ORIGINAL ARTICLE

Lipid Transfer Protein Cross-reactivity Assessed In Vivo and In Vitro in the Office: Pros and Cons

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Abstract

Background: Few studies analyze cross-reactivity between lipid transfer proteins (LTP) from a large spectrum of botanically unrelated plant-derived foods using routine diagnostic tests.
Objective: To assess the clinical usefulness of currently available in vivo and in vitro tests in LTP-hypersensitive patients.
Methods: An in vitro and in vivo study was performed of 15 peach-allergic adults monosensitized to LTP in order to analyze their allergy and hypersensitivity to apple, hazelnut, walnut, peanut, soybean, lentil, maize, celery, carrot, banana, melon, tomato, kiwi, buckwheat, and sunflower, poppy, mustard, and sesame seeds.
Results: The study revealed that 8, 7, 10, 5, 3, 2, 1, 1, and 1 patients were allergic to apple, hazelnut, walnut, peanut, tomato, kiwi, melon, lentil, and maize, respectively. Immunoglobulin (Ig) E levels for peach were strongly associated with the total number of offending foods other than peach and with levels of IgE specific for all the study foods except carrot. Both in vivo and in vitro tests showed excellent sensitivity and negative predictive value, but poor specificity and positive predictive value. Sensitized but tolerant patients showed lower IgE levels than those with a history of local or systemic symptoms, although the difference between the 3 subsets was not statistically significant.
Conclusion: This study confirms that peach is the primary sensitizer to LTP and that the level of IgE to peach LTP is the main factor associated with cross-reactivity (and clinical allergy) to non-Rosaceae foods. Clinically irrelevant sensitization is common in LTP-hypersensitive patients, and positive in vivo and/or in vitro test results are of little help in detecting potential clinical reactors.

Key words: Food allergy. Lipid transfer protein. Cross-reactivity.

Resumen

Antecedentes: Son pocos los estudios que analizan la reactividad cruzada entre las proteínas de transferencia de lípidos (PTL) y un amplio espectro de alimentos de origen vegetal no relacionados botánicamente utilizando pruebas diagnósticas rutinarias.
Objetivo: Evaluar la utilidad clínica de las pruebas in vivo e in vitro disponibles actualmente en pacientes hipersensibles a PTL.
Métodos: Se llevó a cabo un estudio in vitro e in vivo con 15 adultos alérgicos al melocotón monosensibilizados a las PTL para detectar su alergia e hipersensibilidad a: manzana, avellana, nuez, cacahuete, soja, lentejas, maíz, apio, zanahoria, plátano, melón, tomate, kiwi, trigo negro, girasol, amapola, mostaza y semillas de sésamo.
Resultados: Se observó que 8, 7, 10, 5, 3, 2, 1, 1 y 1 pacientes eran alérgicos a manzana, avellana, nuez, cacahuete, tomate, kiwi, melón, lentejas y maíz, respectivamente. Los niveles de inmunoglobulina (Ig) E frente a melocotón estuvieron altamente relacionados con el número total de alimentos desencadenantes distintos al melocotón y con niveles de IgE específicas frente a todos los alimentos del estudio salvo para la zanahoria. Tanto las pruebas in vivo como in vitro mostraron una sensibilidad excelente y un valor predictivo negativo, pero una especificidad deficiente y un valor predictivo positivo. Los pacientes sensibilizados pero tolerantes mostraron niveles más bajos de IgE que aquellos con antecedentes de síntomas locales o sistémicos, si bien la diferencia entre los 3 subgrupos no fue estadísticamente significativa.
Conclusión: Este estudio confirma que el melocotón es el principal sensibilizador a las PTL y que el nivel de IgE frente a PTL del melocotón es el principal factor asociado con la reactividad cruzada (y la alergia clínica) a alimentos de familias diferentes a la de las rosáceas. La sensibilización clínicamente irrelevante es frecuente en pacientes hipersensibles a las PTL, y las pruebas in vivo y/o in vitro positivas resultan de poca ayuda en la detección de posibles pacientes con reacción clínica.

Palabras clave: Alergia alimenticia. Proteína de transferencia de lípidos. Reactividad cruzada.

