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"Latex-fruit syndrome": frequency of cross-reacting IgE antibodies

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An association between allergies to latex proteins and to various foods has been reported and confirmed by RAST and immunoblotting inhibition. However, no significant data had been collected on the frequency of specific IgE antibodies to fruits in these patients and the frequency of a history of fruit intolerance. Serum samples of 136 patients with well-documented, clinically relevant, immediate-type hypersensitivity against latex proteins were analyzed for IgE antibodies against a panel of different fruits. Patient history of food intolerance was documented by a standardized questionnaire. Fruit-specific IgE antibodies were detected in 69.1% of serum samples. Cross-reacting IgE antibodies recognizing latex and fruit allergens (papaya, avocado, banana, chestnut, passion fruit, fig, melon, mango, kiwi, pineapple, peach, and tomato) were demonstrated by RAST-inhibition tests. Of our patients, 42.6% reported allergic symptoms after ingestion of these fruits and a total of 112 intolerance reactions were recorded. However, fruit-specific IgE antibodies were detected only in serum samples from 32.1% of the patients who perceived symptoms due to these fruits. Thus, serologic tests seem to be of low significance for prediction of food allergy in latex-allergic patients.

Key words: cross-reactivity; IgE antibodies; food intolerance; latex allergy.

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The association between latex allergy and hypersensitivity to foods, including avocado, chestnut, peach, apricot, grape, passion fruit, fig, orange, tomato, buckwheat, melon, peanut and pineapple, has been described recently and a "latex-fruit syndrome" has been postulated (1, 2). Cross-reacting IgE antibodies were demonstrated by RAST and immunoblotting inhibition assays, recognizing both latex proteins and allergens in banana, avocado, chestnut, and peanut (1, 3–15). Cross-reacting allergens in *Hevea brasiliensis*, the major source of latex, and phylogenetically dissimilar fruits implies the presence of common antigens in foods and latex. However, the nature and distribution of these common epitopes are unknown.

The purpose of the present study was to investigate the frequency of cross-reactive IgE antibodies in serum samples of latex-allergic patients and to study the relationship between allergen-specific IgE levels and reported intolerance reactions due to ingestion of cross-reactive fruits. RAST-inhibition assays were used to investigate immunologic cross-sensitivity between latex and fruit proteins.

Material and methods

Patients

A total of 136 patients (111 female and 25 male, age range 6–70 years, median 29 years) with well-documented immediate-type hypersensitivity to latex proteins were investigated. All patients had positive skin prick tests with natural ammoniated *H. brasiliensis* tree sap from Malaysia, different high-ammoniated latex solutions obtained from glove manufacturers (Regent Hospitalprodukte/Germany, Hartmann/Germany, and Beiersdorf/Germany), and latex-glove extracts (prepared from different latex gloves by extraction with 0.9% sodium chloride solution overnight at room temperature). All patients had circulating IgE antibodies against latex of between 0.38 and >100 kU/l (median 5.8 kU/l).

The patient history of clinical symptoms after contact with latex devices and symptoms of food intolerance was documented by a standardized questionnaire.

Additionally, a control group consisting of 30 patients (21 female, nine male) without clinical

symptoms of latex allergy was investigated. The skin prick test with latex was negative, and IgE antibodies against latex were not detectable in these patients.

Total and specific IgE determination

The CAP-FEIA method (Pharmacia, Freiburg, Germany) was used to evaluate total serum IgE and allergen-specific IgE. Values of allergen-specific IgE below 0.35 kU/l were considered negative and values above 0.35 kU/l positive. Total serum IgE and specific IgE against papaya, avocado, banana, chestnut, passion fruit, *Ficus* spp., melon, mango, kiwi, peach, and guava were determined in all serum samples, and some sera were also analyzed for specific IgE against pineapple, tomato, and papain.

