ORIGINAL ARTICLE

Food-dependent exercise-induced allergic reactions in LTP hypersensitive subjects: new data and a critical reappraisal

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ABSTRACT

Background: Lipid transfer protein is the main cause of both primary food allergy and food-dependent exercise-induced allergic reactions (FDEIAR) in Italy. What characterizes LTP-hypersensitive patients with FDEIAR is still unclear. We investigated the key characteristics of LTP-hypersensitive patients with or without FDEIAR in a large cohort of individuals sensitized to this allergen.

Methods: 1,203 food-allergic patients, diagnosed on the basis of unequivocal clinical history and presence of circulating food allergen-specific IgE were studied. Serum IgE reactivity was assessed using the Allergen ExplorerALEX® system (Macroarray Diagnostics, Vienna, Austria). Association of specific IgE reactivities with FDEIAR was investigated, and patients with and without FDEIAR sensitized to LTP were compared.

Results: 116 subjects (9.6%) had FDEIAR. Among these, 77 (66.3%) were LTP-reactors and 16 (13.8%) were sensitized to Tri a 19 (omega-5-gliadin). Different LTPs and omega-5-gliadin emerged as the sole allergens clearly associated with FDEIAR. Severity of allergic reactions was paralleled the level of specific IgE to LTPs. Patients with FDEIAR showed significantly lower IgE levels than their counterparts with food allergy at rest, and displayed nearly identical IgE levels regardless of the severity of allergic reactions induced by exercise.

Conclusions: FDEIAR are associated with specific allergens. Specific IgE levels in LTP-hypersensitive patients with FDEIAR show an intermediate titer between those simply sensitized and those showing classic food allergy.

Key Words: Food allergy; Allergens; Lipid Transfer Protein; Anaphylaxis; Food-dependent exercise-induced anaphylaxis.

IMPACT STATEMENT

Food-dependent exercise-induced allergic reactions are associated with specific allergens (LTP proteins and omega-5-gliadin) and are characterized by sIgE levels that are intermediate between simple sensitization and classic food allergy.

1 | INTRODUCTION

Food-dependent exercise-induced allergic reactions (FDEIAR) represent a distinctive expression of IgE-mediated food allergy, characterized by the onset of wheals, angioedema, or anaphylaxis subsequent to exercise. FDEIAR appear within 6 hours, typically within 2-4 hours, of consumption of the offending food (1,2). While the role of exercise and other cofactors in food allergic reactions has already been explored (reviewed in 3), a comprehensive understanding of these phenomena remains elusive. It has been hypothesized that exercise may enhance allergen bioavailability by increasing intestinal permeability and allergen absorption (4,5), but recent studies suggest that this effect is specific to individuals with food allergy and does not occur in normal control subjects (6). Some authors posit that exercise induces heightened blood circulation in various body regions, resulting in relative hypo-perfusion of the gastrointestinal tract and increased permeability (7). Additionally, recent findings suggest a potential influence of exercise-induced prostaglandin inhibition on gut permeability (8).

A distinctive characteristic of patients with FDEIAR is the frequent presence of food-specific IgE at low titers (9), and skin testing reactions that often fall below the established 95% Positive Predictive Value (PPV) for diagnosing food allergy (10). While FDEIAR can be associated with

various foods, certain sources are more commonly linked to these allergic reactions. Notably, wheat (11,12), crustaceans and mollusks (12,13), and fruits (14,15) are frequently implicated. The prevalence of wheat-related reactions is very high and has led to the recognition of a distinct clinical entity termed Wheat-Dependent Exercise-Induced Anaphylaxis (WDEIA) (16). Globally, Omega-5-gliadin is identified as the primary allergen responsible for WDEIA (8,17). In Italy, however, the situation differs, with Lipid Transfer Protein (LTP) being the main allergen responsible for both FDEIAR (18) and WDEIA (19), although the reasons for this discrepancy remain unclear. Previous studies have underscored LTP as the most common cause of primary food allergy in Italy (20) as well as in other Mediterranean countries (21). In this study, we examined the key characteristics of LTP-hypersensitive patients, both with and without FDEIAR, in a large cohort of individuals sensitized to this allergen.

2 | PATIENTS AND METHODS

2.1 | Study design

We conducted a single-center cross-sectional observational clinical survey on patients with FDEIAR who were visited at the Outpatient Allergy Unit of IDI-IRCCS, a National Reference Center for Dermatological Diseases located in Rome, Italy. All patients underwent a comprehensive clinical instrumental assessment, which included the evaluation of IgE sensitization through a commercial multiplex system encompassing key environmental and food allergens.