Introduction

Lipid transfer protein (LTP), the most frequent cause of primary food allergy and of food-induced anaphylaxis in Italy and other Mediterranean countries [1-3], is a highly cross-reactive allergen. Although peach is the most frequently involved food in LTP allergy and the most probable cause of sensitization to this allergen, a large proportion of LTP-sensitized patients develop clinical allergy to other plant-derived foods including Rosaceae, nuts, peanut, cereals, and several fruits and vegetables [4-10]. Cross-reactivity between LTPs from different sources and peach LTP has been addressed by several investigators, but few studies analyze this issue using currently available routine diagnostic tests for a large series of botanically unrelated plant-derived foods. One group found that clinically relevant cross-reactivity to non-Rosaceae plant-derived foods is directly associated with levels of peach-specific immunoglobulin (Ig) E [11], and another observed that high levels of IgE to Pru p 3, the peach LTP, were associated with systemic allergy to this food [12]. This study examined clinical allergy and hypersensitivity to a broad spectrum of botanically unrelated plant-derived foods in a group of LTP-hypersensitive patients in order to assess the clinical usefulness of currently available routine in vivo and in vitro diagnostic tests.

Patients and Methods

Patients

The study sample comprised 15 peach-allergic adults (men/women, 5/10; mean age, 34.2 years [range, 19-78 years]) monosensitized to LTP and attending the Allergy Outpatient Department of Clinica San Carlo (Paderno Dugano, Italy). Sensitization to peach LTP was diagnosed in the presence of skin reactivity to a commercial peach extract containing 30 μg/mL of Pru p 3, the peach LTP, and lacking both Pru p 1 and profilin (ALK-Abelló, Madrid, Spain). Cosensitization to PR-10 protein and profilin, both of which are also highly cross-reactive allergens in plant-derived foods, was ruled out by negative skin test results with commercial extracts of birch and grass pollen (Allergopharma, Reinbeck, Germany). Furthermore, all patients had a negative result in skin prick tests (SPT) with extracts of profilin-enriched date palm pollen and Mal d 1–enriched apple (both kindly provided by ALK-Abelló).

Patients underwent a thorough interview to ascertain previous episodes of oral allergy syndrome (defined as the occurrence of oral itching, with or without angioedema of the lips and/or tongue, some minutes after the ingestion of a food), urticaria with or without angioedema, and/or asthma following the ingestion of plant-derived foods other than peach.

Skin Tests and Specific IgE Measurements

Since the aim of the study was to assess the clinical usefulness of currently available in vivo and in vitro diagnostic tests in identifying LTP-allergic patients who were nonsensitized, sensitized, or allergic to foods other than peach, all patients underwent both SPT and IgE measurements for several popular foods belonging to different botanical families. These included apple (*Malus domestica*, Rosaceae), hazelnut (*Corylus avellana*, Corylaceae), walnut (*Juglans regia*, Juglandaceae), peanut (*Arachis hypogaea*, Leguminosae), soybean (*Glycine max*, Leguminosae), lentil (*Lens culinaris*, Leguminosae), sunflower seed (*Heliantus annuus*, Compositae), poppy seed (*Papaver spp*, Papaveraceae), maize (*Zea mais*, Graminae), celery (*Apium graveolens*, Apiaceae), and carrot (*Daucus carota*, Apiaceae), mustard seed (*Brassica alba*, Brassicaceae), banana (*Musa acuminata*, Musaceae), melon (*Cucumis melo*, Cucurbitaceae), tomato (*Lycopersicon esculentum*, Solanaceae), kiwi (*Actinidia deliciosa*, Actinidaceae), sesame seed (*Sesamum indicum*, Pedaliaceae), and buckwheat (*Fagopyrum esculentum*, Polygonaceae).

Skin tests were carried out using commercial extracts (ALK-Abelló, 1:20 w/v) and disposable 1-mm–tip lancets (ALK Abelló). Readings were taken at 15 minutes, and wheals showing a mean diameter of at least 3 mm were considered positive [13].

IgE specific for all the foods listed above was measured using the ImmunoCAP FEIA system (Phadia, Uppsala, Sweden) following the manufacturer's recommendations. Levels were expressed as kU_A/L; levels exceeding 0.35 kU_A/L were regarded as positive.

