietary proteins are known as *allergens*. The term *IgE-mediated food allergy* is used when immunoglobulin E (IgE) is involved in the reaction [3, 5, 6]. Allergies to food contaminants such as dust mites, mold, and parasites should also be distinguished from food allergy elicited by dietary proteins.

Under the above definitions, all immune-mediated adverse reactions to dietary proteins are considered *food allergy*. Together, *food allergy* encompasses a wide range of clinical disorders, which are grouped in Table 1.1 as IgE, non-IgE, and mixed IgE/non-IgE [2, 5, 6, 22]. These include IgE-mediated food allergy, celiac disease, dermatitis herpetiformis (DH), and clinical conditions such as allergic eosinophilic esophagitis and food protein-induced

TABLE 1.1 Food Allergies: Immune-Mediated Mechanisms, Associated Clinical Presentations, and Most Often Offending Foods

Target Body System	IgE Mediated (Foods: Peanut, Milk, Soy, Egg, Tree Nuts, Wheat, Fish/Shellfish)	Non-IgE and Mixed IgE and Cell Mediated (Foods: Milk, Soy)	IgE and Non-IgE Reactions to Gluten (Foods: Wheat, Rye, Barley, and Related Cereals)
Generalized/systemic reactions	Anaphylaxis Immediate onset Late-onset reactions Food-dependent, exercise-induced anaphylaxis	—	IgE mediated Wheat allergy Wheat-dependent, exercise-induced anaphylaxis
Skin/cutaneous reactions	Urticaria/angioedema/flushing/acute contact urticaria	Atopic dermatitis Contact dermatitis	Non-IgE Dermatitis herpetiformis (skin form of celiac disease [CD])
Digestive system/ gastrointestinal (GI)	Oral allergy syndrome, immediate Immediate gastrointestinal reactions Vomiting/diarrhea/abdominal pain	Allergic eosinophilic esophagitis Allergic eosinophilic gastroenteritis Allergic proctocolitis Food protein-induced enterocolitis syndrome Infantile colic	Non-IgE Celiac disease and related conditions Non-IgE adverse reactions to dietary gluten include a wide scope of conditions with and without GI involvement, for which scientific information is fast evolving (see Section 1.4)
Respiratory system	Acute rhinoconjunctivitis/bronchospasm	Asthma	Pulmonary hemosiderosis (Heiner's syndrome)

TABLE 1.2 Food Allergies

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- Food allergens are generally glycoproteins with molecular weights ranging from 10 to 70kDa.
 - Innate allergenic capacity of foods may be determined by a combination of factors, for example, solubility, resistance to pH, heat, and proteolysis by digestive enzymes.
 - Allergenic capacity of food allergens may be modified (increase or decrease) by food processing and manipulation, for example, heating.
 - The individual must first be sensitized by exposure to the allergenic protein.
 - The route of initial exposure and sensitization can be oral, respiratory (aeroallergens), or dermal (skin) contact.
 - In infants, the route of initial exposure and sensitization can occur in utero or through breast milk.
 - Food allergy occurs when a sensitized individual is exposed to the same or a cross-reactive protein through food ingestion.
 - Food allergies are often encountered by infants or children during a developmental window of immunologic immaturity.
 - IgE-mediated food allergies are characterized by the rapid release of powerful cellular chemicals such as histamine.
 - In IgE-mediated food, allergy reactions can occur within minutes or up to 4 hours after ingestion.
 - Clinical disorders associated to non-IgE-mediated mechanisms or to mixed IgE and non-IgE, typically have delayed onset of symptoms (>2 hours) and a chronic, relapsing course.
 - Severity of reactions and presenting symptoms may vary with time and exposure.
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enterocolitis syndrome (FPIES) [14, 23–25]. Many factors are implicated in the basic pathophysiological mechanisms of *food allergy*, such as host genetics, biochemical characteristics of the proteins, exposure, changes induced through food processing, or genetic engineering in “genetically modified foods” (Table 1.2) [20, 21, 26–28].

During the last two decades, there has been an increasing trend in the prevalence of food allergy in Western countries. It is estimated that food allergy affects between 5% and 8% of infants and young children and approximately 2–4% of adults [2, 7, 15, 17, 29]. Today, food allergies, both IgE and non-IgE mediated, are important health concerns from the point of view of risk management, policy setting, public health, diagnosis, and treatment for the consumers, their families, and the communities where they live, and for the food industry at large [13, 18, 30–32].

An understanding of the basic mechanisms underlying adverse reactions to foods and an enhanced awareness of the various clinical presentations is important for the overall management of food allergies. To this extent, this chapter presents an overview of the current understanding of the basic immune mechanisms mediating adverse reactions to food proteins and their various clinical presentations. For further clarification, refer to the Glossary of Terms on pages xix–xxvii.

Discussion of other aspects relevant to *food allergy*, such as allergen thresholds dose, clinical diagnostic tests, and methods used to detect specific allergenic proteins in food, are beyond the scope of this chapter. The chapter is organized in sections based on the implicated immune-mediated mechanism and associated clinical conditions. With the exception of celiac disease, which is discussed separately, a brief description of symptoms and medical conditions associated with food allergies is presented under each category throughout the text or in the Glossary of Terms.

1.2. ORAL IMMUNE TOLERANCE

The gut is responsible for the digestion and absorption of nutrients while acting as the first line of immune defense against pathogenic microbes within the gastrointestinal tract. The gut mucosal immune system accomplishes this task partly by establishing a tolerance to macronutrients [28, 33]. The gastrointestinal tract is the largest immune organ in the body and is constantly exposed to dietary proteins from ingested food. Immune tolerance to dietary proteins is maintained by active suppressive mechanisms involving antigen-specific regulatory T cells. In the first few years of life, humans gradually develop an intricate balance between tolerance and immune reactivity in the gut mucosa, along with a tremendous expansion of gut-associated lymphoid tissue (GALT). GALT is comprised predominantly of clusters of organized lymphoid tissue in the terminal ileum (Peyer's patches), appendix, and isolated lymphoid follicles located beneath the epithelium throughout the gut [34].

Several factors can cause disturbances at different steps in the process of developing oral tolerances, disrupting intestinal barrier function, and contributing to disease pathogenesis [35]. The factors implicated in the development and/or altering the risk of adverse immune reactions to dietary proteins can include genetic susceptibility, gastrointestinal infection, age, exposure (route, dose, and time), timing and length of initial exposure, association with breastfeeding, gastric pH, and type of protein [2, 13, 36–38]. Food allergies may be the result of a breach in oral tolerance to ingested food or from cross-reactivity between food and nonfood allergens. For example, individuals with allergies to fruits and vegetables may have been sensitized by pollen exposure known as pollen-food allergy syndrome or oral allergy syndrome (OAS) [5, 13].

