

Pollen Food Syndrome: Update on the Allergens

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Pollen food syndrome results from cross-reactivity between pollen-specific IgE and homologous proteins found in fruits and vegetables. These proteins can be grouped into several categories based on structure and include profilins, pathogenesis-related proteins, and cross-reactive carbohydrate determinants. Although cooking the reactive fruits and vegetables has been shown to destroy IgE-binding epitopes, evidence suggests that the remaining linear epitopes can bind cross-reactive T cells and enhance T-cell activation in vitro. Several methods of diagnosing food allergies exist, including skin prick tests and double-blind food challenges; however, diagnosing pollen food syndrome depends almost exclusively on clinical history. Immunotherapy has been studied as a treatment for pollen food syndrome, with highly variable results.

Introduction

Pollen food syndrome is a term describing associations between inhalant pollen allergies and oral symptoms upon ingestion of particular fruits, vegetables, and spices [1,2•]. Previously, pollen food syndrome had been called *oral allergy syndrome* by some authors; however, this term was used by others to describe oral symptoms caused by any food allergen unrelated to pollen allergy. Therefore, the term *pollen food syndrome* was adopted to clarify the relationship between pollen allergy and oral allergy [1,2•].

Estimates of the percentage of patients with pollen allergy who also suffer from pollen food syndrome vary from 47% to 70% [3]. Pollen food syndrome is the most common food allergy in adolescents and adults [3]. Symptoms result from contact of the fruit or vegetable with the oral mucosa and are classically localized to the oropharynx [3,4]. Pruritus and angioedema of the lips, oral mucosa, and

soft palate are the most common symptoms [2•,4,5]. Rarely, patients may experience systemic symptoms after ingesting a particular fruit or vegetable [4]. This is especially the case in the mugwort-celery-spice syndrome [2•,4].

The association of oral symptoms and pollen allergy results from cross-reactivity of pollen-specific IgE with homologous food allergens [2•,6]. Several lines of evidence—including animal studies—and similar geographic location of pollen and allergy to fresh fruits and vegetables indicate that the initial event is sensitization to pollen with subsequent development of cross-reactivity to food allergens [1,2•]. Furthermore, patients often report the development of pollen allergies before the development of oral symptoms. Also, birch pollen-allergic patients with pollen food syndrome had higher birch pollen and total IgE levels and a longer history of pollen allergy than those without pollen food syndrome [7]. Thus, pollen food syndrome is considered a class II food allergy, as the sensitizer is pollen and the elicitor of symptoms is a food allergen [2•,6,8].

Cross-Reactive Pan Allergens

Pollen food syndromes develop as a consequence of shared epitopes in the primary and tertiary structures of pollen and food allergens [2•]. The pollens and foods involved usually are not botanically related but contain conserved homologous proteins [1,2•]. These plant proteins are often referred to as *pan allergens* because they are widely distributed throughout the plant kingdom and are involved in the extensive IgE cross-reactivity between antigens from unrelated plant species [3,9]. Several families of plant proteins have been shown to be involved in pollen food syndrome, including profilins, pathogenesis-related proteins (PRs), and lipid transfer proteins.

Profilin is a monomeric, actin-binding protein that regulates the organization of the actin filaments to form the actin cytoskeleton [8,10,11]. Patients who are sensitized to pollen profilins react to a broad range of inhalant and food allergens. Profilins are prominent allergens in pollens of trees, grasses, and weeds and are recognized by 20% of pollen-allergic patients [10,11]. Therefore, profilins are considered ubiquitous cross-reactive plant allergens. An example is the birch pollen allergen Bet v 2. Patients

who are sensitized to Bet v 2 often have symptoms upon ingesting apple, pear, carrot, and celery in response to IgE cross-linking by homologous profilins found in these foods [8]. Similarly, patients with allergies to grass pollen profilin often have oral symptoms in response to eating celery and carrots, which contain similar profilins [8]. In the mugwort-celery-spice syndrome, patients sensitized to mugwort cross-react to profilins in celery and spices of the Apiaceae, or Umbelliferae, family (carrots, caraway seeds, parsley, coriander, aniseed, or fennel seeds) [2•,8]. Although many pollen food syndromes are related to profilins, it is difficult to purify natural profilins from fruits and vegetables, and only a few isolated, recombinant profilins have been reported [9].