2.2 | Setting

A total of 2,695 unselected participants born in Central or Southern Italy, presenting for a visit due to a history of adverse reactions to foods, allergic rhinitis, bronchial asthma, and/or atopic eczema, were consecutively enrolled. Data collection occurred between January 2021 and December 2023. Demographic information and clinical data were thoroughly documented using a tailored electronic database.

2.3 | Participants

The primary eligibility criterion for inclusion in the study was a history of adverse reaction to food, ranging from oral allergy syndrome to generalized urticaria to overt anaphylaxis requiring medical intervention at the emergency room with antihistamine, steroid, or adrenaline therapy. We subsequently assessed the IgE reactivity profile towards key food allergens using a macroarray method: “Act d 1 Kiwi (Actinidia deliciosa) Cysteine protease, Act d 2 Kiwi (Actinidia deliciosa) Thaumatin-like protein, Act d 5 Kiwi (Actinidia deliciosa) Kiwellin, Act d 10 Kiwi (Actinidia deliciosa) 9kDa nsLTP, Ana o 2 Cashew nut (Anacardium occidentale) 11S Globulin, Ana o 3 Cashew nut (Anacardium occidentale) 2S Albumin, Ani s 1 Anisakis (Anisakis simplex) Serine protease inhibitor, Ani s 3 Anisakis (Anisakis simplex) Tropomyosin, Api g 1 Celery (Apium graveolens) PR-10, Api g 2 Celery (Apium graveolens) 9kDa nsLTP, Api g 6 Celery (Apium graveolens) 7kDa nsLTP, Ara h 1 Peanut (Arachis hypogaea) 7S globulin, Ara h 2 Peanut (Arachis hypogaea) 2S Albumin, Ara h 3 Peanut (Arachis hypogaea) 11S Globulin, Ara h 6 Peanut (Arachis hypogaea) 2S Albumin, Ara h 8 Peanut (Arachis hypogaea) PR-10, Ara h 9 Peanut (Arachis hypogaea) 9kDa nsLTP, Ara h 15 Peanut (Arachis hypogaea) Oleosin, Ber e 1 Brazil nut (Bertholletia excelsa) 2S Albumin, Bos d 2 Cow epithelium (Bos domesticus) Lipocalin, Bos d 4 Cow's milk (Bos domesticus) Alpha-lactalbumin, Bos d 5 Cow's milk (Bos domesticus) Beta-lactoglobulin, Bos d 6 Cow's milk/meat (Bos domesticus) Serum albumin, Bos d 8 Cow's milk (Bos domesticus) Casein, Clu h 1 Atlantic herring (Clupea harengus) β-Parvalbumin, Cor a 8 Hazelnut (Corylus avellana) 9kDa nsLTP, Cor a 9 Hazelnut (Corylus avellana) 11S Globulin, Cor a 11 Hazelnut (Corylus avellana) 7/8S Globulin, Cor a 12RUO Hazelnut (Corylus avellana) Oleosin, Cor a 14 Hazelnut (Corylus avellana) 2S Albumin, Cra c 6 Brown shrimp (Crangon crangon) Troponin C, Cuc m 2 Muskmelon (Cucumis melo) Profilin, Dau c 1 Carrot (Daucus carota) PR-10, Fag e 2 Buckwheat (Fagopyrum esculentum) 2S Albumin, Fra a 1|Fra a 3 Strawberry (Fragaria ananassa) PR-10|LTP, Gad m 1 Atlantic cod (Gadus morhua) β-Parvalbumin, Gad m 2/3 Atlantic cod (Gadus morhua) β-Enolase/Aldolase, Gal d 1 Egg white (Gallus domesticus) Ovomucoid, Gal d 2 Egg white (Gallus domesticus) Ovalbumin, Gal d 3 Egg white (Gallus domesticus) Conalbumin/Ovotransferrin, Gal d 4 Lisozyme C, Gal d 5 Egg yolk/chicken meat (Gallus domesticus) Livetin/Serum albumin, Gly m 4 Soybean (Glycine max) PR-10, Gly m 5 Soybean (Glycine max) 7S globulin, Gly m 6 Soybean