Latex and fruit extracts

Freshly collected Malaysian *H. brasiliensis* tree sap preserved with ammonia was diluted with 0.9% NaCl (1/1 v/v) and shaken overnight at room temperature. After centrifugation, the liquid phase was dialyzed four times against 0.9% NaCl, a membrane with a cutoff of 1 kDa being used. After filtration through a 0.22-µm membrane, extracts were stored at –20°C.

Pulp of fresh fruits was mixed with of 0.9% NaCl solution (2/1 v/v) and shaken overnight at 4°C. After centrifugation and filtration through a 0.22-µm membrane, extracts were stored at –20°C.

The protein concentrations of latex and fruit extracts were measured with a commercial kit by the Pierce BCA protein assay method with bovine serum albumin as standard. The protein concentration of latex extract was 1.6 mg/ml, and that of the fruit extracts 2.4–24.6 mg/ml. The allergenicity was measured by RAST autoinhibition (preincubation serum with fruit extract after determination of IgE antibodies against that fruit) using pooled serum from three patients with IgE antibodies against latex and fruits. With fruit extracts, the autoinhibition was in the range of 65.8% (papaya) and 100% (kiwi, banana, fig). Allergenicity of the latex extract was proved by autoinhibition tests in five different sera. After preincubation with the latex extract, no IgE against latex could be detected in any of these.

RAST-inhibition test

The RAST inhibition test was carried out by preincubating 50 µl serum of each patient overnight with four different concentrations of latex or fruit extracts (0.01, 0.1, 1, and 10 µl), followed by determination of allergen-specific IgE by the CAP-FEIA system. The extent of inhibition of IgE binding was evaluated by comparing the values after preincubation with either physiologic NaCl solution (0.9%) or allergens.

Intra-assay standard deviation of CAP-FEIA was at most 5.2% (2×10 determinations). After addition of fruit extracts, there was a standard deviation of 6.9% (4×10 determinations). Inhibition above 14% was considered significant; inhibition below this threshold may be the result of intra-assay variation.

Nonspecific inhibition by lectins or similar molecules contained in extracts of fruit or latex was excluded by different well-defined serum samples from patients with allergies to birch pollen, grass pollen, and house-dust mites. No significant inhibition of specific IgE against birch pollen (t3), grass pollen (gx1), and house-dust mite (d1) was observed after preincubation with fruit or latex extracts.

Results

Patients

Evaluation of the questionnaires completed by 136 patients suffering from latex allergy revealed that 66.9% of patients were using latex gloves professionally and 52.2% were working in a medical profession. Latex allergy generally occurred after latex gloves were used: 83.8% of patients suffered from localized urticaria, 11.8% from generalized urticaria, 41.2% from rhinoconjunctivitis, and 28.7% from asthma.

At least one surgical procedure had been performed on 81% of the patients, and 60.3% had undergone surgery more than once (average of three procedures). Anaphylaxis during anesthesia had occurred in 11.8% of the patients.

Manifestation of atopic dermatitis, rhinoconjunctivitis, or asthma was reported by 63.2% of the patients; 66.9% had serum IgE levels above 100 kU/l, and the median was 240.5 kU/l.

Allergen-specific IgE

With serum samples from 136 patients, a total of 1642 assays for fruit-specific IgE antibodies were performed. Overall, 428 assays were positive, in 94 different serum samples (69.1%). IgE antibodies were detected most frequently against papaya (50.7%), avocado (46.3%), chestnut (34.6%), and banana (33.1%) (Table 1). In addition, 18/44 samples tested contained IgE antibodies against papain.

