Birch pollen–related food allergy: Clinical aspects and the role of allergen-specific IgE and IgG_4 antibodies

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Background: Patients with birch pollen allergy often develop allergic reactions to plant foods.
Objective: To evaluate the prevalence, main symptoms, and triggers of birch pollen–related food allergy and the role of food-specific IgG_4 antibodies in food tolerance.
Methods: Food-induced symptoms were evaluated in 225 individuals with birch pollen allergy by using a standardized questionnaire. IgE and IgG_4 levels specific for the major birch pollen allergen Bet v 1 and birch profilin Bet v 2 and the Bet v 1 homologs in apple (Mal d 1) and hazelnut (Cor a 1) were quantified by ImmunoCAP. Mock-treated and IgG-depleted sera from patients tolerating hazelnuts in food challenges were compared for their inhibitory activity for binding of Cor a 1–IgE complexes to B cells.
Results: In total, 73% of the study population experienced food allergy, which was perennial in 86% of the affected individuals. The oral allergy syndrome was the main clinical manifestation. However, more than 58% of the patients also experienced food-induced rhinoconjunctivitis. Apples and hazelnuts were identified as the most frequent triggers. Food allergy correlated with IgE reactivity to Bet v 1 but not to Bet v 2. Mal d 1–specific and Cor a 1–specific IgG_4/IgE ratios were significantly higher in food-tolerant individuals than individuals with food allergy. Sera from IgG_4-positive food-tolerant patients possessed IgG-dependent IgE-inhibitory activity.
Conclusion: Birch pollen–related food allergy is highly prevalent and often perennial. High food allergen–specific IgG_4/IgE ratios seem associated with food tolerance, potentially because specific IgG_4 blocks IgE binding to food allergens. Thus, the presence of food allergen–specific IgG_4 antibodies is no diagnostic marker for birch pollen–related food allergy.
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Key words: *Birch pollen allergy, food allergy, oral allergy syndrome, Bet v 1, IgE, blocking antibodies*

Birch pollen is one of the most common causes of rhinoconjunctivitis and allergic asthma in Northern and Central Europe and North America.[1,2] It has long been known that patients with birch pollen allergy may develop immediate reactions to fruits and vegetables in addition to seasonal respiratory symptoms.[3,4] This birch-fruit-vegetable syndrome is characterized by local symptoms at the site of food contact such as itching of the lips, tongue, and throat, sometimes accompanied by swelling of the lips and tongue, referred to as the oral allergy syndrome.[5] Occasionally, systemic and more severe IgE-mediated reactions such as urticaria, asthma, or anaphylactic shock may occur.[6] Although birch pollen–related food allergy is often noticed in clinical practice, no recent data on the prevalence and main triggers of this type of food allergy are available.[7,8]

Birch pollen–related food allergy is considered a consequence of immunologic cross-reactivity between ubiquitous birch pollen allergens and structurally related food proteins. IgE antibodies specific for the major birch pollen allergen, Bet v 1, have been shown to cross-react with homologous proteins identified in different stone-fruits, such as apple (Mal d 1), cherry (Pru av 1), and pear (Pyr c 1), as well as hazelnut (Cor a 1), celery (Api g 1), carrot (Dau c 1), soybean (Gly m 4), peanut (Ara h 8; see summary[9]), jackfruit,[10] and kiwi (Act d 8).[11] These food allergens can also activate Bet v 1–specific T cells to proliferate and produce cytokines,[12] sometimes even resulting in T cell–mediated late-phase responses in target organs, such as flare-ups of atopic eczema in the skin.[12,13] Bet v 2, the birch pollen profilin, is another allergen able to induce cross-reactive IgE antibodies.[14,15] Bet v 2–specific IgE antibodies have been shown to recognize profilins in apple, banana, carrot, celery, cherry, hazelnut, pear, pineapple, potato, and tomato.[16-22] IgE antibodies specific for the minor allergen Bet v 6, an isoflavone reductase–homologous

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Abbreviations used
FAB: Facilitated allergen binding
r: Recombinant
SIT: Allergen-specific immunotherapy

protein of 35 kd, have been shown to cross-react with proteins of comparable size in apple, banana, carrot, lychee, mango, orange, and pear.[23,24]

Often, patients with birch pollen allergy who display IgE reactivity to birch pollen–related allergens in foods do not develop clinical symptoms when consuming the foods.[20,25] Recently, evidence accumulated that allergen-specific IgG, in particular IgG_4 antibodies, might play a role in food tolerance. For example, tolerance to cow's milk in atopic children and adults has been associated with elevated levels of specific IgG_4 in combination with low specific IgE.[26-28] Furthermore, significant increases of food allergen-specific IgG_4 antibodies have been observed during specific oral immunotherapy with milk, egg, and peanut[29-32] and during sublingual immunotherapy with hazelnut and peach extract, respectively.[33,34] These findings prompted us to investigate the role of allergen-specific IgG_4 antibodies in patients tolerant to birch pollen–related foods.