(Glycine max) 11S Globulin, Gly m 8 Soybean (Glycine max) 2S Albumin, Jug r 1 Walnut (Juglans regia) 2S Albumin, Jug r 2 Walnut (Juglans regia) 7/8S Globulina, Jug r 3 Walnut (Juglans regia) 9kDa nsLTP, Jug r 4 Walnut (Juglans regia) 11S Globulin, Jug r 6 Walnut (Juglans regia) 7/8S Globulina, Mac i 2S Albumin Macadamia integrifolia 2S Albumin, Mal d 1 Apple (Malus domestica) PR-10, Mal d 2 Apple (Malus domestica) TLP, Mal d 3 Apple (Malus domestica) 9kDa nsLTP, Pap s 2S Albumin Poppy seed (Papaver somniferum) 2S Albumin, Pen m 1 "Black-Tiger shrimp (Penaeus monodon) " Tropomiosina, Pen m 2 "Black-Tiger shrimp (Penaeus monodon) " Arginine kinase, Pen m 3 "Black-Tiger shrimp, (Penaeus monodon) " Myosin LC, Pen m 4 "Black-Tiger shrimp (Penaeus monodon) " Sarc CBP, Pis v 1 Pistachio (Pistacia vera) 2S Albumin, Pis v 2 Pistachio (Pistacia vera) 11S Globulin, Pis v 3 Pistachio (Pistacia vera) 7/8S Globulin, Pis v 4RUO Pistachio (Pistacia vera) Mn-SOD, Pru p 3 Peach (Prunus persica) 9kDa nsLTP, Pru p 7RUO Peach (Prunus persica) GRP, Raj c α-Parvalbumin Thornback ray (Raja clavata) Parvalbumin, Sal s 1 Salmon (Salmo salar) β-Parvalbumin, Sco s 1 Atlantic mackerel (Scomber scombrus) β-Parvalbumin, Ses i 1 Sesame seed (Sesamum indicum) 2S Albumin, Sin a 1 Mustard (Brassica / Sinapis spp.) 2S Albumin, Sola l 6 Tomato (Solanum lycopersicum) 7kDa nsLTP, Thu a 1 Tuna (Thunnus albacares) β-Parvalbumin, Tri a 14 Wheat (Triticum aestivum) 9kDa nsLTP, Tri a 19 Wheat (Triticum aestivum) ω-5-Gliadina, Tri a aA_TI Wheat (Triticum aestivum) α-AmilasiTI, Vit v 1 Grape (Vitis vinifera) 9kDa nsLTP, Xip g 1 Swordfish (Xiphias gladius) β-Parvalbumin, Zea m 14 Corn, cereals (Zea mays) 9kDa nsLTP". Additionally, we recorded the foods associated with the occurrence of reactive episodes as gathered from the medical history.

2.4 | Variables

The initial variables considered were age, gender, and total IgE levels. Additionally, we assessed specific reactivity to key food allergens, both plant-based and animal-derived.

2.5 | Data sources/ measurement

Serum IgE reactivity was assessed using the Allergen ExplorerALEX® system (Macroarray Diagnostics, Vienna, Austria). In this method, a large number of allergens and extracts are applied to a nitrocellulose membrane within a cartridge chip. The chip is incubated with 0.5 mL of patient's

serum, diluted 1:5 and containing a CCD (cross-reactive carbohydrate determinants) inhibitor, with continuous agitation. Following a two-hour incubation, the chips undergo three washings and a pre-titrated dilution of anti-human IgE labeled with alkaline phosphatase is introduced and incubated for 30 minutes. After another thorough washing cycle, the enzyme substrate is added, and the reaction is halted after eight minutes by the addition of 100 µL of ALEX Stop Solution. The membranes are dried, and a charge-coupled device camera measures the color reaction intensity for each allergen spot. The dedicated software digitizes the images and generates a report listing the allergens and components along with their scores in kUA/L. Finally, an arbitrary calibration curve is established by reacting four spots with decreasing concentrations of specific IgE (<0.3 kUA/L, 0.3-1 kUA/L, 1-5 kUA/L, 5-15 kUA/L, and >50 kUA/L). A concentration of ≥0.3 kUA/L is considered positive.

2.6 | Bias

The diagnosis of food allergy was not confirmed through blinded or open oral food challenges but relied solely on anamnestic findings, supported by records of admissions to the Emergency Room and the administration of therapies aimed at addressing clinical presentations of generalized urticaria or anaphylaxis.

2.7 | Quantitative variables

We examined the quantitative differences in specific IgE levels, comparing them with observations in individuals characterized by clinical conditions distinct from FDEIAR.

2.9 | Statistical methods

All data underwent analysis utilizing the SPSS/PC + statistical package for statistical assessment (IBM SPSS, version 29, Chicago, IL). Demographic (age and gender), clinical, and laboratory data for patients attending the outpatient Allergy clinic and undergoing specific IgE testing were sought and compiled using the TD-Synergy Laboratory Information System.

In the univariate analysis, the non-parametric Mann-Whitney U-test (for two groups) was initially employed to compare continuous IgE values among males, females, and subjects with or without

specific clinical involvement. Subsequently, each variable of interest was dichotomized into negative or positive categories to scrutinize the proportion of subjects exhibiting symptoms in the resulting two groups.

For the assessment of paired observations on two variables expressed in a contingency table, Pearson's χ2 test or Fisher's exact test (utilized for two-by-two contingency tables with fewer than 50 cases) was employed to ascertain independence between them.