In 49.3% of the serum samples, IgE antibodies against more than one fruit were detected, and five

Table 1. Allergen-specific IgE antibodies against fruits in 136 patients

Fruit	Samples tested *n*	Positive tests *n*	Positive tests %	Allergen-specific IgE 0.35–0.7 kU/l *n*	Allergen-specific IgE >0.7 kU/l *n*	Allergen-specific IgE Maximum kU/l
Papaya	136	69	50.7	36	33	30
Papain	41	18	43.9	5	13	7.7
Avocado	136	63	46.3	14	49	>100
Chestnut	136	47	34.6	17	30	86.7
Banana	136	45	33.1	15	30	51.3
Ficus spp.	136	33	24.3	12	21	>100
Passion fruit	136	31	22.8	12	19	84.3
Melon	136	26	19.1	8	18	63.8
Mango	136	24	17.6	7	17	>100
Kiwi	136	22	16.2	6	16	48.8
Peach	136	17	12.5	4	13	44.4
Pineapple	93	18	19.4	9	9	45
Tomato	53	23	43.4	6	17	21.9
Guava	136	10	7.4	10	4	7.6

samples contained IgE antibodies against all fruit antigens tested (Table 2). However, 27 sera contained IgE antibodies specific for only a single fruit (i.e., to papaya, avocado, pineapple, passion fruit, kiwi, or tomato).

In the control group of 30 patients without signs of latex allergy, the sera of eight patients contained total IgE levels of <100 kU/l (median 25.5 kU/l), and 22 patients had circulating total IgE levels of >100 kU/l (median 209.5 kU/l). The serum sample of one atopic patient had total IgE of 1743 kU/l, and allergen-specific IgE against avocado, papaya, chestnut, kiwi, melon, peach, pineapple, and tomato was detectable. In three other serum samples, IgE antibodies against pineapple, papaya, or kiwi were found. Allergic reactions after ingestion of the investigated fruits were not reported by these patients.

Fruit hypersensitivity

Of our patients, 42.6% reported intolerance reactions after ingestion of the investigated fruits, usually kiwi and banana (Table 3). Malaise and gastrointestinal symptoms were most often reported, and eight patients suffered from asthma after eating banana (three patients), pineapple, passion fruit, avocado, mango, or kiwi. Angioedema was reported by two patients (pineapple or passion fruit), and four patients suffered from anaphylactic shock after eating banana (three patients) or fig (one patient). Only in 32.1% of serum samples from patients

Table 2. Number of patients with IgE antibodies to one or more fruits in correlation with single fruits. IgE antibodies against pineapple* were investigated in 93 sera and against tomato** in 53 sera

Fruit / No. of fruits	No. of patients with specific IgE: 0	1	2	3	4	5	6	7	8	9	10	11	12	13	Total
Papaya		17	6	6	6	5	8	4	1	2	2	6	1	5	*69*
Avocado		4	8	8	9	5	6	4	1	3	3	6	1	5	*63*
Pineapple*		3	1					1		2	2	3	1	5	*18*
Passion fruit		1		1	2	1	7	1	1	2	3	6	1	5	*31*
Tomato**		2	1	4	3	2	2	1		1		2		5	*23*
Kiwi			1	1			1	2		2	3	6	1	5	*22*
Chestnut			4	2	7	5	7	3	1	3	3	6	1	5	*47*
Ficus spp.			1	2	2	4	5	4	1	1	3	4	1	5	*33*
Banana			2	3	5	5	8	3	1	3	3	6	1	5	*45*
Mango					1	2	2	1	1	3	2	6	1	5	*24*
Melon					1	1	2	3	1	3	3	6	1	5	*26*
Peach								1		2	2	6	1	5	*17*
Guava											1	3	1	5	*10*
															428
Total	*42*	*27*	*12*	*9*	*9*	*6*	*8*	*4*	*1*	*3*	*3*	*6*	*1*	*5*	*136*

Table 3. Fruit hypersensitivity reported by 58 patients in correlation with *in vitro* assay