1.3. FOOD ALLERGY

Food allergy is defined as an exaggerated immune response (hypersensitivity) to dietary proteins [1–3]. Allergies to food develop when exposure to a food protein is mistakenly identified as harmful by the human body. Failure of the development of gut tolerance for a specific food protein leads to hypersensitivity to that protein [21, 28, 33]. Food allergies are often seen during the early

period of life that coincides with the critical period of development of immune tolerance and typically occurs during this period of immunologic immaturity [2, 15, 17, 28, 39].

Host factors, for example, genetics, age, gut flora, asthma, history of atopy, exercise, and extrinsic factors such as characteristics and dose of the protein (threshold), all influence the potential allergic reaction [2, 5, 33, 36, 40, 41]. The allergenic capacity of the protein may be modified by food processing and manipulation (e.g., heating) [27, 42, 43]. Food proteins that are resistant to digestion are considered to be the most allergenic. The ability of the allergenic protein to trigger direct oral sensitization is modulated by gastric acidity [37].

Although any food protein can potentially provoke an immune reaction, relatively few food proteins are responsible for the vast majority of significant food-induced allergic reactions [21]. The most common food allergens in the pediatric population include cow's milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish, whereas peanuts, tree nuts, fish, and shellfish predominate in adults [2, 5, 13, 14, 25, 44]. Gluten from wheat, barley, and rye are the proteins of most concern for celiac disease, DH, and other gluten-induced conditions (Section 1.4), while rice is emerging as a food of concern for FPIES [45, 46].

The most common food allergies in a given population and the criteria for identification of priority allergenic proteins will vary based on world regions, individual countries, dietary habits, and regulatory systems [30].

1.3.1. IgE-Mediated Food Allergy

IgE-mediated food allergies constitute the majority of food allergic reactions and are the best studied. An IgE-mediated reaction develops when an allergenic protein binds with specific IgE antibodies on mast cells and basophils activating the release of potent compounds such as histamine. The first step in the development of IgE food allergies is sensitization. The first time the susceptible individual is exposed to the specific food allergen, the body's immune system misidentifies the protein as harmful and responds by creating specific antibodies (IgE) to that allergen. Repeat exposures to the same food protein trigger an immune reaction with the release of IgE antibodies [2, 5, 17, 33]. The conjugation of the IgE antibody with the allergens triggers a stimulus to mast cells and basophils, which degranulate, releasing mediators (e.g., histamine) and promoting the synthesis of prostaglandins, leukotrienes, and cytokines [2, 18, 33]. This reaction represents an effort by the immune system to reject/remove the protein, mistakenly identified as harmful, from the body. In turn, the chemicals released have powerful effects on the respiratory system, gastrointestinal tract, skin, and cardiovascular system.

Histamine is a powerful biogenic amine, released during IgE-mediated allergic reactions. It is synthesized by mast cells, basophils, platelets, and other cells such as histaminergic neurons and enterochromaffin cells, where it is stored in the cytoplasm in vesicles and released upon stimulation. Conversely, histamine exerts its effects by binding to a family of receptors on target cells

in various tissues mediating numerous biological reactions. These biological reactions include smooth muscle contraction, vasodilation, increased vascular permeability, mucus secretion, tachycardia, alterations of blood pressure, arrhythmias, and stimulation of gastric acid secretion [12]. This mechanism explains the fast onset of symptoms and potential severity of clinical symptoms observed with IgE-mediated food allergies.

IgE-mediated reactions can start within minutes to 1 hour (rarely past 2 hours) of exposure. Reactions often affect the skin (urticaria, angioedema, morbilliform eruptions, flushing, pruritus) [47] and can involve the respiratory tract (sneezing, rhinorrhea, congestion, cough, wheezing, difficulty breathing) [48], the gastrointestinal tract (OAS, nausea, vomiting, diarrhea, cramping, abdominal pain) [17, 49], and the cardiovascular system (tachycardia, hypotension) [50, 51]. Severe systemic reactions can result in anaphylactic shock and death [52].

A late-phase response may follow the immediate reaction beginning 4–6 hours after contact with the allergen and continuing for several days. This response is caused by chemotactic mediators released at the same time as the immediate reaction, which promote selective recruitment of inflammatory cells, mainly eosinophils and neutrophils, which infiltrate the tissue producing an inflammation that can last for a few days [6].

1.3.1.1. Anaphylaxis. Anaphylaxis is a serious generalized allergic reaction that may cause death. Anaphylaxis represents the most severe form of IgE-mediated food allergy and is clinically defined as a food allergic reaction involving two or more organ systems [50–52]. It can include cutaneous (skin), respiratory, cardiovascular, and gastrointestinal symptoms. The onset of symptoms after exposure to food is usually abrupt. In extremely sensitive individuals, reactions may be triggered by minute amounts of food proteins [31]. Symptoms can start within seconds to 2 hours following allergen ingestion and can include feelings of impending doom, throat tightness, coughing or wheezing, abdominal pain, vomiting, diarrhea, and loss of consciousness. Skin symptoms such as flushing, urticaria, and angioedema are present in most anaphylactic reactions. However, the most rapidly progressive anaphylactic reactions may not have cutaneous manifestations. Severe anaphylaxis is characterized by life-threatening upper airway obstruction, bronchospasm, and/or hypotension. In children, bronchospasm is a common symptom, and a background of atopy and asthma is often present [52].

An international task force on anaphylaxis and the European Academy of Allergology and Clinical Immunology recommend the following working clinical definition of anaphylaxis in which the diagnosis is considered highly likely when any one of the following three criteria are met [50, 51]:

1. acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips, tongue–uvula), with respiratory (e.g., dyspnea,

- bronchospasm, stridor, hypoxia) or/and cardiovascular compromise (e.g., hypotension, collapse); or
2. two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. involvement of the skin or mucosal tissue (e.g., generalized hives, itch, flushing, and swelling),
 - b. respiratory compromise (e.g., dyspnea, bronchospasm, stridor, hypoxia),
 - c. cardiovascular compromise (e.g., hypotension, collapse), and
 - d. persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting);
 3. hypotension after exposure to known allergen for that patient (minutes to several hours).