Statistical Analysis

The correlation between peach-specific IgE levels and levels of IgE specific for all other study foods was assessed using the Pearson coefficient method. The same analysis was performed to evaluate the correlation between peach-specific IgE levels and the number of foods showing a positive SPT result for each patient. A P value <.05 was considered statistically significant.

The usefulness of both skin tests and ImmunoCAP as predictive tests for clinical allergy was assessed by calculating the positive predictive value (PPV) and the negative predictive value (NPV) using the Goldman method [14].

Results

Offending Foods and Peach-Specific IgE

Patients reported clinical allergy to 17 (n=1), 12 (n=1), 9 (n=2), 7 (n=1), 6 (n=1), 5 (n=2), 4 (n=2), 2 (n=2), 1 (n=1), and 0 (n=2) plant-derived foods other than peach. All patients had circulating peach-specific IgE. Levels of peach IgE were strongly correlated with the number of offending foods other than peach reported by the patients (r=0.754; P<.001) (Table 1).

The study foods inducing clinical allergy were apple (n=8), hazelnut (n=7), walnut (n=10), peanut (n=5), tomato (n=3), kiwi (n=2), melon (n=1), lentil (n=1), and maize (n=1). All the patients reported good tolerance to soybean, celery, carrot, buckwheat, banana, sunflower, poppy, sesame, and mustard.

Specific IgE Levels and Their Correlation With Clinical Allergy

Serum specific IgE was detected as follows: apple, 14 patients; walnut and lentil, 10; kiwi, 9; hazelnut, sunflower,

maize, peanut, and soybean, 8; tomato, 6; sesame seed, poppy seed, buckwheat, mustard, celery, banana, and melon in 5, 4, 4, 3, 2, 2, and 1, respectively. No sera reacted to carrot (Figure 1). With the exception of carrot, levels of specific IgE for all study foods were strictly correlated with levels of peach-specific IgE (Table 2); the highest degree of correlation was observed between peach and apple (Table 2 and Figure 2).

Analysis of the in vitro findings for the reported offending foods revealed that the ImmunoCAP assay result was positive in 8/8 apple-allergic patients, 6/7 hazelnut-allergic patients, 9/10 walnut-allergic patients, 2/3 tomato-allergic patients, and patients allergic to lentil (n=1), kiwi (n=2), and maize (n=1). In contrast, the in vitro assay gave a negative result in the only melon-allergic patient. The clinical usefulness of the in vitro assay is shown in Table 3.

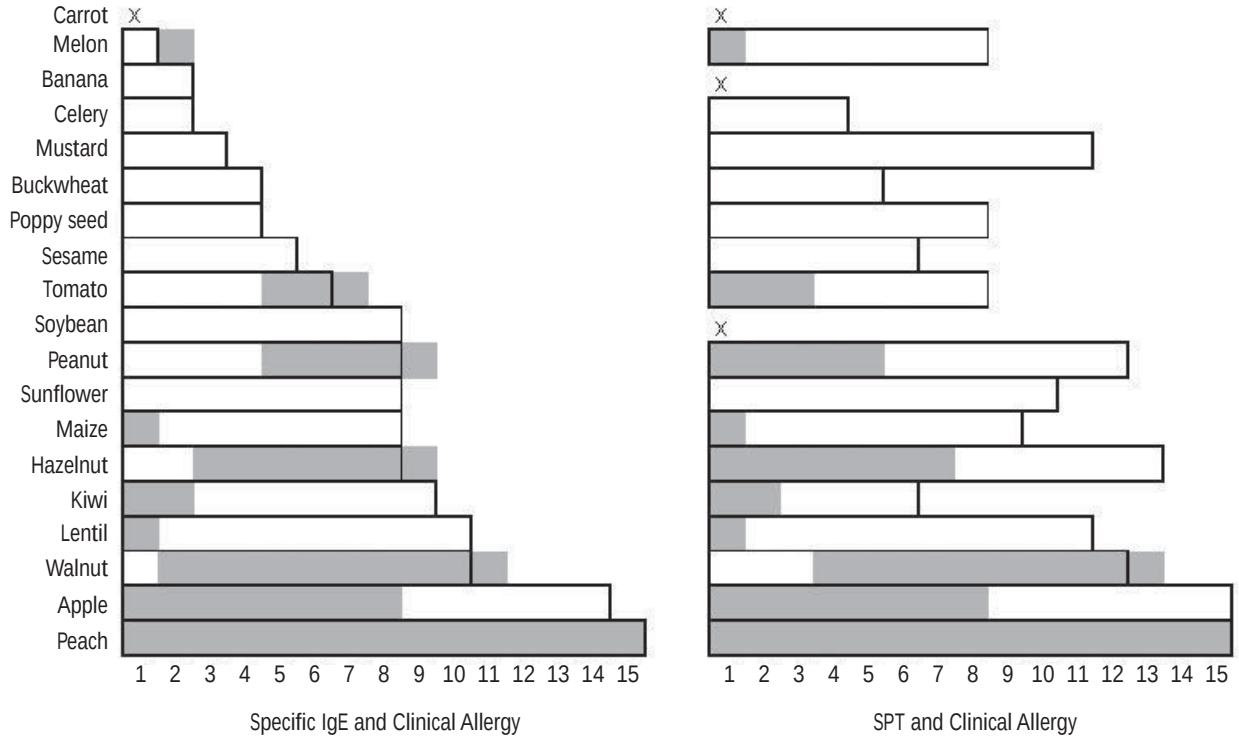
SPT Results and Their Correlation With Clinical Allergy