Fruit	Patients reporting intolerance *n*	Specific IgE <0.35 kU/l *n*	Specific IgE 0.35–0.7 kU/l *n*	Specific IgE >0.7 kU/l *n*	Sensitivity* %	Specificity** %
Kiwi	23	20	0	3	13.0	83.2
Banana	23	14	5	4	39.1	68.1
Peach	12	11	0	1	8.3	87.1
Tomato	11	5	4	2	54.5	59.6
Avocado	9	3	1	5	66.7	55.1
Melon	8	5	0	3	37.5	82.0
Passion fruit	7	5	0	2	28.6	77.5
Pineapple	6	3	1	2	50.0	82.8
Fig	6	4	0	2	33.3	76.2
Mango	4	4	0	0	0.0	81.8
Chestnut	3	2	1	0	33.3	65.4
	112	76	12	24	32.1	74.4

* Sensitivity: positive result of allergen-specific IgE determination (>0.35 kU/l) in patients with history of fruit intolerance.
** Specificity: negative allergen-specific IgE determination (<0.35 kU/l) in patients without history of fruit intolerance.

reporting intolerance reactions could corresponding fruit-specific IgE antibodies be detected. IgE antibodies were more likely to be found in patients with a history of more severe intolerance symptoms such as angioedema, asthma, or anaphylactic shock; in 7/14 serum samples from these patients, corresponding IgE antibodies were detectable.

Hypersensitivity to other foods

Intolerance of fruits other than those investigated was also reported by a number of patients (Table 4). If patients reported symptoms due to nuts and apple (mostly oropharyngeal allergy syndrome), sensitization to birch pollen was almost always found (in 18/20 and 18/18 patients, respectively). Uncommon food reactions to spinach (four patients) or kale (two patients) were also reported. In some of these patients, IgE-mediated hypersensitivity was diagnosed by demonstration of allergen-specific IgE antibodies. Overall, food hypersensitivity was reported by 55.9% of 136 latex-allergic patients.

RAST-inhibition assay

In RAST-inhibition assays, preincubation of sera with latex extracts generally completely inhibited fruit-specific IgE except against tomato (Table 5). Inhibition of latex-specific IgE after preincubation of serum samples with fruit extracts was weaker (Table 6). The highest degree of inhibition was obtained with extracts of avocado, banana, fig, tomato, kiwi, melon, and passion fruit. The inhibition of latex-specific IgE with chestnut and mango extracts was especially weak, with maximum inhibitions of only 22.0% and 45.8%, respectively.

Table 4. Food hypersensitivity reported by 46 patients

Food	No. of patients	Specific IgE detected (*n*)	Food	No. of patients	Specific IgE detected (*n*)
Nut	20	n.d.**	Spinach	4	2
Apple	18	n.d.**	Kale	2	0
Pear	4	n.d.	Turnip	2	1
Cherry	3	n.d.	Cucumber	2	0
Celery	3	2	Potato	4	3
Spices	2	n.d.	Strawberry	2	1
Paprika	7	3	Citrus fruit	9	n.d.
Carrot	4	3	Plum	1	n.d.
Mustard	1	0	Meat	1	n.d.
Pea	1	1	Milk	1	n.d.
Peanut	1	1	Egg	1	n.d.
Grape	1	1	Cheese	1	n.d.
Date	1	1	Fish	1	1

Table 5. Inhibition of allergen-specific IgE antibodies against fruits by latex extract

Specific IgE against	No. investigated	Inhibition of fruit-specific IgE (%) Range	Mean	Median
Avocado	10	77.3–100	96.7	100
Banana	5	100	100	100
Papaya	5	70–100	99.7	100
Ficus spp.	4	100	100	100
Mango	4	100	100	100
Melon	5	81–100	96.2	100
Passion fruit	3	100	100	100
Chestnut	6	94–100	99	100
Kiwi	4	100	100	100
Pineapple	4	65.5–100	91.4	100
Peach	5	50–100	90	100
Tomato	4	61–100	81.7	83

Table 6. Inhibition of allergen-specific IgE antibodies against latex by fruit extracts