In the literature, grading systems for acute systemic hypersensitivity reactions vary considerably, have a number of deficiencies, and lack a consistent definition of anaphylaxis. Despite limitations, the following clinical criteria and grading system of anaphylaxis [52] provide general guidance:

- I. Severe reactions include symptoms that are strongly associated with hypotension and hypoxia: confusion, collapse, unconsciousness, and incontinence. Preexisting asthma and lung disease are viewed as an increased risk of hypoxia.
- II. Moderate reactions include diaphoresis, vomiting, pre-syncope, dyspnea, stridor, wheeze, chest/throat tightness, nausea, vomiting, and abdominal pain.
- III. Mild reactions are limited to the skin (urticaria, erythema, and angioedema); however, when angioedema includes the face with involvement of the glottis, this is considered severe, since it is associated with hypoxia.

Anaphylaxis may have a biphasic course of onset in as many as 20–25% of cases, with initial improvement occurring with or without treatment followed by the recurrence of severe symptoms within 1–2 hours. The severity of late symptoms cannot be predicted based on the early symptoms; for instance, early mild symptoms may be followed by anaphylactic shock. Given the potential for late-phase reactions, an observation period of at least 4 hours is recommended following a reaction. Peanut, tree nuts (e.g., almond, cashew, hazelnut, pecan, and walnut), fish, and shellfish are most often responsible for food-induced anaphylaxis [2]. Cross-reactivity among food allergens or with aeroallergens may be the eliciting cause [2]. In rare circumstances, anaphylaxis may have a protracted course of onset, with symptoms lasting for days.

1.3.1.2. Skin (Cutaneous) Manifestations of Food Allergy. The skin is the target organ most often involved in food allergy. Both mixed IgE and non-IgE cell-mediated mechanisms have been implicated in various skin manifestations associated with food allergy [5–7, 47]. Acute generalized urticaria characterized by pruritus and hives, with or without angioedema, is the most common clinical presentation of IgE-mediated allergic reactions to ingested foods in both children and adults. Onset of symptoms may be rapid (e.g., within minutes of ingesting the responsible food). Skin involvement may be isolated or associated with other organ systems in food anaphylaxis. Acute IgE-mediated urticaria can also be induced by skin contact with cow's milk, raw egg white, raw meats, fish, vegetables, and fruits. Urticaria symptoms lasting longer than 6 weeks are rarely caused by food allergy.

Atopic dermatitis is the most common mixed IgE/cell-mediated skin manifestation of food allergy [5–7, 47]. It is characterized by eczema that generally begins in early infancy, often associated with extreme pruritus, and a chronically relapsing course [53, 54]. DH is a non-IgE-immune-mediated condition elicited by gluten in susceptible individuals and is discussed under celiac disease (Section 1.4).

1.3.1.3. Oral Allergy Syndrome (OAS). OAS is a very common manifestation of food allergy, especially in adults that are allergic to tree pollen (pollen-food allergy syndrome) and, to a lesser extent, among those who are allergic to grass, ragweed, and mugwort pollens [2, 5, 13, 17]. It is seen in response to contact to raw fruits and vegetables and is usually confined to the oral cavity. It affects approximately 50% of pollen-allergic adults and represents the most common adult food allergy. OAS can occur as a result of cross-reactivity between the allergenic proteins in pollens and plant foods such as birch (apple, cherry, peach, carrot), grass (tomato, kiwi), ragweed (melon, banana, tomato), and mugwort (carrot, celery) [2, 5, 13, 17]. Upon contact with an allergenic food protein, the susceptible individual develops a reaction characterized by oral itching, lip swelling, and oral angioedema. Symptoms can also involve other organs and become more severe. There are four levels of increasing severity: (1) oral mucosal symptoms only, (2) oral mucosal plus gastrointestinal symptoms, (3) oral mucosal plus systemic symptoms (urticaria, rhinoconjunctivitis, or asthma), and (4) oral mucosal symptoms plus life-threatening problems (glottis edema, anaphylactic shock) [6, 52].

1.3.1.4. Respiratory Manifestation of Food Allergy. Allergic rhinoconjunctivitis, bronchospasm, laryngeal edema, and asthma may follow the ingestion of food allergens in allergic individuals [2, 6, 48, 52]. It is rare that patients present with isolated respiratory symptoms. They usually present in association with clinical symptoms involving the skin or the gastrointestinal tract or in the context of food anaphylaxis. Food-induced upper respiratory tract symptoms seem to be more common in infants and young children. Allergic

rhinoconjunctivitis is characterized by periocular pruritus, tearing and conjunctival erythema, nasal congestion, rhinorrhea, and sneezing shortly after the ingestion of the allergenic food [48]. Chronic serous otitis media may develop secondary to chronic rhinitis and eustachian tube dysfunction, or the middle ear itself can be the primary involved organ [48]. Food-induced asthma is more common in young children, particularly in association with atopic eczema. Acute bronchospasm is a feature of severe food-induced anaphylaxis. Food allergy is considered a risk factor for severe asthma.

The Heiner syndrome is a chronic pulmonary disease caused by non-IgE food allergy, particularly to cow's milk proteins during infancy. It is characterized by recurrent pneumonia, pulmonary infiltrates, iron deficiency anemia, and a failure to thrive in small children [48]. If the associated pulmonary vasculitis is severe, alveolar bleeding occurs and causes pulmonary hemosiderosis (iron deposits in the form of hemosiderin).

1.3.1.5. Adverse Reactions to Dietary Gluten. Cereals including wheat, barley, and rye are consumed in large quantities all over the world. Worldwide, cereal grains account for about 70% of protein consumption. The cereals form part of the Gramineae (grasses) family and are divided into four subfamilies: the Bambusoideae (rice), the Chloridoideae (including ragi and teff), the Panicoideae (most millets, maize, and sorghum), and the Pooideae, which are further divided into the Triticeae (wheat, barley, and rye) and the Aveneae (oats) [41].

The wheat grain comprises three major components: starch, protein, and fiber (cell wall polysaccharides), with proteins accounting for about 10–15% of the dry weight [41]. Gluten is a generic term used for the storage proteins from wheat, barley, and rye and is discussed in more detail under celiac disease (Section 1.4).

Dietary intake of gluten can cause distinct immunologically mediated adverse reactions manifesting with gastrointestinal symptoms. These include celiac disease, other non-IgE-mediated gluten induced clinical conditions, and IgE-mediated food allergy. The pathogenic mechanisms underlying these diseases are different. The coexistence of gluten-induced IgE and non-IgE-mediated reactions in one individual seems to be rare. Diagnosis and management are also different. Hence, establishing a differential diagnosis between cereal (e.g., wheat) induced IgE allergy, celiac disease, and other related non-IgE reactions (Section 1.4) is important for the management of these conditions [44, 55–57].