We included 225 patients with birch pollen allergy to analyze the prevalence, symptoms, and foods involved in birch pollen–related food allergy. Furthermore, the relevance of IgE reactivity to Bet v 1 and Bet v 2 for food-induced reactions was elucidated. Allergen-specific IgG_4 levels in patients tolerating and reacting to birch pollen–related foods were compared. Mock-treated and IgG-depleted sera from food-tolerant patients were investigated for their capacity to block IgE binding to Bet v 1–related food allergens.

METHODS

Study population and questionnaire

In total, 225 patients who attended Austrian Allergy Clinics in Innsbruck, Graz, and Vienna from May to June 2007 and were diagnosed as having birch pollen allergy were included. The diagnosis was made on the basis of clinical history, positive skin prick test responses to birch pollen extract, and specific IgE to birch pollen (≥0.35 kilo units [kU_A/L], ImmunoCAP; Phadia, Uppsala, Sweden). In 140 individuals, skin prick tests to grass pollen were performed and were positive in 65.7%. None of the individuals had undergone allergen-specific immunotherapy (SIT). All patients gave written informed consent. Patients were interviewed by using a standardized questionnaire in German adopted from Fernandez-Rivas et al[35] (see this article's Fig E1 in the Online Repository at www.jacionline.org) including 16 foods, namely fruits of the Rosaceae family (almond, apple, apricot, cherry, nectarine/peach, pear, plum), vegetables of the Apiaceae (carrot, celery) and Solanaceae families (potato peel, tomato), Leguminosae (peanuts, soybean), hazelnut, walnut, and kiwi.

Allergens

Recombinant (r) Bet v 1.0101 (termed Bet v 1 in this article), Bet v 2.0101 (termed Bet v 2), and Mal d 1.0108 (termed Mal d 1) were purchased from Biomay (Vienna, Austria). rCor a 1.0401 (termed Cor a 1) was kindly provided by Stephan Scheurer, Paul Ehrlich Institut, Langen, Germany.

Determination of allergen-specific IgE and IgG_4

IgE and IgG4 levels specific for the different allergens were determined by ImmunoCAP (Phadia) and ELISA. For the latter, microtiter plates (Maxisorp, Nunc, Denmark) were coated with the recombinant allergens (2 μg/mL each) in carbonate buffer (pH 9.6) overnight at 4°C. After washing and saturation, sera were incubated in duplicate overnight at 4°C. Bound IgE antibodies were detected by using alkaline phosphatase-conjugated antihuman IgE (BD Biosciences, San Jose, Calif). Bound IgG_4 was detected by mouse antihuman IgG_4 (BD Biosciences) followed by horseradish peroxidase–conjugated sheep antimouse IgG_4 (GE Healthcare, Buckinghamshire, United Kingdom). Sera from 10 subjects without allergy were used as negative controls in IgE-ELISA. The mean value of all negative controls plus 5 times the SD was set as the cutoff value for positive IgE reactivity.

TABLE I. Demographic data of the study population

Characteristics	Values
Sex, n (%)	
Female	136 (60.4)
Male	89 (39.6)
Age (y)	
Median	35.0
Range	6-76
Total IgE (kU/L)	
Median	143.0
Range	2.0->5000
Birch-specific IgE (kU_A/L)	
Median	20.0
Range	0.37->100

Depletion of IgG antibodies

Sera from patients tolerating hazelnuts in double-blind placebo-controlled food challenges[36] were incubated with either protein G–Sepharose beads (Bio Vision Research Products, Mountain View, Calif) or Sepharose beads for 4 hours at room temperature. Thereafter, sera were centrifuged and incubated with fresh beads overnight at room temperature. These steps were repeated until ELISA results showed successful depletion of allergen-specific IgG_4. As controls, sera were used from 4 patients undergoing birch pollen SIT for 24 months who showed improved clinical symptoms to birch pollen and associated foods.