Another group of pan allergens are the PRs. These proteins are related to the defense responses of higher plants and are induced upon infection, wounding, or environmental stresses (eg, drought, flooding, freezing temperature, and ozone) [12]. Some are also constitutively expressed in organs (eg, the seed during certain developmental stages) [13]. Of the plant allergens listed in the Official Allergen Database of the International Union of Immunological Societies, approximately 25% belong to the group of PRs [14]. These proteins are small (with molecular weights of 5–70 kD), stable at low pH, and resistant to proteolysis [12,13]. They have been classified into 14 PR families based on similarities in their amino acid sequence, enzymatic activities, or other functional properties [12]. Plant-derived allergens have been identified with sequence similarities to PR families 2, 3, 4, 5, 8, 10, and 14 [13,14].

Plant strains express different amounts of PRs depending on the environmental conditions in which they grow. Plants with higher levels of these proteins may have a selective advantage and often are chosen for widespread agricultural use [12]. In addition, chemicals and pesticides applied to plants may increase PR expression [12,13]. Furthermore, ripeness and storage conditions affect PR content (ripening seems to increase expression) [12]. This increased expression of the PRs may enhance the allergenicity of fruits and vegetables [12].

The PR-2 family consists of beta 1,3 glucanases that catalyze the hydrolytic cleavage of 1,3 beta-D-glucosidic beta 1,3 glucans, which are abundant components of the plant cell wall [13]. These proteins are expressed constitutively during pollen germination, tube growth, and seed germination and induced upon wounding, cold, ozone, and UVB exposure [13]. One of the latex allergens, Hev b 2, has sequence similarity to the beta 1,3 glucanases [8,12,13]. Cross-reactivity between Hev b 2 and beta 1,3-glucanase-like allergens in banana, potato, and tomato is responsible for the latex food syndrome seen in some patients [4,13].

The class I, II, and IV chitanases form the PR-3 family [13]. However, only class I chitanases have been associated with allergy [8,13]. These proteins hydrolyze chitin found in the exoskeletons of insects and the cell wall of fungi [8,13].

The class I chitanases have an N-terminal hevein domain that is shared by latex prohevein (Hev b 6.01) [8,13,15]. In addition, avocado, chestnut, and banana have been found to have sequence similarity to the class I chitanases [8,13,15]. This explains the cross-reactivity of latex-allergic patients to avocado, chestnut, and banana [15].

The PR-4 family consists of class I and class II chitanases [13], of which the major latex allergen, Hev b 6.01, is a member [8,13]. The N-terminal domain consists of the latex allergen Hev b 6.02, and the C-terminal domain consists of Hev b 6.03 [8,13]. Sequence homology has been found in turnips and elderberry [8,13]. Also, the wound-induced proteins from tomato and potato share sequence homology with Hev b 6.01 [8]. However, the contribution of these proteins to food allergy is unclear.

Thaumatococcal proteins are found in the PR-5 family. These proteins are named after the sweet-tasting protein thaumatin from the African shrub *Thaumatococcus daniellii* [12,13,15]. They are thought to be antifungal proteins that rapidly accumulate in high levels upon stress of the plant [8,14]. They also seem to give plants resistance against freeze and drought [12]. The full function of the thaumatin-like proteins has not been defined. Mal d 2, the minor allergen of apple, and Pru av 2, the major allergen of cherry, have been shown to be homologous to the thaumatin-like proteins [8,12,13]. Cap a 1, from paprika and bell pepper, and Jun a 3, from mountain cedar, are also members of this family [12].