Patients with a positive SPT result for the study foods are shown in Figure 1. All patients reacted to apple, whereas skin reactivity to the other foods was as follows: hazelnut, 13 patients; walnut and peanut, 12; lentil and mustard, 11; sunflower, 10; maize, 9; and tomato, poppy seed, and melon, 8 each. The SPT result was positive to kiwi, sesame, buckwheat, and celery in a minority of patients, whereas the result with carrot, banana, and soybean was negative in all patients.

Table 1. Peach-Specific IgE Levels and Number of Offending Foods[a]

Patient	Peach IgE	No. of Offending Foods
1	4.58	9
2	11.60	12
3	7.04	6
4	3.81	0
5	12.10	9
6	1.08	4
7	1.11	1
8	1.75	5
9	1.44	2
10	0.41	0
11	2.75	4
12	11.40	7
13	58.10	17
14	3.12	5
15	16.60	2

Abbreviation: Ig, immunoglobulin.
[a]IgE levels are expressed in kU_A/L.



Boxes represent the number of positive in vitro or in vivo tests; allergic patients are represented as grey squares. A white space in the box represents a false positive result; a grey space outside the box a false negative one.

Figure 1. Prevalence of clinical allergy, specific IgE, and positive SPT for all the study foods in 15 peach-allergic patients sensitized to LTP. Ig indicates immunoglobulin; LTP, lipid transfer protein; SPT, skin prick test.

Table 2. Correlation Between Peach-Specific IgE Levels and IgE to All Study Foods

Food	Correlation Coefficient	*P* Value
Apple	0.995	< .001
Hazelnut	0.815	< .001
Walnut	0.994	< .001
Peanut	0.962	< .001
Soybean	0.957	< .001
Lentil	0.960	< .001
Celery	0.840	< .001
Carrot	0.2	NS
Kiwi	0.70	< .001
Maize	0.948	< .001
Buckwheat	0.938	< .001
Tomato	0.912	< .001
Banana	0.940	< .001
Melon	0.970	< .001
Sunflower seed	0.856	< .001
Poppy	0.659	< .001
Sesame seed	0.948	< .001
Mustard	0.964	< .001

Abbreviation: Ig, immunoglobulin; NS, nonsignificant.

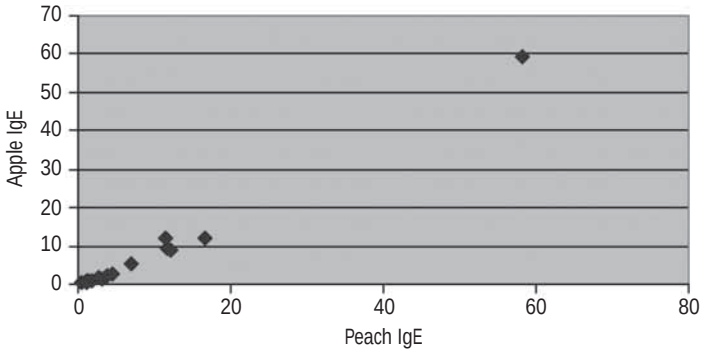


Figure 2. Correlation between IgE levels to peach and apple in the study population. The levels measured show an extremely high correlation coefficient (r=0.995). Ig indicates immunoglobulin.