Preincubation with	No. investigated	Inhibition of latex-specific IgE (%)		
		Inhibition	Mean	Median
Avocado	10	8.5–100	55.3	54.3
Banana	8	0–100	43.1	39.3
Papaya	6	8.5–65.5	24.2	18.7
Fig	6	21.1–100	57.4	56.3
Mango	5	9.4–45.8	30.5	27.9
Melon	5	26.2–100	54.7	50.8
Passion fruit	5	9.8–59.3	42.4	43.5
Chestnut	3	14.6–22	19	20.3
Kiwi	3	32.8–52.2	45.3	50.8
Tomato	6	0–100	46.6	36.8
Pineapple	4	0–100	27.9	26

Discussion

IgE-mediated hypersensitivity to latex proteins is an increasing problem, especially among medical personnel, who frequently wear latex gloves (16–21), as well as in patients with congenital malformations (22–24). In the general population, the prevalence of sensitization to latex proteins was estimated to be around 3.5% (25). Among medical personnel, latex allergy is now considered an important occupational disease. Of the patients in this study, 71 were working in a medical profession, and 91 had to use latex gloves regularly. There is also evidence that most patients with latex allergy had a history of atopy (20). This is further supported by the data of the present study, demonstrating that 63.2% of the patients reported manifestations of atopic diseases (allergic rhinoconjunctivitis, allergic asthma, and atopic eczema), and 66.9% had increased total serum IgE levels (>100 kU/l).

Patients with latex allergy frequently suffer from food intolerance causing oropharyngeal allergy syndrome and sometimes anaphylaxis. Association of latex allergy and sensitization to banana (1, 5–8, 10–15, 26–31), avocado (1, 3, 5, 6, 8, 10, 11, 26–30), chestnut (1, 4, 7, 14, 31), passion fruit (6, 10, 28), fig (5, 10, 27, 31), pineapple (5, 8), kiwi (1, 5, 8), potato (5), papaya (5), peach (30), grape (28), orange (28), tomato (26), buckwheat (26), melon (8), celery (6), and peanut (9) has been reported. Thus, an association between latex allergy and hypersensitivity to foods has been postulated (latex-fruit syndrome). A study of 25 latex-allergic patients from Gran Canaria (Canary Islands) found 52% to have fruit intolerance, most frequently of avocado and chestnut; 76% of these reactions were classified as systemic anaphylaxis (5). In our study, 55.9% of patients reported food intolerance, and 42.6% had symptoms after ingestion of the investigated fruits. Of a total of 112 fruit-intolerance reactions, symptoms were reported mostly after eating banana or kiwi (each 23%), while only 9% of the patients had symptoms after avocado. The differences between our study and the investigation performed in Gran Canaria may be explained by differences in the nutritional habits. For example, avocado and chestnut are rather uncommon in Germany. Most of our patients suffered from oropharyngeal or gastrointestinal symptoms, and only 11.6% reported severe reactions such as asthma, angioedema, or severe anaphylaxis. Additionally, some of these patients had a history of intolerance reactions after ingestion of spinach, turnip, and kale.

The study in Gran Canaria found the sensitivity of the CAP-FEIA method for food allergy in general to be 37% (5). Sensitivity to avocado was 79% and thus significantly better (5). In the present study, fruit-specific IgE antibodies were detected by the CAP-FEIA method in 36/112 serum samples from patients perceiving fruit intolerance, indicating a sensitivity of 32.1%. Sensitivity was increased to 50% for patients reporting severe intolerance reactions (7/14). In agreement with the data of the Gran Canaria study, the best CAP-FEIA sensitivity was found for avocado (66.7%). The low sensitivity of serum investigations may reflect the discrepancy between perception of food intolerance and the results of double-blind, placebo-controlled food challenge; in a study by Young et al., food provocation tests were positive in only 19.9% of the patients who perceived food intolerance (32).

The finding of many patients with detectable allergen-specific IgE to fruits without clinical signs of food intolerance may indicate that many of the patients enrolled in this study did not eat tropical fruits frequently. Therefore, the history of patients for food intolerance needs to be evaluated very critically.