IgE-facilitated allergen binding inhibition assay

The facilitated allergen binding (FAB) inhibition assay measures the capacity of IgG antibodies to inhibit the formation of IgE-allergen complexes that bind to the low-affinity IgE receptor (CD23) on B cells.[37] In preliminary experiments, indicator sera with an ImmunoCAP >50 kU_A/L to rCor a 1 were incubated with different concentrations of rCor a 1 (1, 0.3, 0.1, and 0.03 μg/mL) to form IgE-allergen complexes. We determined 0.03 μg/mL as the optimum concentration. Thereafter, indicator serum (15 μL) plus either mock-treated or IgG-depleted sera (20 μL) were incubated with 5 μL rCor a 1 (0.03 μg/mL) for 1 hour at 37°C. Then 1×10^5 EBV-transformed B cells (5 μL) were added and incubated for 1 hour at 4°C. Cells were washed, and bound complexes were detected by using a fluorescein isothiocyanate–labeled affinity purified goat-antihuman IgE antibody (KPL, Gaithersburg, Md) with a FACS Canto (BD Biosciences).

Statistical analysis

Statistical analysis was performed with SPSS 14.0 (SPSS Inc, Chicago, Ill). Differences of allergen-specific antibody levels between patients with food allergy and food-tolerant patients were evaluated by using the Wilcoxon signed-ranks test, and the Spearman rank test was used to determine correlation. Two-sided P values <.05 were considered significant.

TABLE II. Bet v 1 homologs and profilins in birch pollen–related foods

Food	Frequency of food hypersensitivity (%)*	Bet v 1 homolog	GenBank accession no.	Profilin	GenBank accession no.
Apple	80.0	Mal d 1	AJ417551	Mal d 4	AF129426 AF129427 AF129428
Hazelnut	59.4	Cor a 1	AF136945	Cor a 2	AF327622 AF327623
Nectarine/peach	50.9	Pru p 1	DQ251187	Pru p 4	AJ491881 AJ491882
Kiwi	47.9	Act d 8	AM489568	Act d 9	FG438715
Walnut	41.2	—	—	—	—
Carrot	34.5	Dau c 1	AF456481	Dau c 4	AF456482
Apricot	33.3	Pru ar 1	U93165	—	—
Cherry	32.1	Pru av 1	U66076	Pru av 4	AF129425
Pear	32.1	Pyr c 1	AF057030	Pyr c 4	AF129424
Almond	31.5	—	—	Pru du 4	AY081850 AY081852
Peanut	24.2	Ara h 8	AY328088	Ara h 5	AF059616
Plum	24.2	Pru d 1	—	Pru d 4	—
Tomato	21.2	—	—	Lyc e 1	AJ417553
Potato	18.8	—	—	—	—
Celery	15.8	Api g 1	Z48967	Api g 4	AF129423
Soybean	13.9	Gly m 4	X60043	Gly m 3	AJ223982

—, Not identified.
*Percentage of positive reactions in 225 patients with birch pollen allergy.

RESULTS

Study population

Data on sex, age, and total and birch pollen–specific IgE levels of the 225 patients with birch pollen allergy are summarized in Table I. Testing all sera for IgE reactivity to rBet v 1 in ELISA revealed 205 positive patients (91%). In immunoblots with birch pollen extract 210 sera (93.3%) showed IgE reactivity to Bet v 1, and 73% of these patients were exclusively sensitized to the major birch pollen allergen (data not shown). The ImmunoCAP for rBet v 1 performed with 147 sera positively correlated with the respective ELISA results ($R = 0.827$; $P < .001$). ImmunoCAP results for rBet v 1–specific IgE also correlated highly with ImmunoCAP results for birch pollen ($R = 0.969$; $P < .001$). Of 147 patients, 22 (15%) were positive for rBet v 2 (ImmunoCAP ≥0.35 kU_A/L), and all but 1 were also sensitized to Bet v 1.

Main triggers and symptoms of birch pollen–related food allergy

In summary, 165 of 225 (73%) reported allergic reactions to at least 1 of the 16 foods included in the questionnaire. Among food-reactive patients, apple induced symptoms in 80% and hazelnut in 59.4%, followed by peach, kiwi, walnut, carrot, apricot, cherry, pear, almond, plum, peanut, tomato, potato peel, raw celery, and soybean (Table II). The most prevalent symptom was itching in the oral cavity (89.2%), followed by rhinitis (58.2%), conjunctivitis (57.6%), swelling of the lips (50.6%), tightness of the throat (50.8%), and itching in the ear (36.7%). Dyspnea (28.5%), cramps (18.4%), nausea (9.5%), urticaria (15.2%), and drop of blood pressure (8.9%) were less frequent. Of 121 food-reactive individuals who could comment on the onset of their food-induced symptoms, 85 (70.2%) reported that food allergy had started after birch pollinosis. Fifty-nine of 134 patients with food allergy (44%) experienced a worsening of food-induced symptoms during the birch pollen season, and 138 of 159 (86.8%) patients also had food allergy in winter, out of the birch pollen season.