Analysis of the SPT results for the reported offending foods revealed that sensitivity and NPV were excellent in most instances, whereas specificity and PPV were much poorer (Table 4).

Oral Food Challenges

An open oral challenge with peanut performed in a patient with a history of peanut-induced oral allergy syndrome showed a discrepancy between the in vivo and in vitro tests, namely, a negative in vitro result (peanut-specific IgE, 0.34 kU_A/L) and a positive SPT result as a confirmation of the reported history. After providing written informed consent, the patient

Table 3. Clinical Usefulness of ImmunoCAP Assay for Foods Other Than Peach in 15 LTP-Hypersensitive Patients

Food	No. of Allergic Patients	TP	FP	TN	FN	SE	SP	PPV	NPV
Apple	8	8	6	1	0	100	14	57	100
Hazelnut	7	6	2	6	1	86	75	75	86
Walnut	10	9	1	4	1	90	80	90	80
Peanut	5	4	4	6	1	80	60	50	86
Tomato	3	2	4	8	1	67	67	33	89
Kiwi	2	2	7	6	0	100	46	22	100
Lentil	1	1	9	5	0	100	36	10	100
Maize	1	1	8	6	0	100	43	11	100
Melon	1	0	1	13	1	0	93	0	93
Soybean	0	0	8	7	0	–	47	–	–
Celery	0	0	3	12	0	–	80	–	–
Carrot	0	0	1	14	0	–	93	–	–
Buckwheat	0	0	3	12	0	–	80	–	–
Banana	0	0	2	13	0	–	87	–	–
Sunflower	0	0	8	7	0	–	47	–	–
Poppy	0	0	4	11	0	–	73	–	–
Sesame	0	0	5	10	0	–	67	–	–
Mustard	0	0	3	12	0	–	80	–	–

Abbreviations: FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; TN, true negative; TP, true positive.

Table 4. Clinical Usefulness of SPT With Commercial Extracts of Plant-Derived Foods Other Than Peach in 15 LTP-Hypersensitive Patients

Food	No. of Allergic Patients	TP	FP	TN	FN	SE	SP	PPV	NPV
Apple	8	8	7	0	0	100	0	53	–
Hazelnut	7	7	6	2	0	100	25	54	100
Walnut	10	9	3	2	1	90	40	75	66
Peanut	5	5	7	3	0	100	30	42	100
Tomato	3	3	5	7	0	100	58	38	100
Kiwi	2	2	4	9	0	100	69	33	100
Lentil	1	1	10	4	0	100	29	9	100
Maize	1	1	8	6	0	100	43	11	100
Melon	1	1	7	7	0	100	50	13	100
Soybean	0	0	0	15	0	–	100	–	–
Celery	0	0	4	11	0	–	73	0	–
Carrot	0	0	0	15	0	–	100	–	–
Buckwheat	0	0	5	10	0	–	67	0	–
Banana	0	0	0	15	0	–	100	–	–
Sunflower	0	0	10	5	0	–	33	0	–
Poppy	0	0	8	7	0	–	47	–	–
Sesame	0	0	6	9	0	–	60	–	–
Mustard	0	0	11	4	0	–	27	–	–

Abbreviations: FN, false negative; FP, false positive; LTP, lipid transfer protein; NPV, negative predictive value; PPV, positive predictive value; SE, sensitivity; SP, specificity; SPT, skin prick test; TN, true negative; TP, true positive.