1.3.1.5.1. IgE-Mediated Wheat Allergy. Wheat is the cereal most often implicated in IgE cereal-induced food allergy. Dietary wheat allergy is observed in adults and children, and like other IgE-mediated food allergies, there is a risk of anaphylaxis [44, 55–57]. The best known IgE allergic response to wheat ingestion is wheat-dependent, exercise-induced anaphylaxis (WDEIA). WDEIA is the most common type of food-dependent, exercise-induced anaphylaxis (FDEIA) (Section 1.3.1.6). This syndrome is associated with one

major type of wheat gluten protein known as ω -gliadins. Other IgE-mediated allergic responses to dietary wheat include atopic dermatitis, urticaria, and anaphylaxis. These reactions may vary between populations and may be related to a wider range of wheat proteins and to nonspecific lipid transfer proteins. The other known type of allergy to wheat is baker's asthma, which results from the inhalation of flour and dust during grain processing [41].

1.3.1.6. FDEIA. FDEIA is a rare, potentially life-threatening condition reported in young, athletic individuals, especially women in late teens to mid-30s [40]. FDEIA can occur in two ways: anaphylaxis may occur when exercise follows the ingestion of a particular food to which IgE sensitivity can be identified (e.g., wheat, shellfish, fish, and celery) or, less commonly, 2–4 hours after the ingestion of these foods (postprandial anaphylaxis) in association with physical exertion. When food intake and exercise are independent of each other, there are no allergic symptoms. Although the pathogenesis of FDEIA is not yet known, multiple factors may be involved in eliciting or mediating these adverse reactions [58, 59]. For example, affected patients frequently identify hot and humid weather as an aggravating factor, and afflicted patients generally have asthma and/or other atopic disorders. Wheat gluten is the most common dietary protein associated with FDEIA.

1.3.2. Non-IgE and Mixed Food Allergy

In non-IgE-mediated food allergy, multiple inflammatory cells and their mediators play a role in the immunopathogenesis [2, 5, 6, 22]. These include activation of lymphocytes and recruitment of eosinophils and mast cells. Other immune-mediated factors such as immune complexes formed by food and food antibodies or cell-mediated immunity have been suggested as the mediating mechanism. In non-IgE-mediated disorders (Table 1.1), clinical manifestations of adverse reactions usually become evident hours to days after exposure to the dietary protein (*allergen*). Symptoms and signs may include diarrhea, vomiting, protein-losing enteropathy, rectal bleeding, and enterocolitis [2, 5, 6, 25]. Growth retardation may also be seen in some children. Milk and soy are the most common eliciting foods [21, 39, 45].

Non-IgE-mediated gastrointestinal allergic conditions include food protein-induced enterocolitis, allergic proctocolitis, and enteropathy (Table 1.1) [2, 5, 6, 25]. Celiac disease and DH are also considered non-IgE-mediated adverse reactions and are discussed separately in Section 1.4. Clinical disorders associated with non-IgE cell-mediated mechanisms, or with mixed IgE and non-IgE reactions, typically have delayed onset of symptoms (>2 hours) and a chronic, relapsing course. Therefore, the allergen cause–effect relationship may be difficult to establish.

In conditions such as allergic eosinophilic gastroenteropathy (allergic eosinophilic esophago-gastroenteritis, allergic eosinophilic esophagitis, allergic eosinophilic enterocolitis, dietary protein enterocolitis), IgE-mediated food

allergy often cannot be demonstrated. The presence of eosinophils alone is not conclusive evidence of food allergy. However, food has been incriminated as the cause in a subset of patients [2, 25, 60].

1.3.2.1. Eosinophilic Esophagitis. The American Gastroenterological Association Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition sponsored a systematic review that provides consensus recommendations for diagnosis and treatment of eosinophilic esophagitis in children and adults [60]. These authors define eosinophilic esophagitis as a primary clinicopathologic disorder of the esophagus, characterized by symptoms such as food impaction and dysphagia in adults, and feeding intolerance and gastroesophageal reflux disease symptoms in children. Children can also present with epigastric abdominal pain, dysphagia, and failure to thrive. The esophageal biopsy is characterized by high eosinophil count (≥ 15 eosinophils/high power field). Other disorders associated with similar clinical, histological, or endoscopic features, need to be excluded. The differential diagnosis includes conditions such as gastroesophageal reflux disease, Crohn's disease, hypereosinophilic syndrome, and drug hypersensitivity response. Appropriate treatments include dietary approaches based on eliminating exposure to food allergens [60].

Most studies characterizing the allergic phenotype of this condition have been performed in children [60]. The allergic etiology of eosinophilic esophagitis is based on several lines of evidence. The majority of patients with eosinophilic esophagitis (50–80%) are atopic. Usually, there is coexistence of atopic dermatitis, allergic rhinitis, and/or asthma and the presence of allergic antigen sensitization. Importantly, most patients improve on allergen-free diets, providing supportive evidence that antigenic dietary protein is eliciting the disease.

Evidence suggests that eosinophilic esophagitis is associated with T helper cell (Th2)-type immune responses. Elevated levels of Th2 cytokines (e.g., interleukin IL-4, IL-5, and IL-13) as well as mast cells are present in the esophagus of these patients. This view is further supported by experimental systems that demonstrate an intimate connection between the development of eosinophilic inflammation in the respiratory tract and esophagus not only in response to external allergic triggers but also to intrinsic Th2 cytokines [60].

1.3.2.2. FPIES. FPIES is an uncommon, pediatric, non-IgE-mediated disorder [45, 46]. The adverse reaction is triggered by dietary proteins with rice, soy, and cow's milk being the most common eliciting foods [45, 46, 49].

The pathophysiology of FPIES remains poorly understood. However, the most likely implicated mechanism is stimulation of T cells by food proteins in the gastrointestinal mucosa. The clinical presentation includes profuse vomiting and/or diarrhea about 2 hours after ingestion of the eliciting protein. Associated features may include pallor, lethargy, cyanosis, metabolic acidosis, and neutrophilia. The cutaneous or respiratory symptoms seen in IgE food allergies are often absent. Most children recover within a few hours, but there is up to 20% of them that may present with a hypovolemic shock. The diag-

nosis and link to food adverse reaction is often missed, due to the delay in the presentation of symptoms after food intake. The moribund appearance that many children have at presentation is often attributable to sepsis, a metabolic disorder, or a surgical abdominal emergency. Most children develop tolerance to the triggering food by 3 years of age. Although the most common presentation is acute, some children may present a chronic form of the condition characterized by chronic vomiting, diarrhea, and failure to thrive when continuously exposed to the offending food [25, 45, 49].