Birch pollen–related food allergy is clearly associated with sensitization to Bet v 1

All foods included in the questionnaire contain Bet v 1 homologs and profilins (Table II). To evaluate the involvement of these birch pollen allergens in birch pollen–related food allergy, we compared the levels of total and birch pollen–specific IgE in 149 patients with food allergy and 56 food-tolerant patients, and Bet v 1–specific and Bet v 2–specific IgE levels in 115 patients with food allergy and 32 food-tolerant patients (Fig 1, *A*). No difference in total IgE levels between the groups was found (median, 163 kU_A/L, range, 11.2-5000 kU_A/L; and median, 140 kU_A/L, range, 2.0-3503 kU_A/L, respectively). Birch pollen–specific IgE levels were significantly higher in the group with food allergy (median, 19.1 kU_A/L; range, 0.6->100 kU_A/L) than in food-tolerant individuals (median, 6.1 kU_A/L; range, 0.4-68.4 kU_A/L; $P < .001$). Similarly, Bet v 1–specific IgE levels were significantly higher in patients with food allergy than tolerant patients (median, 26.7 kU_A/L, range, 0.9-381 kU_A/L; and median, 7.5 kU_A/L, range, 0.7-63.84 kU_A/L, respectively; $P < .001$). All patients with Bet v 1–specific IgE levels of >65 kU_A/L had food allergy. A significantly larger number of food-reactive individuals (96%) were sensitized to Bet v 1 than tolerant individuals (79%; $P = .046$; Fig 1, *B*). Fifteen of 115 (13.0%) of the individuals with food allergy and 7 of 32 (21.8%) of the tolerant individuals displayed IgE to Bet v 2 (Fig 1, *B*). Although all patients with higher Bet v 2–specific IgE levels (≥3.5 kU_A/L) belonged to the food-allergic group, these individuals were all concomitantly

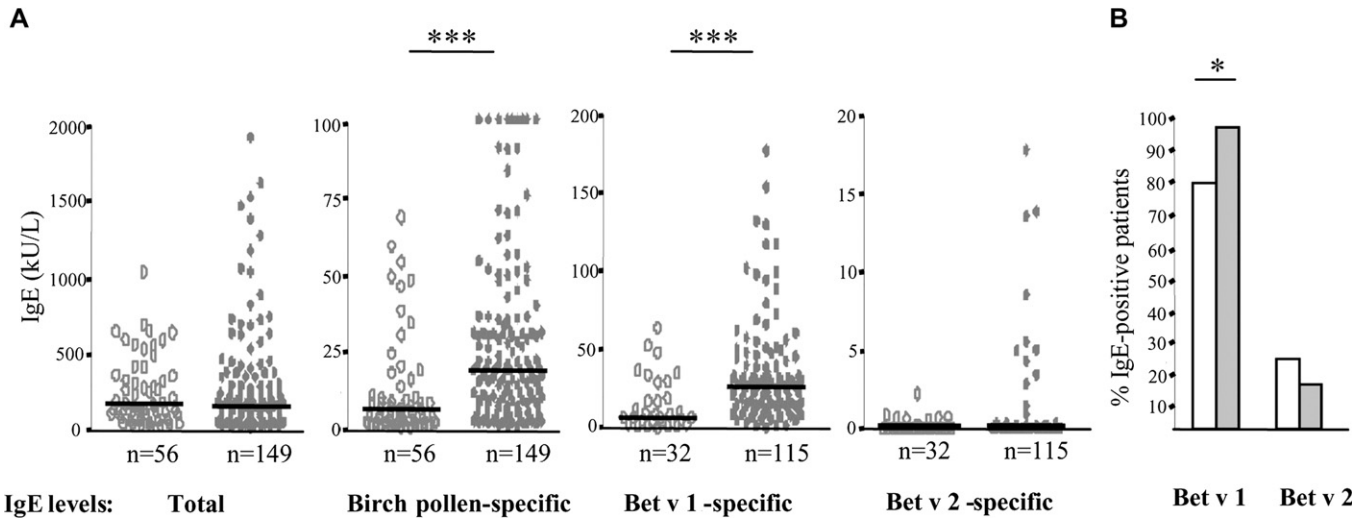


FIG 1. IgE levels of patients with birch pollen allergy with and without food allergy. **A,** Levels of total IgE and IgE specific for birch pollen, Bet v 1, and Bet v 2 were compared in food-tolerant *(open circles)* and food-reactive *(filled circles)* patients. **B,** Percentage of Bet v 1–sensitized and Bet v 2–sensitized patients in tolerant *(white bars)* and food-reactive *(gray bars)* individuals. *Horizontal lines* indicate median values. Wilcoxon signed-ranks test, $*P < .05$, $***P < .001$.