2.10| Ethical issues

The study received approval from the Ethical Committee of IDI-IRCCS (IDI-IRCCS CE | 495-17). Data collection was carried out in an anonymous manner, utilizing solely information gathered from routine specialist surveys. Enlisted patients granted informed consent for the use of their clinical data in an anonymized format.

3 | RESULTS

A total of 1,203 patients (804 [66.8%] females, mean age 36.9±18.6), diagnosed as having food allergy or hypersensitivity, were included in the analysis. Among them, 116 participants (9.6%, 75 females, mean age 34.3±14.7) had exercise-induced allergic reactions to foods (FDEIAR). Patients with and without FDEIAR did not differ in terms of mean age and sex distribution.

Focusing on the subset of participants with FDEIAR, 77 (66.3%) of these individuals showed both a positive clinical history and IgE reactivity to at least one of the non-specific Lipid Transfer Proteins (nsLTPs) included in the proteomic test, whereas 16 individuals exhibited reactivity to Tri a 19 (omega-5 gliadin), 16 to PR10, 8 to profilins, 8 to Tropomyosin, 7 to seed storage proteins, 6 to Act d 1 from kiwi, while none showed reactivity to egg or milk molecules. Participants reactive to nsLTPs affected by FDEIAR reported adverse reactions mainly correlated with the intake of Rosaceae (peach, apricot, and more rarely cherry) or walnut.

Figure 1 illustrates the association of allergy to various food allergens with exercise as a co-factor. Different Lipid Transfer Proteins (LTPs) along with omega-5-gliadin emerged as the sole allergens

clearly associated with FDEIAR. Molecules not significantly associated with the occurrence of a reactive episode due to physical exercise after food intake are not depicted in the figure.

The subgroup of patients hypersensitive to LTPs (631 individuals, 52.4% of participants with food allergy) was specifically investigated. These patients were categorized into: a) sensitized but not allergic (18.6%); b) allergic with only local symptoms (oral allergy syndrome) (33.5%); c) allergic with urticaria at rest (31.4%); d) allergic with anaphylaxis (4.3%) and e) allergic with FDEIAR (n = 77; 12.2%). Among FDEIAR patients, 42.8% had experienced an anaphylactic reaction requiring the use of adrenaline, while the remaining had a history of generalized urticaria with or without angioedema that responded to steroids and antihistamines. As illustrated in Figure 2, the severity of allergic reactions was associated with an increase in specific IgE to LTPs. Interestingly, patients with FDEIA exhibited reduced IgE levels compared to those with anaphylaxis at rest. Further, IgE levels in FDEIA were in several cases lower than in patients with urticaria/angioedema at rest (Pru p 3, Vit v 1, Zea m 14) and similar in the other cases (Figure 2). Finally, notably, FDEIAR patients displayed nearly identical IgE levels regardless of the severity of allergic reactions induced by exercise (Figure 2)).

4| DISCUSSION

Several lines of evidence indicate that patients with Food-Dependent Exercise-Induced Allergic Reactions (FDEIAR) are clinically similar to those with classical food allergy at rest. In studies of Wheat-Dependent Exercise-Induced Anaphylaxis (WDEIA), Christensen and colleagues demonstrated that exercise significantly lowered the threshold of the offending dose (22,23). Importantly, they also found that a substantial proportion of patients with a history of WDEIA react to the offending food also at rest if they are challenged with a sufficiently elevated dose of allergen (23). Furthermore, they observed that exercise causes a drop in the offending dose of food and an increase in the severity of the reaction (23). Reactivity also at rest by WDEIA patients was confirmed in another study by the same group (24), which also showed that exercise and nonsteroidal anti-inflammatory drugs (NSAID) act synergistically in reducing the offending food dose and increasing the severity of allergic reactions. Interestingly, exercise does not cause any

increase in circulating gliadin in healthy subjects (6), suggesting that patients with WDEIA may have a predisposition to the additional effect of cofactors, such as hyperresponsivity of the intestinal epithelium, possibly secondary to a specific damage (6).

Surprisingly enough, studies on FDEIAR have rarely addressed the other two main variables in this type of food allergy: the nature and characteristics of the offending allergen(s) and specific IgE levels. This is now feasible thanks to the widespread availability of recombinant food allergens for component-resolved diagnosis. It is evident that the intrinsic nature of the allergen plays a relevant role if most cases of FDEIAR are reported in patients hypersensitive to omega-5-gliadin worldwide or lipid transfer protein in the Mediterranean area, as also clearly shown in the present study. The relevance of specific, particular food allergens is supported by studies of patients with FDEIA induced by crustaceans, whose clinical reactions rarely seem to involve the major allergens of this food source (25,26). Similarly, an old study by one of us showed that a patient with egg and poultry-induced FDEIA reacted to a common, cross-reacting allergen at about 77 kDa, possibly conalbumin (27). Another emerging food allergen as a possible cause of FDEIA is gibberellin-regulated protein, a recently discovered cause of pollen-food allergy syndrome that occurs in patients primarily sensitized to Cup a 7, a minor allergen in cypress pollen (28-30). Taken together, the study of a wide range of components related to food allergy has unequivocally demonstrated that only LTPs and Tri a 19 may have a correlation as factors favoring an adverse reaction induced by physical exertion. All other tested foods do not exhibit this behavior. It will be interesting to evaluate and understand the biological, metabolic, or catabolic reasons that may underlie what has been observed. To date, only certain plant-based foods, specifically LTPs and omega-5-gliadin, are capable of eliciting an adverse reaction induced by physical exertion, both compartmental and anaphylactic.

