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FOOD ALLERGY AND BIRCH POLLEN: MOLECULAR MECHANISMS AND IMMUNOTHERAPY POSSIBILITIES

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ABSTRACT

Introduction and Aim of the Study: During the birch pollen season, cross-reactions between the allergen Bet v 1 and the Mal d 1 allergen from apples can induce pollen-related food allergy (prFA), particularly after apple consumption. The aim of this study is to investigate the molecular mechanisms of this allergy and present effective treatment and prevention methods, which could significantly improve the quality of life for allergy sufferers.
Review Methods: The PubMed database was used for the literature review. English search terms included: “allergy,” “apple varieties,” “birch pollinosis,” “allergen-specific immunotherapy,” “birch pollen-associated food allergy syndrome,” and “Mal d 1.”
Overview of Current Knowledge: Birch pollen allergy is one of the most common pollen allergies, with the Bet v 1 protein responsible for cross-reactive allergic responses following apple consumption. In apples, the Mal d 1 allergen triggers these reactions, which is particularly significant in Central and Northern Europe. Apples with red flesh are considered hypoallergenic due to their low Mal d 1 content and are a beneficial choice for allergic individuals. Various immunotherapy approaches, including sublingual immunotherapy, are utilized effectively to alleviate symptoms and support allergen tolerance.
Conclusion: Pollen-related food allergy associated with birch pollen significantly affects the daily lives of allergy sufferers, especially during the birch pollen season. Advances in molecular mechanism research have allowed the identification of apple varieties with lower allergenic potential, enabling their use in immunotherapy and offering hope for improving patients' quality of life.

KEYWORDS

Allergy, Birch Pollinosis, Apple Varieties, Allergen-Specific Immunotherapy, Birch Pollen-Associated Food Allergy Syndrome

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Introduction and Aim of The Study

During the spring season, particularly from March to May, birch pollen can trigger allergic reactions after apple consumption. This phenomenon, known as pollen-related food allergy (prFA), affects many patients allergic to birch pollen. In such cases, cross-reactive allergic responses are caused by the primary apple allergen, Mal d 1, due to its significant clinical homology with the birch allergen Bet v 1. Symptoms may be mild, including itching and tingling in the mouth, but in rare cases, they can lead to severe anaphylactic reactions. The aim of this study is to understand the molecular mechanisms underlying this allergy, analyze allergens, assess factors influencing their allergenicity, and present therapy methods and strategies for avoiding allergic reactions.

Review Methods

A literature review was conducted using the PubMed and Google Scholar databases. The search criteria were limited to articles available electronically in English. To ensure accurate and precise results, English search terms included: “allergy,” “apple varieties,” “birch pollinosis,” “allergen-specific immunotherapy,” “birch pollen-associated food allergy syndrome,” and “Mal d 1.” Open-access studies were prioritized, and a final analysis included 19 scientific publications.

Overview of Current Knowledge

Introduction

Pollen allergies affect 30–40% of the global population, with birch pollen among the most common allergens, impacting 8–16% of individuals suffering from pollen allergies. The birch pollen season occurs from March to May. Birch (Betula verrucosa), belonging to the Betulaceae and Fagaceae families, is mainly found in Europe, North America, and Asia. Birch pollen contains seven identified allergens, the most important being Bet v 1. This allergen is crucial for allergy diagnosis and developing effective immunotherapy methods. Symptoms of birch pollen allergy include allergic rhinitis, allergic conjunctivitis, and asthma. Increasingly, pollen-food syndrome (PFSA) is observed, which results from cross-reactivity between birch pollen and certain foods, with apples being the most common trigger.

Apples (Malus × domestica Borkh.) are a valuable source of nutrients and nutraceutical compounds such as polyphenols and various phytochemicals. The main chemical compounds found in apples include phenolic acids, dihydrochalcones, flavonoids (e.g., quercetin glycosides), catechins, and oligomeric procyanidins. These substances exhibit numerous health benefits, including antioxidant, antiproliferative, digestive-supportive, and weight-regulating properties [1,2,3]. Unfortunately, despite their health benefits, apples can also cause allergic reactions, especially in sensitized individuals.

Pollen-related food allergy caused by birch pollen sensitization, particularly the cross-reaction with apple allergens, is one of the most significant allergological challenges in Central and Northern Europe [4]. The key factor is the Mal d 1 protein, which, due to its structural homology with Bet v 1 (the main birch pollen allergen), provokes allergic reactions in affected individuals [5]. This type of allergy exemplifies the complexity of cross-reactivity between airborne and food allergens. Research on this topic focuses on better understanding allergen mechanisms and developing effective immunotherapy strategies that may help individuals suffering from such conditions.

Molecular Mechanisms of Cross-Reactive Allergy

Exposure to birch pollen leads to respiratory sensitization, and IgE antibodies specific to Bet v 1 may cross-react with Mal d 1. This interaction arises due to cross-reactivity at the immune system level via shared IgE and T-cell epitopes [6,7]. Consequently, an allergic individual may experience an allergic reaction after consuming apples. Symptoms of allergy related to oral allergy syndrome (OAS) include tingling, itching, swelling in the oral cavity, and ear itching. In severe cases, it can lead to angioedema, a deeper and more extensive tissue swelling that may require urgent medical intervention [8]. Through the activation of Bet v 1-specific effector T cells, Mal d 1 may induce late-phase allergic responses, exacerbating atopic dermatitis, increasing inflammation, and reducing the patient's quality of life [9,10].

Impact of Mal d 1 Content in Apples

The primary allergens present in apples are Mal d 1, Mal d 2, Mal d 3, and Mal d 4. In Central and Northern Europe, Mal d 1 is the dominant allergen, while Mal d 3 plays a significant role in Southern Europe. In the Mediterranean region, both Mal d 3 and Mal d 4 are relevant.