Table 5. Food-Specific IgE Levels and Clinical Expression of Food Allergy

Patient	Apple		Halzelnut		Walnut		Peanut		Tomato	
1	2.57	L	0.18	L	2.05	L	0.34	L	0.28	L
2	9.25	S	3.05	S	4.52	S	3.75	S	1.1	N
3	5.34	L	1.86	L	4.39	L	2.14	N	2.8	L
4	2.33	N	0.49	N	1.32	N	1.86	N	1.02	N
5	9.1	N	1.12	S	4.93	S	1.9	S	0.47	N
6	0.39	N	0	N	0.13	L	0	N	0	N
7	0.84	S	0	N	0	N	0	N	0	N
8	0.74	L	0	N	0	N	0	N	0	N
9	0.77	N	0	N	0.16	N	0.17	N	0	N
10	0.25	N	0	N	0.14	N	0.25	N	0	N
11	1.92	L	1.18	N	1.59	S	0.86	N	0.29	N
12	11.9	N	6.29	L	6.61	L	2.05	L	0.67	N
13	59.2	S	7.66	S	43.3	S	20.9	S	7.37	S
14	1.44	S	0	N	0.38	L	0	N	0	N
15	12	N	1.17	L	11.1	L	0.65	N	0.3	N

Abbreviations: L, local symptoms (oral allergy syndrome); N, food tolerated; S, systemic symptoms.
Immunoglobulin E levels are expressed in kU_A/L. Values >0.35 are considered positive. All values <0.1 are reported as 0.

chewed 1 peanut for 1 minute before swallowing it and was subsequently kept under observation for 1 hour; the appearance of oral allergy syndrome (defined as above) or urticaria was considered a positive response. Peanut caused oral allergy syndrome (itching of the oral mucosa and the lips) with slight angioedema of the lower lip that occurred about 5-10 minutes after ingestion, lasted for about 15 minutes, and resolved spontaneously. No other adverse events were recorded.

Specific IgE Levels: Sensitization vs Clinical Expression of Allergy

Table 5 presents IgE specific for the main foods causing clinical allergy and the type of symptoms induced by the most frequently offending foods. With exception of apple, median IgE levels in patients with a history of food allergy largely exceeded those of tolerant patients (1.86 vs 0.1 kU_A/L for

hazelnut, 4.46 vs 0.14 kU_A/L for walnut, 2.05 vs 0.21 kU_A/L for peanut, and 2.8 vs 0.15 kU_A/L for tomato); however, due to the low numbers, in most cases the difference did not reach statistical significance. Furthermore, median specific IgE levels in all patients with a history of food-induced systemic reactions exceeded those found in patients with a history of oral allergy syndrome (5.34 vs 2.24 kU_A/L for apple, 3.05 vs 1.5 kU_A/L for hazelnut, 4.73 vs 3.22 for walnut, 3.75 vs 1.2 kU_A/L for peanut, and 7.37 vs 1.54 for tomato); however, the differences did not reach statistical significance in this case either.

Discussion

The present study investigated cross-reactivity between LTP as seen in daily clinical practice; to this end, a group of 15 peach-allergic patients monosensitized to this allergen were studied both in vivo and in vitro to determine their reactivity to a panel of 18 botanically unrelated plant-derived foods. The study also assessed the clinical usefulness of currently available diagnostic tests in LTP-allergic patients. The study group was representative of LTP-allergic patients seen in clinical practice, as it included patients allergic only to peach as well as patients allergic to peach and other Rosaceae, to Rosaceae and tree nuts and/or peanut, or to a large number of botanically unrelated foods [4,15]. The prevalence of allergy to single foods mirrored that observed in previous studies [4,10,15]. Confirmative oral challenges were not systematically performed, as this would have posed a risk in patients with a history of systemic allergic reactions and would have been unfeasible in those with multiple allergies. Nonetheless, the only open challenge with peanut that was carried out in a patient with a suggestive clinical history but showing a discrepancy between in vivo and in vitro tests clearly confirmed the patient's history.

The strong correlation found between peach-specific IgE levels and the levels of IgE specific for all the other study foods again confirmed that peach has to be considered the primary sensitizer to LTP, at least in Mediterranean countries such as Italy. It also confirmed that the level of IgE to peach LTP is the main factor associated with the occurrence of cross-reactivity (and clinical allergy) to non-Rosaceae foods [11]. We might speculate that peach LTP has several epitopes, some of which are peach-specific and others shared with different botanically related or unrelated foods, and that the level of IgE to peach LTP reflects the number of epitopes recognized by IgE antibodies. Alternatively, one might hypothesize that cross-reactivity between LTPs is a matter of IgE affinity, and that the high levels of peach-specific IgE are a marker of the presence of high-affinity antibodies.