Regarding the levels of IgE specific for the offending foods, older studies already noted that these were generally lower than usual (9), a finding that was confirmed at a molecular level in our patients hypersensitive to Lipid Transfer Protein (LTP). We did not observe any difference in the dosage of IgE synthesized towards different LTP when comparing values in patients with non-

anaphylactic FDEIAR to those with post-prandial exertion-induced anaphylaxis. Interestingly, IgE levels observed in cases of anaphylaxis directly related to food intake without the need for any cofactor (neither physical exertion nor the use of anti-inflammatories, data not shown) were significantly higher in the case of reactivity to LTP from peanuts, nuts, apples, peaches (notably the most significantly different), and corn.

In conclusion, food allergic reactions induced by exercise appear to be preferentially associated with specific allergens. Patients produce a limited amount of IgE that demonstrate an intermediate titer between subjects simply sensitized but tolerant and patients with a classic food allergy. Based on literature data, FDEIAR and classic food allergy seem capable to coexist in patients sensitized to these allergens.

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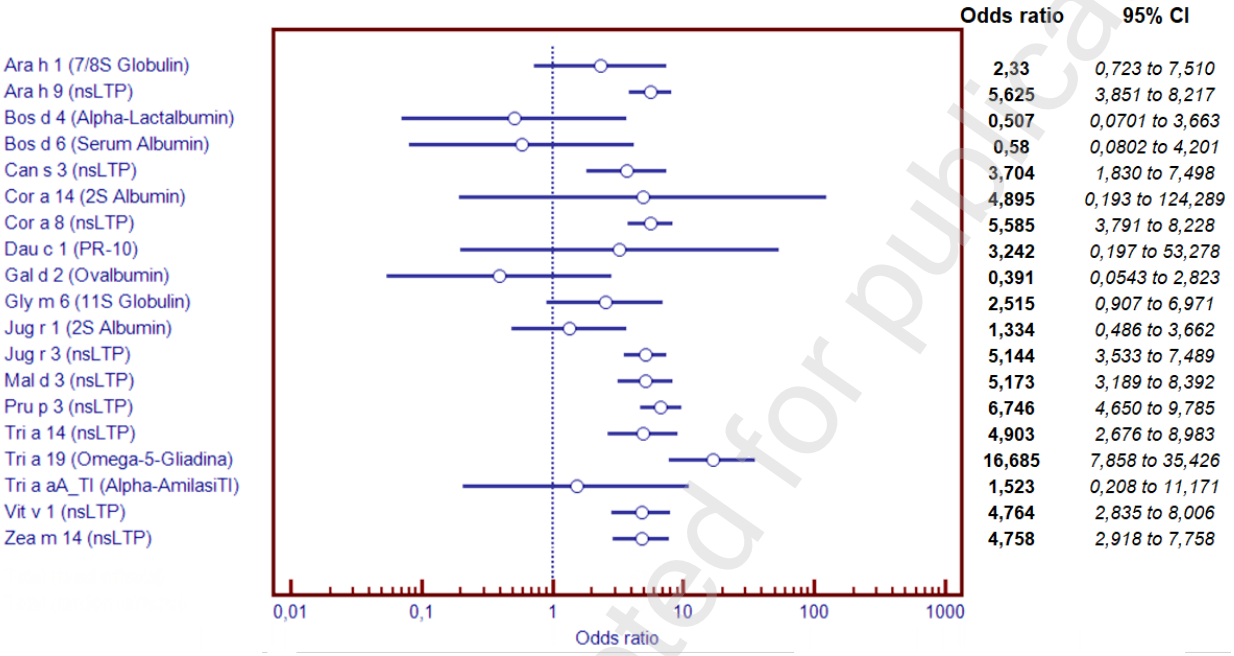
	Sensitized		FDEIA		SOA		Systemic Reaction		Anaphylaxis	
Act d 1 (Pectate lyase)	*11*	0,9%	*6*	0,5 %	*39*	3,2%	*45*	3,7%	*22*	1,8%
Act d 10 (nsLTP)	*25*	2,1%	*18*	1,5 %	*85*	7,1%	*119*	9,9%	*51*	4,2%
Act d 2 (TLP)	*8*	0,7%	*8*	0,7 %	*21*	1,7%	*32*	2,7%	*13*	1,1%