1.4. CELIAC DISEASE (CD) AND RELATED CONDITIONS

Celiac disease is a complex, systemic, autoimmune-mediated disorder, observed in genetically susceptible individuals in response to exposure to dietary gluten. It has been regarded primarily as a disease of the gastrointestinal tract and is characterized by chronic inflammation of the small intestinal mucosa [61–66]. This inflammation may result in atrophy of intestinal villi, malabsorption, and a variety of clinical manifestations [62, 63, 67–71]. Celiac disease has also been referred to as celiac sprue and gluten-sensitive enteropathy. More recently, the term “gluten syndrome” has been suggested to cover the myriad of extra-intestinal symptoms and clinical conditions described in association with celiac disease and the absence of gastrointestinal involvement in some cases [72]. These include neurological dysfunctions such as gluten ataxia and gluten neuropathy [97, 135].

The worldwide prevalence of celiac disease has been estimated to be between 1 in 100–200 individuals [63, 64, 73, 74]. Certain groups of people have markedly elevated risks of developing celiac disease. First-degree relatives of individuals diagnosed with celiac disease have a 10–20% increased risk of developing celiac disease [29, 75, 76]. A high prevalence of celiac disease is also found in individuals with Down syndrome, diabetes type 1 and IgA deficiency [65, 77, 78].

Celiac disease can be present in both silent and symptomatic forms affecting survival and risk of complications [79]. Silent celiac disease is characterized by positive serology and limited involvement of the gastrointestinal tract. Latent celiac disease includes individuals who are positive for serological markers or genetic susceptibility to disease but no pathology on biopsy. These individuals are asymptomatic but may later develop symptoms and/or histological changes [64, 79]. The difference between the number of clinically diagnosed celiac disease individuals with the vast amount of undetected cases has been described as the celiac disease iceberg, with those undetected lying beneath the surface. Gluten toxicity encompasses a wide spectrum of end target organ pathology, clinical disorders, and mechanisms involved [80, 81, 135, 136].

The clinical manifestations of celiac disease are highly variable in both character and severity. They are influenced by factors such as age, immunologic status, exposure to gluten (amount, duration, or timing of introduction to gluten), and the extent and severity of damage caused to the gastrointestinal

tract [23, 61, 69, 70, 82–86] and other organs, for example, the nervous system [97, 135, 136]. The wide spectrum of clinical presentation results in frequent delays in diagnosis, and/or misdiagnoses [71, 85, 87]. Common examples of misdiagnoses include irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia [85].

Celiac disease can present with gastrointestinal, or “classic,” and nongastrointestinal manifestations. Infants and children are more frequently afflicted with gastrointestinal manifestations including diarrhea, abdominal distension, or symptoms of malnutrition such as anemia [63–66, 69, 70, 88, 89]. For adults, non-specific gastrointestinal complaints are common and include abdominal pain, flatulence, diarrhea, and, in severe cases, steatorrhea [63–65, 69, 71, 85, 88, 90].

Celiac disease is associated with various extraintestinal disorders and complications in addition to gastrointestinal symptoms and is therefore considered a multisystem disorder [68, 82, 84, 91]. Patients with celiac disease also have an increased risk of developing other autoimmune diseases, such as type 1 diabetes mellitus [78, 84, 86].

Nongastrointestinal manifestations are more insidious, are highly variable, and are the common presenting symptoms in older children and adults. These manifestations are either the result of long-term nutrient malabsorption and/or are part of the autoimmune systemic spectrum [65, 69, 81, 85, 86, 92, 93]. In children, nongastrointestinal manifestations may include short stature, enamel defects, neurological developmental delays, and delayed puberty [63, 66, 70, 94–96]. Many celiac patients experience neurological symptoms, frequently associated with malfunction of the autonomic nervous system, cerebella ataxia, learning disorders, depression, migraine, and headache [97, 135]. The absence of an enteropathy should not preclude patients from treatment with a gluten-free diet [97, 135].

In addition to neurological symptoms, there are many long-term consequences and complications for individuals undiagnosed, untreated, or undertreated [83, 93, 98–100].

Celiac disease is a lifelong condition. If celiac disease is not diagnosed early and treated with a strict gluten-free diet, it can be associated with serious complications, including osteoporosis, increased risk of fractures, recurrent miscarriage and infertility in both sexes, malignancy such as small bowel lymphoma, and higher mortality rate [79, 85, 92, 101–103]. Of special concern is the association of long-term untreated celiac disease with malignancy. These malignancies include small bowel lymphoma and both Hodgkin’s and non-Hodgkin’s lymphoma. Refractory celiac disease, which occurs when both symptoms and intestinal damage persist or recur despite strict adherence to a gluten-free diet, is associated with increased risk of lymphoma and high mortality [103].

1.4.1. Dermatitis Herpetiformis (DH)

DH is a condition of the skin that is also triggered by the ingestion of gluten in genetically susceptible individuals and is considered the dermatological form

of celiac disease [23, 24, 88, 104]. DH is a chronic papulovesicular skin disorder in which lesions are symmetrically distributed over the extensor surfaces of the elbows, knees, and buttocks [23, 24, 88, 104]. The disorder is associated with a specific non-IgE-mediated immune sensitivity to gluten. A majority of DH patients have IgA specific for epidermal transglutaminase (TGe) and closely related tissue transglutaminase (tTG), and both TGe and tTG are considered to be autoantigens [105]. The concentration of these antibodies in these patients is reported to be independent of the degree of villous atrophy [105]. The test for establishing the diagnosis of DH is a biopsy from uninvolved skin for the detection of IgA [106]. Classically, in DH, there is granular IgA deposition along the dermo-epidermal junction with concentration at the papillary tips.

Patients with DH often do not have associated gastrointestinal symptoms. The extent of involvement of the small bowel varies, and 20% show apparently normal mucosa, but inflammatory changes consistent with celiac disease are present in most cases [107, 108]. The treatment of this condition includes a gluten-free diet, which helps to recover the injured small bowel and controls the rash even in those who do not have an abnormal small bowel biopsy [107, 108]. Other skin disorders such as psoriasis or vitiligo can also be seen in celiac disease [23, 109].