sensitized to Bet v 1. In total, 14 of 225 patients with birch pollen allergy showed no IgE reactivity to Bet v 1, of whom 7 individuals (50%) were tolerant to all foods asked about in the questionnaire. The IgE reactivity patterns to birch pollen allergens of the 7 Bet v 1–negative, food-reactive patients were analyzed in immunoblots (data not shown). Six individuals showed IgE reactivity to an allergen of 35 kd (presumably Bet v 6). Of these 6 patients, 2 showed IgE reactivity to Bet v 2 and 2 to an allergen of 9 kd (presumably Bet v 4). For 1 patient (birch pollen–specific IgE, 1.78 kU_A/L) who had reported allergic symptoms to stone-fruits, no IgE reactivity to any birch pollen allergen was detectable.

Food-tolerant patients show higher ratios of food allergen–specific IgG_4/IgE than patients with food allergy

Apple and hazelnut containing Mal d 1 and Cor a 1, respectively, were identified as the most frequent triggers for birch pollen–related food allergy. In patients with apple allergy, a strong positive correlation between IgE specific for Bet v 1 and Mal d 1 was found ($R = 0.811$; $P < .001$). Similarly, IgE levels specific for Bet v 1 and Cor a 1 highly correlated in patients with hazelnut allergy ($R = 0.927$; $P < .001$). Not all individuals who showed IgE reactivity to the Bet v 1–related food allergens also experienced food-induced allergic symptoms. Accordingly, 113 Mal d 1–sensitized patients were grouped into 85 individuals with apple allergy and 28 apple-tolerant individuals and 105 Cor a 1–sensitized patients into 62 patients with hazelnut allergy and 43 hazelnut-tolerant patients. IgG_4 levels specific for Mal d 1 and Cor a 1 were determined by ImmunoCAP (Fig 2). Apple-tolerant patients displayed significantly lower levels of Mal d 1–specific IgE ($P = .002$) and similar levels of IgG_4 compared with patients with apple allergy. In contrast, hazelnut-tolerant individuals displayed similar Cor a 1–specific IgE levels and significantly higher IgG_4 levels ($P = .03$) compared with patients with hazelnut allergy (Fig 2). When IgG_4/IgE ratios were calculated for each individual, food-tolerant patients showed significantly higher IgG_4/IgE ratios than patients with food allergy (Fig 2). In apple-tolerant patients, the median of Mal d 1–specific IgG_4/IgE ratios was 27 (range, 6.1-202.7) compared with 14.5 (range, 1.5-426.4) in patients with apple allergy ($P = .005$). The median of Cor a 1–specific IgG_4/IgE ratios in hazelnut-tolerant patients was 4.73 (range, 0.43-212.7) compared with 2.49 (range, 0.14-72.8) in hazelnut-tolerant individuals ($P = .045$).

Specific IgG_4 antibodies in food-tolerant individuals block IgE binding to the allergen

We compared mock-treated and IgG-depleted sera from 6 patients with birch pollen allergy who tolerated hazelnuts in food challenges in the FAB inhibition assay.[37] All patients displayed Cor a 1–specific IgG_4 and IgE (≥4.8 kU_A/L), excluding that food tolerance is caused by very low allergen-specific IgE levels (Table III). In addition, we used sera from 4 patients with birch pollen allergy who had undergone successful birch pollen SIT and had developed Cor a 1–IgG_4 antibodies during therapy (Table III). Similar to SIT-treated individuals, sera from hazelnut-tolerant patients showed IgE inhibitory activity. Treatment with protein-G–Sepharose beads effectively removed allergen-specific IgG_4 antibodies in each serum (Fig 3, *A*). The depletion of IgG antibodies abolished the inhibitory activity of all sera (Fig 3, *B*). Sera collected from the same SIT-treated patients before the onset of therapy that contained no Cor a 1–specific IgG_4 showed no inhibitory activity (Fig 3, *B*).