The PR-8 family of proteins consists of class III chitanases and contains minor allergens [8]. Hevamine, a protein from Hevea latex and a minor latex allergen [12,13], and cucumber chitinase are considered members of this group [14].

The PR-10 family is the most important PR family of proteins in pollen food syndrome. It consists of intracellular proteins with enzymatic activity of unknown function [13]. These proteins are widespread throughout the plant kingdom and highly conserved [13]. Their expression is induced upon wounding, microbial infection, fungal infection, or stress [13]. Bet v 1, the major birch allergen, is a member of the PR-10 family of proteins [6,13,14]. Approximately 70% of birch pollen-allergic individuals suffer from pollen food syndrome and have IgE cross-reactivity to Bet v 1 and its food homologues [6,8,12,13]. Mal d 1, a PR-10 homologue and a major allergen in ripe apples, can cause oral symptoms in birch-allergic patients. Many members of the Rosaceae and Prunoideae fruits and the Apiaceae vegetables contain PR-10 homologues, including cherries (Pru av 1), apricots (Pru ar 1), pears (Pyr c 1), celery (Api g 1), carrots (Dau c 1), and hazelnuts (Cor a 1) [2•,4,13]. These proteins share a high degree of amino acid sequence similarity (28% to 67%) with the major birch allergen, Bet v 1 [10]. Bet v 1-specific IgE located on mast cells can bind these food allergens upon ingestion, causing mediator release and oral symptoms [16].

Lipid transfer proteins constitute the PR-14 family of proteins. These proteins transfer phospholipids from liposomes to mitochondria and have antimicrobial activities [2•,13,14]. Lipid transfer proteins are widespread throughout the plant kingdom. They are found on the outer cell layer of plant organs and are important allergens of the Prunoideae family of fruits, which includes peaches, apricots, plums, and cherries, and the Rosaceae fruits (eg, apples and pears) [2•,13]. Lipid transfer proteins often cause food allergy to fruit in the absence of pollen allergy. However, mugwort pollen lipid transfer protein has been shown to cross-react with peach lipid transfer protein and may be involved with the mugwort peach allergy association frequently seen in the Mediterranean [17]. Patients who have allergy to PR-14 allergens in fruit have been shown to have a higher rate of anaphylaxis (36%) than patients who have PR-10 fruit allergies (18%) [12,14].

Controversy exists regarding the role of cross-reactive carbohydrate determinants in pollen food syndromes. The N-linked carbohydrate groups of glycoproteins induce IgE, leading to cross-reactivity between foods and pollens [11,18–20]. These cross-reactive carbohydrate determinants are present on the glycoproteins of vegetables such as celery, tomato, peanut, and potato and in ragweed, timothy grass, and birch pollen [2•]. However, debate continues over whether these cross-reactive carbohydrate determinants can cause clinical symptoms [11]. Many glycoproteins carry only one IgE-binding glycan and therefore cannot cross-link IgE bound to receptors and cannot induce activation of mast cells and basophils [19]. However, other glycoproteins have been identified that contain more than one N-linked glycan [19]. In one study by van der Veen and van Ree [18], 29 of 32 patients with grass pollen allergy, positive IgE to peanut, negative skin prick tests to peanut, and no oral symptoms upon peanut ingestion were found to have IgE to the cross-reactive carbohydrate determinants of peanut. Upon further analysis, this cross-reactive IgE had low biologic activity. In another study, 25% of celery-allergic patients were shown to have IgE to cross-reactive carbohydrate determinants [18]. In a study by Foetisch et al. [20], the sera of 4 of 10 tomato-allergic patients with IgE to cross-reactive carbohydrates showed biologic activity in the basophil histamine release assay with tomato glycoproteins only. The sera failed to react to nonglycosylated, recombinant tomato proteins [20]. Because of the variability of biologic activity of cross-reactive IgE to carbohydrates, the debate over their importance in allergy continues.