1.4.2. Genetic Factors in Celiac Disease

Although the etiology of celiac disease is not fully understood, it is considered to be an autoimmune disease with tTG suggested as the major autoantigen. The current consensus is that celiac disease is associated with human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes [63, 69, 110, 111]. Virtually all celiac individuals express HLA-DQ2 or HLA-DQ8. These two class II molecules are chiefly responsible for the presentation of gluten peptides to the gluten-specific T cells that are found only in the gut of celiac patients. These predisposing HLA-DQ molecules bind enzymatically modified gluten peptides, and these HLA-DQ peptide complexes trigger inflammatory T-cell responses in the small intestine. In addition, gluten induces innate immune responses that contribute to the tissue damage that is characteristic of this condition (Figs. 1.2 and 1.3) [69, 112–115]. Thus, a combination of adaptive and innate immune responses triggered by gluten has been implicated as the cause of the clinical presentation of the disease (Fig. 1.4) [69, 111, 113]. Continued gluten exposure makes the adverse immune reactions self-perpetuating and increases the risk of serious complications [69, 111, 113].

However, many people with similar risk factors do not develop celiac disease. This suggests a multifactorial etiology [63, 64, 69]. Other genetic and environmental factors have been implicated in playing a role in the manifestation of this disease, such as gastrointestinal infections and stress [116, 117]. Regardless of the possible confounding etiological factors, it is agreed in the literature that early diagnosis and dietary treatment can prevent severe, sometimes life-threatening, complications.

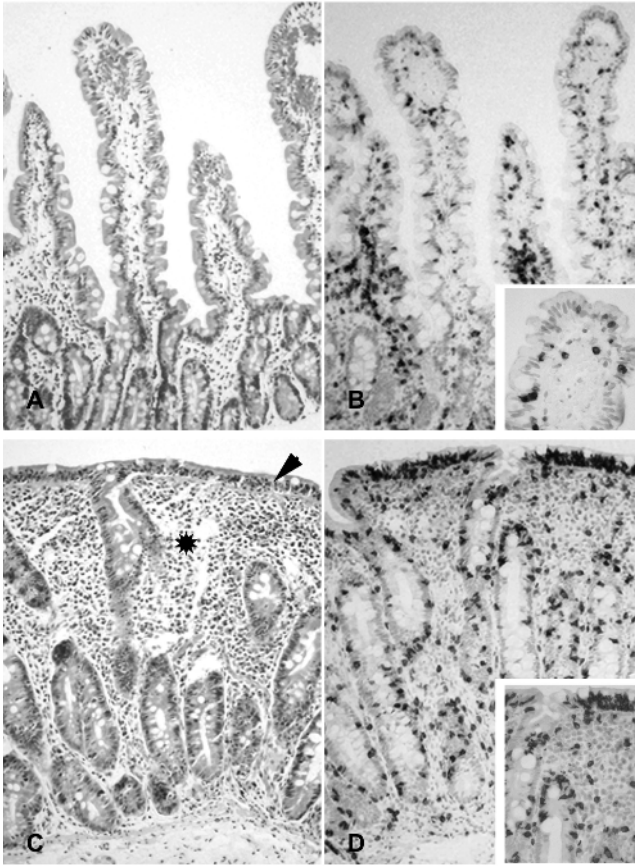


Fig. 1.2 Microscopic view of small intestinal biopsy stained with haematoxylin and eosin (A,C) and with CD3 immunohistochemistry (B,D). From Dr. Mohsin Rashid. A and B show the normal mucosa of the small bowel with well-maintained architecture, easily seen villi, and sparse CD3+ intraepithelial lymphocytes (IELs). Inset shows the tip of the villi. C and D are sections from the small bowel of an untreated celiac individual showing injured mucosa, characterized by villous atrophy (arrow), absence of villi, crypt hyperplasia, dense inflammatory infiltrate (asterisk), and marked increase of CD3+ IELs best seen at the upper portion of the mucosa D (insert).

1.4.3. Gluten and the Pathogenesis of Celiac Disease

1.4.3.1. Gluten Proteins. The major endosperm storage proteins of most cereal grains are prolamins [118]. Approximately 80% of the total grain protein is accounted for by this major storage protein fraction [41]. Early classification based on extraction in a series of solvents, defined four protein fractions, which are extracted sequentially in water (albumins), dilute saline (globulins), alcohol/water mixture (prolamins), and dilute acid (glutenins). Prolamins of

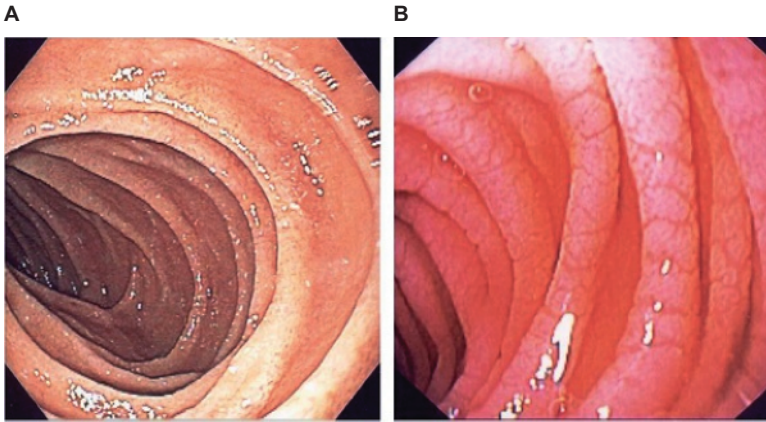


Fig. 1.3 Endoscopic view of the duodenum. (A) Normal (right). (B) Untreated celiac patient showing scalloping of the mucosal folds (left). From Dr. Mohsin Rashid.

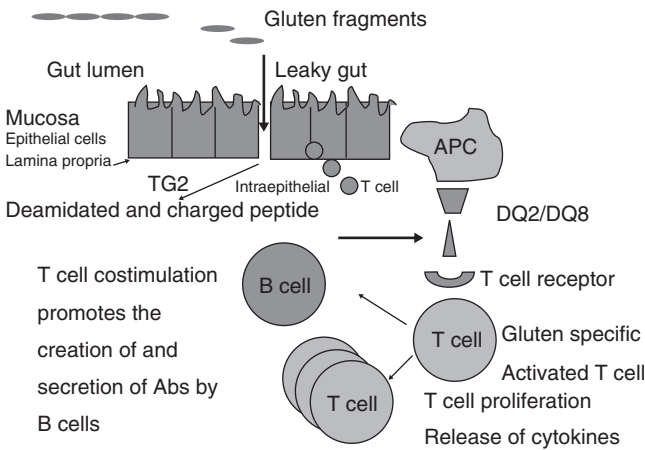


Fig. 1.4 Schematic representation of the immunopathology of celiac disease (CD). CD involves a complex interplay of many factors, including environmental, genetic, and immunologic. Under certain conditions, incompletely digested peptides of gluten from wheat, barley, and rye can cross the epithelium in the mucosa of the small intestine. Factors such as gastrointestinal infections may affect the permeability of the mucosa (leaky gut). After absorption, glutamine residues from gluten peptides are converted to negatively charged glutamic acids through deamidation by tissue transglutaminase (tTG2). Antigen-presenting cells (APCs) expressing the human leukocyte antigens HLA-DQ2 and HLA-DQ8 have an increased affinity for these deamidated peptides, resulting in peptide complexes that can activate a range of inappropriate immunogenic responses including reactivity against host tissues. Both innate and adaptive immune responses are involved, including antibodies (Abs) to gluten and to tissue proteins, for example, IgA anti-transglutaminase, T cell reactivity to gluten, increased number of intraepithelial T cells, and increased cytokines that can in turn promote inflammation and villous damage in the small intestine. tTG is pivotal in the pathogenesis of CD and is the main autoantigen.