Act d 5 (Kiwellin)	*0*	0,0%	*0*	0,0 %	*0*	0,0%	*2*	0,2%	*2*	0,2%
Ana o 2 (11S Globulin)	*3*	0,2%	*0*	0,0 %	*3*	0,2%	*3*	0,2%	*1*	0,1%
Ana o 3 (2S Albumin)	*4*	0,3%	*1*	0,1 %	*11*	0,9%	*20*	1,7%	*8*	0,7%
Ani s 1 (Kunitz Serin PI)	*7*	0,6%	*2*	0,2 %	*9*	0,7%	*16*	1,3%	*2*	0,2%
Ani s 3 (Tropomyosin)	*16*	1,3%	*5*	0,4 %	*23*	1,9%	*38*	3,2%	*12*	1,0%
Api g 1 (PR-10)	*11*	0,9%	*3*	0,2 %	*30*	2,5%	*29*	2,4%	*6*	0,5%
Api g 2 (nsLTP)	*23*	1,9%	*16*	1,3 %	*74*	6,2%	*97*	8,1%	*52*	4,3%
Api g 6 (nsLTP)	*13*	1,1%	*5*	0,4 %	*30*	2,5%	*40*	3,3%	*16*	1,3%
Ara h 1 (7/8S Globulin)	*5*	0,4%	*1*	0,1 %	*19*	1,6%	*23*	1,9%	*9*	0,7%
Ara h 15 (Oleosin)	*0*	0,0%	*1*	0,1 %	*2*	0,2%	*2*	0,2%	*0*	0,0%
Ara h 2 (2S Albumin)	*4*	0,3%	*0*	0,0 %	*8*	0,7%	*14*	1,2%	*4*	0,3%
Ara h 3 (11S Globulin)	*5*	0,4%	*0*	0,0 %	*10*	0,8%	*13*	1,1%	*3*	0,2%
Ara h 6 (2S Albumin)	*5*	0,4%	*1*	0,1 %	*13*	1,1%	*16*	1,3%	*3*	0,2%
Ara h 8 (PR-10)	*16*	1,3%	*4*	0,3 %	*33*	2,7%	*26*	2,2%	*7*	0,6%
Ara h 9 (nsLTP)	*32*	2,7%	*55*	4,6 %	*138*	11,5 %	*193*	16,0 %	*83*	6,9%
Ber e 1 (2S Albumin)	*1*	0,1%	*0*	0,0 %	*4*	0,3%	*4*	0,3%	*1*	0,1%
Bos d 2 (Lipocalin)	*2*	0,2%	*0*	0,0 %	*2*	0,2%	*3*	0,2%	*2*	0,2%
Bos d 4 (α-Lactalbumin)	*2*	0,2%	*0*	0,0 %	*5*	0,4%	*12*	1,0%	*8*	0,7%
Bos d 5 (β-Lactoglobulin	*2*	0,2%	*0*	0,0 %	*6*	0,5%	*14*	1,2%	*8*	0,7%
Bos d 6 (Serum Albumin)	*3*	0,2%	*0*	0,0 %	*5*	0,4%	*9*	0,7%	*5*	0,4%
Bos d 8 (Casein)	*2*	0,2%	*0*	0,0 %	*8*	0,7%	*16*	1,3%	*10*	0,8%
Can s 3 (nsLTP)	*15*	1,2%	*10*	0,8 %	*43*	3,6%	*58*	4,8%	*33*	2,7%
Clu h 1 (β-ParvAlbumin)	*6*	0,5%	*1*	0,1 %	*9*	0,7%	*21*	1,7%	*6*	0,5%