Natural latex is known to contain multiple allergenic proteins in the range 5–100 kDa (16, 33–38). Rubber elongation factor, hevein and prohevein are known to be major allergens (35, 36, 39). In RAST-inhibition studies, immunologic cross-reactivity has been reported between allergens of latex and banana (1, 5, 6, 8, 11–15), avocado (1, 5, 8, 10, 11), chestnut (1, 4, 5, 7, 14), and peanut (9). In agreement with these data, we were able to demonstrate cross-sensitivity between allergens in latex and banana, avocado, and chestnut. Additionally, cross-reactivity between latex and papaya, passion fruit, fig, melon, pineapple, kiwi, and tomato could be detected. In most cases, complete inhibition was observed when serum samples were preincubated with latex extract and subsequently evaluated for specific IgE against fruits. In contrast, preincubation of sera with fruit extracts yielded a

Table 7. Use of extracts of investigated fruits

Fruit	Extract	Use of extracts
Papaya (*Carica papaya*)	Papain, chymopapain	Chemonucleolysis, antiphlogistic drug, enzyme-containing antitumour drug, gastrointestinal drug, laxative, diet pills; cleaners for dental prosthesis; meat, beer, and cracker production
Pineapple (*Ananas comosus*)	Bromelain	Antiphlogistic drug, diet pill; meat and beer production
Fig (*Ficus carica*)	Ficin	Deworming drug, laxative; meat, beer, and cheese production; leather and textile industry
Avocado (*Persea americana*)	Oil	Cosmetics

significantly weaker inhibition of latex-specific IgE. These findings may be explained by the occurrence of IgE antibodies specific for several latex proteins of which only some will cross-react with fruit proteins. Accordingly, with sera from 10 latex-allergic patients with cross-reacting IgE antibodies against avocado, preincubation with latex proteins completely inhibited IgE antibody binding to nearly all avocado proteins. After preincubation of the same sera with avocado proteins, only IgE antibodies binding to a 14-kDa protein were completely inhibited, whereas inhibition of other proteins occurred heterogeneously (3).

Our data indicate that IgE antibodies against guava, peach, melon, kiwi, mango, banana, *Ficus* spp., and chestnut can be detected in sera only in combination with IgE antibodies against other fruits, while single IgE antibodies against papaya, avocado, pineapple, passion fruit, and tomato are detected in sera of patients with latex allergy. This finding may be due to the presence of a number of different cross-reacting antigenic structures in the latex proteins and the variability of IgE antibodies of different patients directed against different latex proteins and different epitopes. In addition, a few latex allergens may be strictly latex specific (3).

The proteins responsible for cross-sensitivity have not yet been identified. Phylogenetic dissimilarity between *H. brasiliensis* and cross-reacting fruits implies the presence of common antigens in foods and latex. Accordingly, lysozyme activity has been demonstrated for allergens in latex (40), avocado, papaya (41), and fig (42), and cross-reactivity between papain contained in papaya and latex proteins has been demonstrated (43, 44). However, the relevance of these enzymes for cross-sensitivity is not clear. Cross-sensitivity by ubiquitous plant proteins such as profilins (45, 46), plant endo-1,3-β-glucosidases (35), and patatin, a structural protein in plants (36, 47), is suggested by recent studies.

This study indicates that it may be advisable to warn patients with latex allergy about cross-sensitivity between latex and fruits, because latex allergy often precedes clinically relevant food hypersensitivity (5). Not only should information about the use of these fruits in juice, liqueur, wine, fruit salad, ice cream, jam, chewing gum, potato chips, muesli, etc. be given to patients, but they should also be informed of the fruit enzymes (papain, bromelain, and ficin) that are used in food and drugs (Table 7). Ingestion of these fruit extracts may be dangerous for sensitized patients.

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