Diagnosis

Diagnosing pollen food syndrome is complicated by several issues. Commercially available fruit and vegetable extracts are highly heat labile and easily degradable [2•,4,8]. They often lose their potency and sensitivity when used in skin prick tests [2•,8]. This has led many people to perform prick-prick skin tests with the suspected fresh fruit or veg-

etable. Anhej et al. [21] evaluated grass pollen- or birch pollen-allergic patients with pollen food syndrome for clinical sensitivity using skin prick tests or basophil histamine release assays with fresh fruit. The study showed that in grass pollen- or birch pollen-allergic patients with confirmed oral allergy symptoms to apple, hazelnut, or melon, the diagnosis was best obtained with case history and skin prick tests with fresh fruit. In this study, skin prick tests had a negative predictive value of greater than 90% [21]. However, other studies have shown that skin prick tests and in vitro IgE levels are poor predictors of clinical sensitivity and pollen food syndrome in patients with grass-pollen or birch-pollen allergy [2•,22]. These patients may have cross-reactive IgE that does not result in clinical symptoms. It has been suggested that a panel of cross-reactive allergens in recombinant form could be used to classify patients as allergic to the PR-10 family or to profilins [8].

Double-blind, placebo-controlled food challenges are considered the gold standard to diagnose food allergy. However, there are several problems with using the double-blind, placebo-controlled food challenge to diagnose pollen food syndrome. One is that fruits and vegetables may contain varying amounts of the allergen depending on their growth conditions and ripening stage [12]. Another is that lyophilization, a process usually used in the insertion of food into capsules, may destroy the relevant fruit or vegetable allergen [4]. Third, ingesting the food in a capsule bypasses the oral mucosa, and the allergen may be degraded upon release in the stomach by gastric acid and gastric enzymes and thus fail to cause symptoms [4]. Therefore, clinical history is key in diagnosing pollen food syndrome.

Management

Pollen food syndrome is managed in several ways, depending on the clinician. One survey of allergists on managing oral allergy syndrome found that 53% recommended complete avoidance of the offending foods, 9% did not advocate food restrictions, and 38% reported giving different recommendations based specifically on each patient [22]. Also, 4% of clinicians recommended avoiding potentially cross-reactive foods [22]. Studies have assessed cross-reactivity, particularly in the Rosaceae family of fruits. Anywhere from 46% to 63% of patients with confirmed pollen food syndrome to one fruit have been shown to have clinical reactivity to other Rosaceae fruits [23]. Based on these studies and others, Rodriguez et al. [23] recommended that if a reported reaction is confirmed, tolerance to other Rosaceae fruits, particularly apricot, apple, and plum, should be evaluated unless the patient has eaten them without symptoms after the initial reaction.

Patients with pollen food syndrome generally tolerate cooked forms of the fruit or vegetable to which they are allergic, and allergists often recommend that they cook reactive fruits and vegetables before ingesting them [16,24•]. Thermal processing of PR-10-like food proteins causes

denaturation of the proteins and loss of conformational structure that translates into loss of IgE binding ability [16,24•]. Therefore, thermal processing makes these foods clinically tolerable. Bohle et al. [24•] found that cooked food allergens quickly lost the capacity to bind IgE and to cause mediator release. However, these same cooked food allergens retained their ability to stimulate Bet v 1-specific T cells [16,24•]. T-cell epitopes are short, linear peptides that tend to survive gastrointestinal digestion and thermal processing [16]. This may be important for several reasons. One is that patients with atopic dermatitis and pollen food syndrome who eat cooked fruits and vegetables may experience an exacerbation of their atopic dermatitis from activation of Bet v 1-specific T cells that can migrate to the skin and induce effector responses [16]. Second, ingestion of cooked fruits and vegetables may cause perennial activation of pollen-specific T cells and B cells, leading to maintenance of perennially increased allergen-specific IgE levels in pollen-allergic patients outside the pollen season [7,24•].