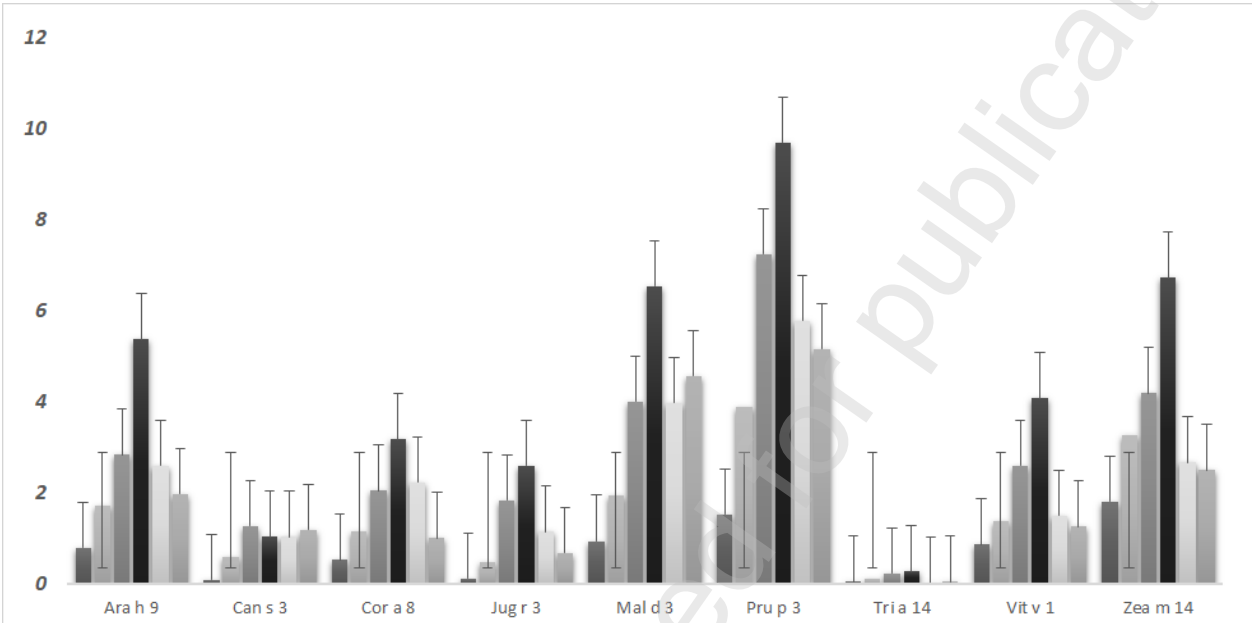
Cor a 1.0401 (PR-10)	*38*	3,2%	*9*	0,7 %	*84*	7,0%	*82*	6,8%	*21*	1,7%
Cor a 11 (7/8S Globulin)	*14*	1,2%	*3*	0,2 %	*23*	1,9%	*28*	2,3%	*12*	1,0%
Cor a 12RUO (Oleosin)	*1*	0,1%	*0*	0,0 %	*0*	0,0%	*1*	0,1%	*0*	0,0%
Cor a 14 (2S Albumin)	*4*	0,3%	*2*	0,2 %	*13*	1,1%	*23*	1,9%	*10*	0,8%
Cor a 8 (nsLTP)	*24*	2,0%	*39*	3,2 %	*101*	8,4%	*155*	12,9 %	*64*	5,3%
Cor a 9 (11S Globulin)	*6*	0,5%	*3*	0,2 %	*14*	1,2%	*21*	1,7%	*9*	0,7%
Cra c 6 (Troponina C)	*4*	0,3%	*0*	0,0 %	*6*	0,5%	*7*	0,6%	*1*	0,1%
Cuc m 2 (Profilin)	*30*	2,5%	*4*	0,3 %	*74*	6,2%	*71*	5,9%	*18*	1,5%
Dau c 1 (PR-10)	*11*	0,9%	*1*	0,1 %	*33*	2,7%	*27*	2,2%	*7*	0,6%
Fag e 2 (2S Albumin)	*2*	0,2%	*0*	0,0 %	*3*	0,2%	*3*	0,2%	*0*	0,0%
Gad m 1 (β-Parvalbumin)	*5*	0,4%	*1*	0,1 %	*9*	0,7%	*20*	1,7%	*7*	0,6%
Gad m 2/3 (Enolase/Aldolase)	*1*	0,1%	*0*	0,0 %	*2*	0,2%	*4*	0,3%	*1*	0,1%
Gal d 1 (Ovomucoid)	*4*	0,3%	*0*	0,0 %	*4*	0,3%	*13*	1,1%	*8*	0,7%
Gal d 2 (Ovalbumin)	*4*	0,3%	*0*	0,0 %	*5*	0,4%	*17*	1,4%	*11*	0,9%
Gal d 3 (Ovotransferrin)	*4*	0,3%	*0*	0,0 %	*5*	0,4%	*10*	0,8%	*6*	0,5%
Gal d 4 (Lisozima C)	*10*	0,8%	*0*	0,0 %	*4*	0,3%	*11*	0,9%	*4*	0,3%
Gal d 5 (Serum Albumin)	*1*	0,1%	*0*	0,0 %	*2*	0,2%	*3*	0,2%	*3*	0,2%
Gly m 4 (PR-10)	*14*	1,2%	*2*	0,2 %	*31*	2,6%	*26*	2,2%	*8*	0,7%
Gly m 5 (7/8S Globulin)	*0*	0,0%	*0*	0,0 %	*2*	0,2%	*2*	0,2%	*2*	0,2%
Gly m 6 (11S Globulin)	*9*	0,7%	*2*	0,2 %	*10*	0,8%	*15*	1,2%	*8*	0,7%
Gly m 8 (2S Albumin)	*1*	0,1%	*0*	0,0 %	*0*	0,0%	*3*	0,2%	*3*	0,2%
Jug r 1 (2S Albumin)	*7*	0,6%	*5*	0,4 %	*33*	2,7%	*44*	3,7%	*16*	1,3%
Jug r 2 (7/8S Globulin)	*12*	1,0%	*9*	0,7 %	*32*	2,7%	*42*	3,5%	*14*	1,2%
Jug r 3 (nsLTP)	*22*	1,8%	*51*	4,2 %	*95*	7,9%	*145*	12,1 %	*55*	4,6%
Jug r 4 (11S Globulin)	*8*	0,7%	*3*	0,2 %	*23*	1,9%	*30*	2,5%	*13*	1,1%
Jug r 6 (7/8S Globulin)	*12*	1,0%	*1*	0,1 %	*27*	2,2%	*23*	1,9%	*7*	0,6%
Mac i 2S Albumina	*1*	0,1%	*1*	0,1 %	*9*	0,7%	*11*	0,9%	*6*	0,5%
Mal d 1 (PR-10)	*35*	2,9%	*9*	0,7 %	*80*	6,7%	*70*	5,8%	*15*	1,2%
Mal d 2 (TLP)	*0*	0,0%	*0*	0,0 %	*1*	0,1%	*5*	0,4%	*2*	0,2%
Mal d 3 (nsLTP)	*32*	2,7%	*31*	2,6 %	*139*	11,6 %	*195*	16,2 %	*87*	7,2%