DISCUSSION

We found that 73% of adult Austrian patients with birch pollen allergy experienced food allergy and identified apple and hazelnut as the most frequent triggers (Table II). These results match previous studies performed in Sweden,[7,38] Italy,[8] and Denmark.[39] Sensitization to Bet v 1 and/or Bet v 2 may cause

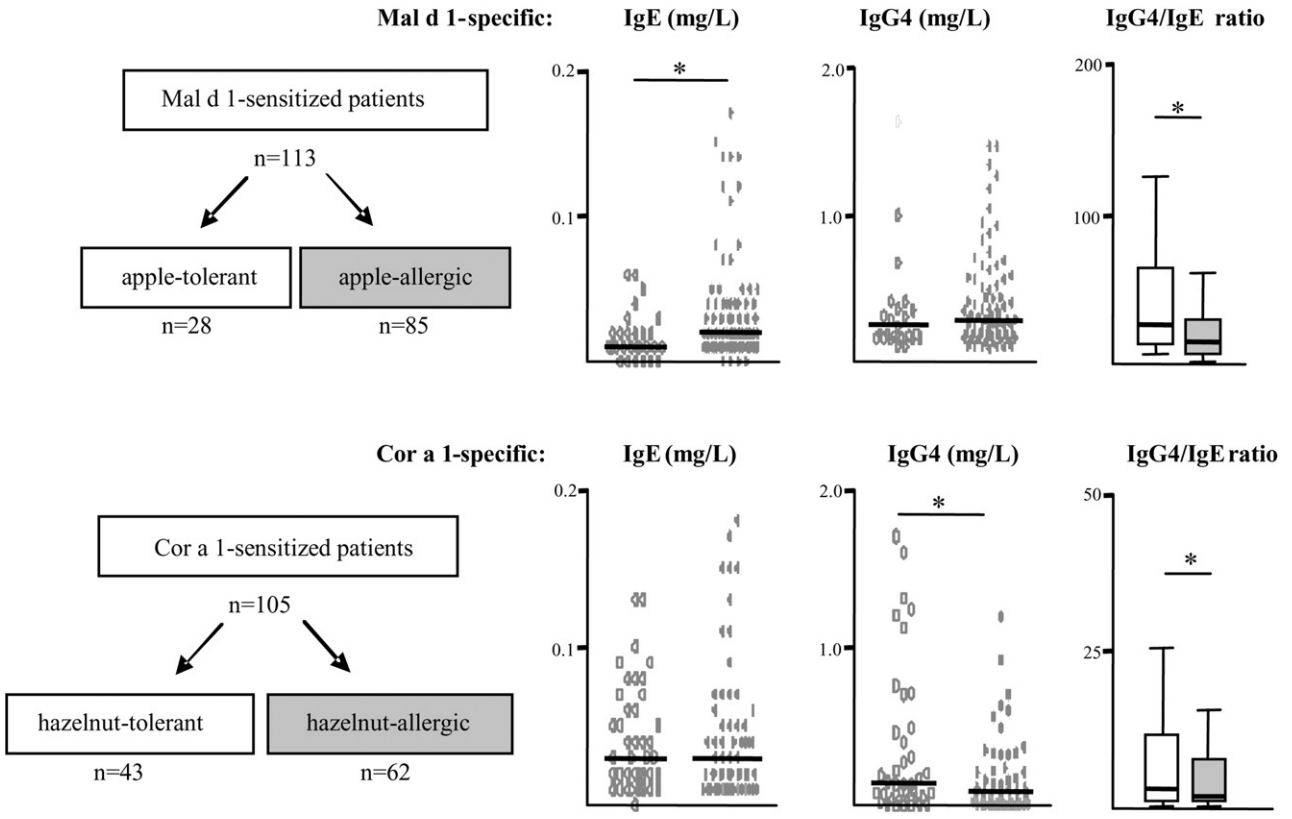


FIG 2. Specific IgE and IgG_4 levels in patients with and without food allergy. Patients with IgE >0.35 kU_A/L to Mal d 1 or Cor a 1 were grouped into food-tolerant *(white)* or food-reactive *(gray)*. Food allergen–specific IgG_4 and IgG_4/IgE ratios were determined. For IgG_4/IgE ratios, *box plots* are shown. Wilcoxon signed-ranks test, $*P < .05$.

food hypersensitivity.[40] In our study population, the frequency of Bet v 1–sensitized subjects as well as the levels of Bet v 1–specific IgE antibodies were significantly higher in food-reactive than food-tolerant patients (Fig 1). Moreover, 99 of 165 food-reactive patients (60%) showed exclusive IgE reactivity to Bet v 1 as determined by immunoblotting (data not shown). In contrast, neither the frequency nor the quantity of Bet v 2–specific IgE antibodies could be associated with food-induced reactions, and no patient with food allergy exclusively sensitized to Bet v 2 was found in our study population. In line with a previous study suggesting that Bet v 1–specific but not Bet v 2–specific IgE antibodies induced clinically relevant cross-reactivity to foods,[41] our data underline the major role of Bet v 1 and the potential inferior role of Bet v 2 in birch pollen–related food allergy.