Allergy to pollen is often treated with subcutaneous immunotherapy. As clinical symptoms of pollen food syndrome relate to cross-reactivity of food allergens to pollen IgE, it was hypothesized that immunotherapy for pollen allergy also may treat pollen food syndrome. Several studies have addressed this issue in regard to birch pollen and pollen food syndrome, with varying results. Asero [25] conducted one of the most successful studies. In this study, 84% of birch pollen-sensitive patients with pollen food syndrome to apple who were treated with birch pollen subcutaneous immunotherapy reported a significant reduction or disappearance of oral symptoms to apples [25]. In addition, 88% of these patients experienced a marked reduction in their reactivity to skin prick tests with apple [25]. In another study, 87% of birch-allergic patients with pollen food syndrome who were treated with subcutaneous immunotherapy could eat significantly more apple or hazelnut with no resulting symptoms or signs. However, the amount of apple or hazelnut tolerated remained small [26].

In contrast to the above studies, Moller [27] found that during the course of subcutaneous or oral birch-pollen immunotherapy in a cohort of birch pollen-allergic children with pollen food allergies, no significant improvement was observed in the food allergy symptoms as compared with a control cohort. However, their pollen-related rhinoconjunctivitis improved substantially [27]. In another study of birch subcutaneous immunotherapy and apple allergy, 2 of 12 patients developed pollen food syndrome, and 5 of 12 developed IgE to Bet v 2 at some point during therapy [28]. There was no evidence of pollen food syndrome or Bet v 2 IgE in controls who did not undergo birch immunotherapy [28]. These authors concluded that it was possible to induce allergies to additional components in pollen immunotherapy preparations that may cause new symptoms (eg, pollen food syndrome) [28].

Other investigators examined the effects of sublingual immunotherapy with birch pollen on pollen food syn-

drome to apple to clarify the hypothesis that administering birch pollen at the site of food allergic symptoms may enhance the therapeutic efficacy in pollen food allergy. No improvement in oral symptoms to apple ingestion was noted in nine patients with improved nasal provocation scores to birch pollen after sublingual immunotherapy [29•]. Therefore, debates continue on the therapeutic benefits of pollen immunotherapy for pollen food syndrome.

Conclusions

Pollen food syndrome affects up to 70% of patients with birch pollen allergy. Prevalence will likely continue to increase as the prevalence of inhalant allergies rises. Homologous proteins in fruits, vegetables, and pollens of grasses, trees, and weeds are responsible for pollen food syndrome. As environmental conditions change and cultivation practices select for more resistant plants, increased expression of these homologous proteins may occur in fruits and vegetables, leading to increased allergenicity of these foods. Currently, there is no proven therapy for pollen food syndrome. Avoidance is the only option for affected patients. Given the likelihood that more people will experience pollen food syndrome in the near future, it is important that we investigate new therapies for this disease.

Disclosures

Dr. Burks serves as a consultant for Novartis, McNeil Nutritionals, and Mead Johnson Nutritionals; is a minority stockholder in Allertein Therapeutics and MastCell; serves on the advisory board for Dannon Co. Probiotics; serves on the speakers' bureau for EpiPen/Dey; serves on the data monitoring committee for Genentech; serves on an expert panel for Nutricia; has received grants from the National Institutes of Health, Food Allergy and Anaphylaxis Network, Gerber, and Mead Johnson Nutritionals; has held a volunteer position on the medical board of directors for the Food Allergy and Anaphylaxis Network; has held a volunteer position as a dermatologic allergy committee member for the American College of Allergy, Asthma, and Immunology; has held a volunteer position as a study section member for the National Institutes of Health Hypersensitivity, Autoimmune, and Immune mediated Diseases Study Section; and has held a volunteer position on the reviewer board for the *Journal of Allergy and Clinical Immunology*. No other potential conflicts of interest relevant to this article were reported.

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