In view of the extreme heat and pepsin stability of LTP, it was not surprising that both SPT with commercial extracts and ImmunoCAP showed excellent sensitivity. Unfortunately, specificity was often unsatisfactory; this problem has often been encountered with cross-reactive allergens and is due to the high rate of clinically irrelevant sensitization in the population. Apple is a typical example: virtually all patients in this study had a positive SPT or CAP result with apple, but only half of them were allergic. Although oral food challenges were not carried out in those reporting tolerance to specific foods, previous studies showed that only a small proportion of these turn out to be allergic if challenged [16]. From a practical point of view, positive in vivo and/or in vitro test results are of little help in detecting potential clinical reactors within the LTP-hypersensitive population. In general, the sensitivity of skin tests with commercial extracts was superior to that of the corresponding in vitro assays, but, inevitably, this was counterbalanced by a loss in specificity. In vitro, low specific IgE levels were more frequently associated with asymptomatic sensitization, and progressively increasing levels were more frequently found in allergic patients with a history of local or systemic symptoms. However, as recently observed in another study of the identification of possible predictive threshold IgE levels for LTP-hypersensitive patients [17], there was much overlap between the different subgroups.

Some of the study foods were tolerated by all the patients. For example, with carrot and banana, tolerance was associated with negative in vivo and in vitro test results. For carrot, this is in keeping with the observation that LTP is not present in the edible part of this vegetable [18]. Banana was already identified as a "safe" food for LTP-allergic patients [19], and, in view of the absence of both in vitro and in vivo reactivity, one wonders whether the edible part of banana lacks LTP, as is the case for carrot. With other foods, most patients showed clinical tolerance despite frequent and significant cross-sensitization. Legumes are a typical example [20]; in this study, only 1 patient reported allergy to lentil and all reported good tolerance to soy. Interestingly, SPT with soybean was always negative, whereas most patients showed specific IgE in vitro, suggesting the absence of the cross-reacting LTP in the SPT extract. A similar situation was observed in the diagnostic tests for mustard, a food that certainly contains LTP [21] but rarely causes symptoms, although some allergic patients have been reported [4,15]. The same probably holds true for the other seeds studied here, namely, sunflower, poppy seed, and sesame. The reasons why allergic reactions to seeds are rarely observed among LTP-allergic patients despite clear-cut sensitization remain to be established; the limited amount of these seeds eaten as such and the fact that refined oils seem to contain reduced amounts of proteins [22] might be a reasonable explanation. Kiwi, maize, melon, and tomato seem to pose a risk in a small proportion of LTP-hypersensitive patients. Maize allergy in LTP-allergic patients is well documented [7], and tomato LTP has recently been described as a clinically relevant allergen [23]; in contrast, although an LTP has been detected in kiwi (Act d 10) [24], clinical data about its relevance are lacking, and the present study shows that it may sometimes be clinically relevant. Regarding melon, the results of skin tests clearly suggest that a cross-reactive LTP is present in melon extract, although this fruit has previously been included in a list of "safe" foods [19] and, to the best of our knowledge, no melon LTP has been described to date.

Finally, an important clinical problem in LTP-hypersensitive patients is which advice give to those with positive in vitro and/or in vivo results but who are clinically tolerant when seen in the office; this is particularly true for the foods that are most frequently involved in clinically relevant cross-reactions with peach LTP, such as apple (and other Rosaceae), walnut, hazelnut, and peanut. The excellent NPVs of both commercial

SPTs and in vitro assays suggest that patients with negative results are very unlikely to develop clinical allergy. By contrast, PPVs are frequently low and many patients score positive without being clinically allergic. Performing blinded or open oral challenges in these patients is of little help, because in most cases they will only confirm a patient's negative history without providing any predictive value. Although clear-cut threshold levels of IgE to specific foods were not detected in a recent large-scale study [17], elevated IgE levels are nonetheless associated with a high probability of clinical allergy; thus, in the absence of better prognostic tests, in vitro data combined with a history of systemic reactions following ingestion of peach or other plant foods should be sufficient to warn patients about possible risks of a severe reaction following the ingestion of a specific food.

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