More than 90% of our study population displayed IgE antibodies to Bet v 1, but not all individuals had food allergy. To investigate a potential role of specific IgG_4 antibodies in the tolerance to birch pollen–related foods, we compared IgG_4 levels specific for Mal d 1 and Cor a 1 in patients tolerant or allergic to apple or hazelnut, respectively. No difference between Mal d 1–specific IgG_4 levels in apple-tolerant patients and patients with apple allergy was found (Fig 2). This observation may be explained by the fact that many patients with apple allergy continue to consume apple cultivars that induce only mild allergic reactions.[42] This exposure to the food may raise specific IgG_4 antibody levels as observed in patients without allergy.[43] In contrast, hazelnuts were strictly avoided by the majority of patients with hazelnut allergy, and patients tolerating hazelnut showed significantly higher Cor a 1–specific IgG_4 levels than patients with hazelnut allergy (Fig 2). When individual food-specific IgG_4/IgE ratios were calculated, patients tolerating either apple or hazelnut displayed significantly higher ratios than individuals with food allergy. Together, these results suggest that the individual specific IgG_4/IgE ratio might

TABLE III. Antibody levels in sera from patients tested in the FAB inhibition assay

		Cor a 1–specific IgE		Cor a 1–specific IgG_4	IgG_4/IgE
Patient	Status*	kU_A/L	μg/L	μg/L	ratio
1	Tolerant	4.8	11.4	2538.3	222.1
2	Tolerant	13.4	32.2	6840.0	212.7
3	Tolerant	37.7	90.5	460.0	5.1
4	Tolerant	48.3	115.9	208.7	1.8
5	Tolerant	28.1	67.5	358.2	5.3
6	Tolerant	42.64	102.2	227.8	2.2
7	SIT-treated	0.0	0.0	1600	
8	SIT-treated	0.0	0.0	1800	
9	SIT-treated	36.5	87.6	1291	14.7
10	SIT-treated	49.7	119.4	847	7.1

*Patients 1 to 6 tolerated hazelnuts in food challenges, and patients 8 to 11 underwent birch pollen SIT.