the Triticeae (wheat, barley, and rye) comprise three broad groups: (1) sulfur-rich (S-rich): α/β -gliadins, γ -gliadins, B- and C-type low-molecular-weight (LMW) subunits of glutenin; (2) sulfur-poor (S-poor): ω -gliadins and D-type LMW subunits of glutenin; and (3) high-molecular-weight (HMW) subunits [41, 118].

Wheat proteins are cohesive with each other in wheat dough, giving elasticity to the dough called “gluten” [41, 118]. It is the gluten in wheat flour that binds and gives structure to bread, baked goods, and other foods, making it widely used in the production of many processed and packaged foods. The alcohol-soluble fractions from barley (hordein) and rye (secalin) have similar amino acid sequences to wheat (gliadin), but they lack the cohesive ability of wheat gluten [119]. Nonetheless, the term “gluten” encompasses the homologous prolamins of wheat, rye, barley, and related cereals [119]. Hence, gluten is a generic name given to storage proteins in wheat, barley, rye, and other closely related cereal grains.

The alcohol-soluble fractions (prolamins) of wheat (gliadin), rye (secalin), and barley (hordein) are considered to be the protein constituents of most concern to celiac individuals. The wheat gliadins are monomeric proteins and are classified on the basis of their electrophoretic mobility at low pH: these are α/β -gliadins (fast), γ -gliadins (intermediate), and ω -gliadins (slow). The glutenins are polymers of individual proteins linked by interchain disulfide bonds and include HMW and LMW groups after separation by gel electrophoresis [41]. The presence of amino acid sequences consisting of repeated blocks of peptide motifs is responsible for the high proportions of glutamine (Q), proline (P), and other specific amino acids in some prolamin groups. These proteins consist almost entirely of repetitive sequences rich in glutamine (Q) and proline (P) (e.g., PQQPFPQQ) [120]. The repetitive units of α/β -gliadins are dodecapeptides such as QPQFPQQPYP, which are usually repeated five times and modified by the substitution of a single residue [120]. The typical unit of γ -gliadins is QPQQPFP, which is repeated 16 times and interspaced by additional residues. The total wheat gluten protein is characterized by ≈ 28 – 33% of α/β -gliadins units and ≈ 23 – 31% of γ -gliadins [120]. The distribution of total gliadins among different types is strongly dependent on wheat variety (genotype) and growing conditions (soil, climate, fertilization) [120].

The glutenin fraction comprises proteins linked by disulfide bonds and their molecular weight distribution has been recognized as one of the main determinants of dough properties and baking performance [120]. After the reduction of disulfide bonds, the resulting glutenin subunits show solubility in aqueous alcohols similar to gliadins. The predominant protein type are LMW glutenin subunits (LMW-GSs) representing $\approx 20\%$ of the total gluten protein, whereas the HMW (HMW-GS) represents $\approx 10\%$ of the gluten proteins [120]. The LMW-GSs are related to α/β - and γ -gliadins in molecular weight and amino acid composition. They consist of an N-terminal domain rich in repetitive glutamine (Q) and proline (P) units (e.g., QQQPPFS), and a C-terminal

domain homologous to that of α/β - and γ -gliadins. Both wheat prolamins (gliadins) and glutenins subunits (LMW-GS and HMW-GS) are characterized by high glutamine and proline content, all having protein fragments of concern to individuals with celiac disease [119–122].

1.4.3.2. Gluten and Celiac Disease. Gluten is partially digested by humans. A 33-amino acid peptide molecule (33mer) and other immunogenic peptides remain after the action of gastric, duodenal, and pancreatic enzymes. It is this fragment (33mer) α_2 -gliadin 57–89 (LQLQPFQPOLPYQPQLPYQPQLPYQPQPF) that is considered to elicit the immune response in genetically susceptible individuals [123] and can bind to the DQ molecule [124]. The 33mer contains partly overlapping copies of specific T-cell epitopes [125], which are PFQPQLPY, PQPQLPYQ (three copies), and PYPQQLPY (two copies) [123]. HLA-DQ2 binds to the ligands via anchor residues that are at positions 1, 4, 6, and 9 [119]. Molecules acting as DQ2 ligand have selectively large hydrophobic residues both at the terminal positions 1 and 9. Glutamate residues (E) formed by tTG-mediated deamidation in positions P4 and P6, and rarely in P7, are required for T-cell recognition [119, 124]. The T-cell stimulatory gluten sequence is a 9-amino acid peptide, and the ideal sequence is (PQ)₁, X₂, X₃, Q₄, X₅, P₆, Q₇, P₈, X₉. The presence of at least two P in epitope sequence is necessary for the peptide to survive the gastrointestinal digestion [119]. Gluten sequence with 10 amino acid peptides and a P in position 1 can also bind the DQ2 molecule. The binding motif of DQ8 also displays a preference for binding negatively charged residues at several positions, for example, P1, P4, and P9 [126]. Hence, both DQ2 and DQ8 molecules share a preference for negatively charged residues at some of the anchor positions.

It is unclear how the toxic and immunogenic peptides enter the intestinal mucosa [119]. Many factors and mechanisms have been investigated [69, 91, 110, 111, 117, 126]. For individuals with celiac disease, undigested gluten protein fragments trigger an immune-mediated adverse response resulting in an inflammatory injury in the mucosal surface (site of absorption) of the small intestine [69, 112–114, 119]. This results in malabsorption of protein, fat, carbohydrate, fat-soluble vitamins, folate, and minerals, especially iron and calcium [69, 83, 111, 127].