Mal d 1 is a protein with a molecular weight of 17–18 kDa, consisting of 158–159 amino acids. The sequence of this protein is encoded by a gene of 480–483 nucleotides. It is the major allergen in apples, responsible for cross-reactivity in individuals allergic to birch pollen [11]. Biologically, Mal d 1 functions in plant responses to fungal and bacterial infections due to ribonuclease activity characteristic of pathogenesis-related proteins (PR-10). Additionally, Mal d 1 participates in plant steroid transport and intracellular signaling, highlighting its role in metabolic and defense processes [12].

The concentration of Mal d 1 varies depending on apple variety and fruit location. The lowest levels are found in the pulp, while concentrations increase toward the peel. The highest levels are observed near the stem, just beneath the skin, making that part the most allergenic [13,14]. Understanding Mal d 1 distribution in apples is crucial for allergic individuals, as removing the peel and stem can significantly reduce allergen intake. This approach helps minimize the risk of allergic reactions. Studies also indicate that Mal d 1 levels are lowest at harvest (1–30 μg Mal d 1 per gram of fresh apple) but increase to 100 μg Mal d 1 per gram during storage [15].

In 2017, the Apple Care study was conducted by the Departments of Dermatology, Venereology, and Allergology at the Medical University of Innsbruck (Austria) and the Central University Hospital in Bolzano (Italy). The study involved 52 volunteers aged 18 to 70 with apple allergies related to birch pollen. The aim was to identify apple varieties with the lowest allergenic potential for use in treating birch pollen and apple allergies. The study included 23 apple varieties grouped into red-fleshed, new, and old varieties. Skin prick tests showed reactions within minutes for white-fleshed varieties, whereas red-fleshed varieties caused no reactions. Similarly, oral provocation revealed that red-fleshed apples did not induce allergic responses, while white-fleshed apples triggered symptoms such as throat itching, scratching, and tearing within minutes [16].

Organic farming, characterized by reduced pesticide use, has contributed to lowering Mal d 1 protein levels in apples, benefiting individuals with allergies. However, commercial apple varieties prioritized for yield and aesthetics are more susceptible to diseases, making them unsuitable for organic farming. Older apple varieties like Santa, known for greater disease resistance (such as apple scab and powdery mildew) and genetic diversity, may be more suitable for organic cultivation. However, reintroducing these varieties in organic farming remains challenging, as modern breeding prioritizes yield and appearance over natural disease resistance [17,18].

Potential Treatment Methods for Cross-Reactive Allergy

Due to strong structural similarity and high homology between Bet v 1 (birch's primary allergen) and Mal d 1 (apple's main allergenic protein), Mal d 1 could potentially be used in birch pollen allergy therapy, and Bet v 1 in apple allergy treatment. Oral exposure to Mal d 1 has been found to lower Bet v 1-specific IgE serum levels and initiate immunological reactions that promote peripheral tolerance [19]. Long-term apple consumption might aid birch pollen and prFA allergy treatment, offering a convenient and time-efficient therapeutic approach.

Sublingual immunotherapy (SLIT) is an allergy treatment method involving administering small allergen doses under the tongue to desensitize the immune system to allergens such as pollen, dust mites, or foods—including cross-reactive allergens like Bet v 1 and Mal d 1. SLIT works by controlled immune system stimulation, reducing allergic responses. The procedure is convenient as it can be performed at home and is less invasive than injection-based immunotherapy.

In birch pollen allergy treatment, SLIT using recombinant Mal d 1 has demonstrated the ability to lower Th2 responses, reduce specific IgE levels, and suppress cross-reactive T cells. Additionally, this method may serve as an alternative to conventional therapies due to its efficacy and safety.

SLIT for birch pollen allergy can involve consuming hypoallergenic apples, such as red-fleshed varieties like 'Red Moon.' Therapy involves chewing an apple piece for about two minutes, then placing it sublingually for a short duration. For the next 15 minutes, patients must avoid eating or drinking. If no adverse allergic reactions occur, apple consumption gradually increases over a month until a whole apple can be tolerated. Next, medium-allergenicity varieties like 'Pink Lady,' 'Gloster,' or 'Topaz' are consumed for six weeks. In the final therapy phase, highly allergenic varieties, such as 'Gala,' 'Natyra,' 'Goldparmäne,' 'Golden Delicious,' or 'Sonnenglanz,' are introduced over approximately five months [16].

For individuals opting against immunotherapy, a practical alternative is consuming peeled apples, older varieties, and red-fleshed apples, particularly during the birch pollen season and shortly after pollen dispersal. In cases of birch pollen allergy, raw apples should ideally be avoided during peak pollen periods. Consumption should be limited to peeled fruits with low allergenicity, such as red-fleshed or older varieties. Additionally, avoiding other cross-reactive fruits and vegetables, including carrots and celery, is advisable. Heat treatment (such as cooking) and peeling can significantly reduce allergic reaction risks. Monitoring pollen calendars to minimize exposure is also essential, and wearing sunglasses and protective masks during outdoor activities can further reduce allergen exposure.

Conclusions

In Northern and Central Europe, apple allergies often result from birch pollen sensitization due to cross-reactive proteins like Bet v 1 in birch pollen and Mal d 1 in apples. During the birch pollen season, apple allergies may intensify, causing mild symptoms such as itching and tingling in the mouth or progressing to food allergy reactions. Sublingual immunotherapy is an effective treatment, and apple varieties like Santana and Red Moon induce fewer allergic responses, making them suitable for initial tolerance induction. After controlled consumption increases, more allergenic varieties can be gradually introduced into patients' diets. Additionally, avoiding apples high in allergens during the birch pollen season and using methods like peeling or thermal processing can substantially lower allergic reaction risks.

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