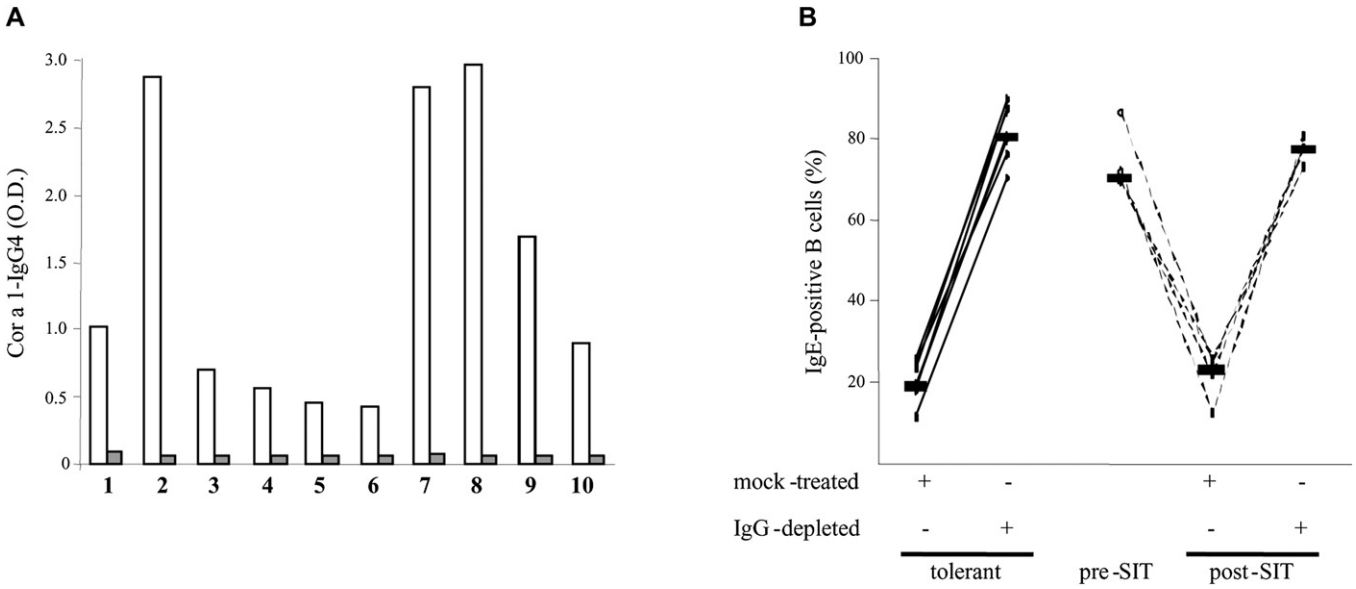


FIG 3. IgG_4 in food-tolerant patients shows IgE inhibitory activity. Sera from Cor a 1–sensitized, hazelnut-tolerant patients (1-6) and patients who underwent birch pollen SIT (7-10; Table III) were included. **A,** Cor a 1–specific IgG_4 in mock-treated *(white bars)* and IgG-depleted *(gray bars)* sera assessed by ELISA. **B,** Serum inhibitory activity tested in FAB inhibition assays. Sera obtained from SIT-treated patients before therapy served as controls. *Horizontal lines* indicate median values.

be involved in tolerance to birch pollen–related foods as it has been postulated for tolerance to cow's milk in atopic children.[26-28] In line with the EAACI Task Force report, our study confirms that the detection of food-specific IgG_4 antibodies is no diagnostic marker for food allergy.[43] Moreover, because of the high variation of the ratios between the individual patients, we do not consider IgG_4/IgE ratios suitable to predict or diagnose birch pollen–related food allergy.

Effective blocking of IgE binding to food allergens by specific IgG_4 may be one possible immune mechanism underlying food tolerance in patients with a clear food sensitization.[44] To evaluate this hypothesis, we used the FAB inhibition assay, a test system often used to test the blocking capacity of SIT-induced allergen-specific IgG antibodies.[45,46] Accordingly, patients who underwent successful birch pollen SIT had developed IgG antibodies with IgE inhibitory capacity (Fig 3). Sera from 6 patients who tolerated hazelnuts in food challenges and displayed high Cor a 1–specific IgG_4/IgE ratios (Table III) also effectively inhibited the formation of Cor a 1–IgE complexes (Fig 3). The inhibitory activity of all sera could be attributed to the presence of IgG antibodies because depletion of IgG resulted in the loss of IgE-blocking capacity. Although based on a limited number of patients, these data provide the first evidence that naturally occurring food-specific IgG_4 antibodies block IgE binding to the respective allergens. To translate this blocking capacity into clinical food tolerance, the individual IgG_4/IgE ratio may be decisive.

Although often regarded as a nonsevere syndrome, birch pollen–related food allergy is highly prevalent and often perennial. This situation demands effective treatment strategies. However, it is debated whether successful birch pollen SIT concomitantly cures the associated food allergy. Therefore, the immune mechanisms underlying birch pollen–related food allergy should be further investigated to develop efficient treatment strategies for this important allergic disease.

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Clinical implications: The vast majority of patients with birch pollen allergy develops allergy to apple and hazelnut. The detection of food-specific IgG_4 is no diagnostic marker for this food allergy.

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Standardized questionnaire to evaluate the cause and symptoms of birch pollen-related food allergy

1. Do you have hay fever (allergic rhinoconjunctivitis) during the months March - May?

Yes ☐ No ☐

2. Have you noticed any reaction during and/or after consumption of:

	Yes	No	Never tried
Hazelnuts			
Walnuts			
Peanuts			
Almonds			
Apple			
Pear			
Peach/ Nectarine			
Apricot			
Cherry			
Plum			
Celery (raw)			
Soy/Soymilk			
Kiwi			
Tomato			
Carrot (raw)			
Potato (raw, reaction during peeling)			
Others:			

3. What kind of reactions to these foods have you experienced?

	Yes	No
Itching in the mouth		
Itching in the ears		
Swelling of lips		
Lump in the throat		
Sneezing and/or running nose		
Streaming eyes		
Rush on the hands after contact		
Body rush after consumption		
Swelling of the face		
Difficulties in breathing		
Abdominal cramping		
Nausea and/or emesis		
Drop of the blood pressure		
Others:		

4. Are food-induced reactions worsening during the pollen season in spring?

Yes ☐ No ☐

5. Do you experience food-induced reactions in winter as well?

Yes ☐ No ☐

6. Did you notice food-induced reactions before or after you have developed birch pollen allergy?

Before ☐ After ☐

7. Do you have neurodermitis?

Yes ☐ No ☐

FIG E1. Standardized questionnaire to evaluate the cause and symptoms of birch pollen–related food allergy.