Although the precise molecular mechanisms of the toxic reaction to gluten are not fully elucidated, the primary event requires that the gliadin oligopeptides gain access to their antigen-binding sites, presumably within the lamina propria region interior to the relatively impermeable surface of the intestinal epithelial layer (Fig. 1.4) [91, 126, 128]. Ordinarily, such oligopeptides, generated through the action of pancreatic proteases, are efficiently hydrolyzed into amino acids, di-, or tripeptides by peptidases located in the brush-border membrane of the intestinal enterocyte before they can be transported across the epithelial layer. Homologous gluten proteins from wheat, rye, and barley are rich in proline (P) and glutamine (Q). The large amount of P residues

in the sequence of these proteins, blocks the cleavage of the polypeptide by gastrointestinal enzymes at positions immediately next to P [119, 126]. The size of the digested peptides and the position of the Q residues in the primary structure of the peptides, both play a pivotal role in their capacity to elicit an immune-mediated response in individuals with celiac disease [119, 126].

Under certain conditions, the partially digested peptides of gluten from wheat, or their homologous epitopes from barley and rye, can cross the epithelium in the mucosa of the small intestine [91, 113, 126]. Factors such as gastrointestinal infections may affect the permeability of the mucosa (leaky gut) [116, 117]. After absorption, glutamine (Q) residues from gluten peptides are converted to negatively charged glutamic acids (E) through deamidation by transglutaminase-TG2, which is mainly localized in the lamina propria [126, 128]. The affinity of gliadin peptides for tTG depends on the relative position of Q residues and on the amino acid located nearby the target amino acid, particularly P [119, 124, 126, 129]. Once the gluten-derived peptide enters into the immunologic compartment of the intestinal mucosa and gets deamidated by tTG, it binds to the DQ2/8 molecule on the antigen-presenting cell (APC) membranes (Fig. 1.4) [126]. These APCs expressing the HLAs HLA-DQ2 and HLA-DQ8 have an increased affinity for these deamidated peptides, resulting in peptide complexes that can activate a range of inappropriate immunogenic responses including reactivity against host tissues [68, 91, 110, 111, 126]. Both innate and adaptive immune responses are involved, including antibodies (Abs) to gluten and to tissue proteins, for example, IgA anti-transglutaminase, T-cell reactivity to gluten, increased number of intraepithelial T cells, and increased cytokines that can in turn promote inflammation and villous damage in the small intestine (Figs. 1.2–1.4) [111–113, 126].

1.4.3.3. Grains of Concern and Gluten Threshold. Presently, the only treatment of celiac disease is a strict lifelong exclusion of wheat, rye, barley, and other related cereal grains from the diet [87, 93, 130]. The amount of gluten that can be tolerated varies among people with celiac disease. Some individuals tolerate an average of 34–36 mg of gluten per day without any clinical manifestations of celiac disease, while others who consume approximately 10 mg of gluten per day developed mucosal abnormalities [131, 132]. Although there is no evidence to suggest a single definitive threshold for a tolerable gluten intake, there is evidence that a daily gluten intake of <10 mg is unlikely to cause significant histological abnormalities in the small bowel mucosa [131, 132]. Little is known about thresholds for those with other gluten-induced conditions [135, 136].

The taxonomy and biochemistry of the cereal is relevant to its potential toxicity [119, 121, 126, 127]. Cereal grains that are known to trigger celiac disease/DH reactions include the following: wheat (including durum wheat or “durum,” spelt wheat or “spelt,” kamut), barley, rye, triticale, bulgur, einkorn, emmer, and farro [85, 87, 130].

The introduction of oats in the diet of celiac individuals has been a source of controversy. However, we have recently conducted a systematic review on the safety of oats in celiac disease and concluded that most celiac individuals can tolerate moderate amounts of pure oats, not contaminated with gluten from wheat, barley, and rye [133]. Wheat, rye, and barley have a common ancestral origin in the grass family, whereas oats are more distantly related to wheat, rye, and barley. The oat prolamins (avenin) have substantially lower proline content. Avenin accounts for 5–15% of the total protein in oats, whereas in wheat, barley, and rye, prolamins constitute 40–50% of the total protein [120, 121].

1.5. CONCLUSIONS

The significance of food allergy to public health has been recognized by the World Health Organization (WHO) and other food safety authorities. An expert group appointed by the Food Allergy Task Force of the International Life Sciences Institute ILSI Europe proposed a revised set of criteria together with a framework to help to decide which allergenic foods are of sufficient public health importance to be included in allergen lists [30]. The criteria include the demonstration of an IgE-mediated adverse reaction, estimates of the prevalence, severity of reactions, allergenic potency of the food and the extent, pattern, and nature of exposure to the food. In their proposed framework, the first stage is to assess the available evidence to decide whether or not the allergen in question induces an IgE-mediated food allergy. The public health importance given to IgE-mediated food allergy is due to the high prevalence and potential acute severity of the condition. However, this set of proposed criteria (diagnosis, potency of allergenic protein, severity of reactions, prevalence, exposure, and modulating factors such as food processing) could also be applied when assessing the risk of dietary proteins triggering non-IgE and mixed adverse reactions. Of particular relevance are gluten proteins from wheat, barley, rye, and closely related cereals, which can elicit both an IgE-mediated (e.g., wheat allergy) and a non-IgE-mediated immune response (celiac disease, DH), depending on the genetic susceptibility of the population. Gluten proteins from wheat, barley, rye, and related cereals are also included in allergen priority lists by regulatory authorities, including Canada (<http://www.hc-sc.gc.ca/fn-an/label-etiquet/allergen/index-eng.php>).

Food allergies, both IgE- and non-IgE-mediated, are important health concerns to consumers who are predisposed to these illnesses. Food allergies are known to impose a significant impact on the daily life of those affected, their families, and communities [87, 134]. The present-day diagnosis of various disorders elicited by dietary proteins can be impeded by intrinsic limitations in generating accurate information from patient history, diagnostic criteria, and methods. Distinguishing among the various conditions elicited by adverse

reaction to food proteins is important in the management of these disorders [2, 6, 11]. Food allergy encompasses a variety of clinical conditions with diverse underlying mechanisms presenting in many instances with common symptoms, for example, gastrointestinal symptoms. Increased awareness of the clinical presentations, and the foods eliciting these adverse reactions, is the first step in the identification of cause–effect and in the management of these conditions.

Employing food process technologies to eliminate food constituents, which can be harmful to susceptible individuals, is a potentially viable approach for reducing risk to food-related disorders. The development of practice guidelines and standardization of diagnostic tests, methods for food testing, approaches to establishing thresholds, food labeling policies, and regulations are all positive steps toward the diagnosis, prevention, and management of adverse food reactions in hypersensitive individuals [2, 13, 18]. A continued joint effort is needed from the public, the food industry, governments, health-care providers, researchers, and others to support the needs of these consumers by minimizing risk while maximizing the availability of healthy foods.

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