Pap s 2S Albumin	*3*	0,2%	*0*	0,0 %	*4*	0,3%	*5*	0,4%	*1*	0,1%
Pen m 1 (Tropomyosin)	*14*	1,2%	*3*	0,2 %	*21*	1,7%	*30*	2,5%	*11*	0,9%
Pen m 2 (Arginin chinasi)	*15*	1,2%	*1*	0,1 %	*13*	1,1%	*19*	1,6%	*6*	0,5%
Pen m 3 (Myosin light chain)	*3*	0,2%	*1*	0,1 %	*3*	0,2%	*8*	0,7%	*1*	0,1%
Pen m 4 (Sarcoplasmic CBP)	*0*	0,0%	*0*	0,0 %	*3*	0,2%	*5*	0,4%	*2*	0,2%
Pis v 1 (2S Albumin)	*6*	0,5%	*1*	0,1 %	*11*	0,9%	*17*	1,4%	*6*	0,5%
Pis v 2 (11S Globulin)	*2*	0,2%	*1*	0,1 %	*9*	0,7%	*10*	0,8%	*5*	0,4%
Pis v 3 (7/8S Globulin)	*3*	0,2%	*0*	0,0 %	*10*	0,8%	*12*	1,0%	*7*	0,6%
Pru p 3 (nsLTP)	*49*	4,1%	*70*	5,8 %	*204*	17,0 %	*284*	23,6 %	*108*	9,0%
Pru p 7RUO	*4*	0,3%	*0*	0,0 %	*8*	0,7%	*14*	1,2%	*9*	0,7%
Raj c α-Parvalbumin	*2*	0,2%	*1*	0,1 %	*4*	0,3%	*5*	0,4%	*1*	0,1%
Sal s 1 (β-Parvalbumin)	*7*	0,6%	*1*	0,1 %	*11*	0,9%	*24*	2,0%	*9*	0,7%
Sco s 1 (β-Parvalbumin)	*7*	0,6%	*1*	0,1 %	*10*	0,8%	*26*	2,2%	*9*	0,7%
Ses i 1 (2S Albumin)	*9*	0,7%	*3*	0,2 %	*17*	1,4%	*20*	1,7%	*10*	0,8%
Sin a 1 (2S Albumin)	*1*	0,1%	*0*	0,0 %	*2*	0,2%	*2*	0,2%	*1*	0,1%
Sola l 6 (nsLTP)	*15*	1,2%	*4*	0,3 %	*21*	1,7%	*33*	2,7%	*19*	1,6%
Thu a 1 (β-Parvalbumin)	*8*	0,7%	*1*	0,1 %	*13*	1,1%	*25*	2,1%	*8*	0,7%
Tri a 14 (nsLTP)	*3*	0,2%	*13*	1,1 %	*12*	1,0%	*24*	2,0%	*9*	0,7%
Tri a 19 (ω-5-Gliadin)	*1*	0,1%	*16*	1,3 %	*6*	0,5%	*30*	2,5%	*7*	0,6%
Tri a 30 (α-amylase inhibitor)	*2*	0,2%	*0*	0,0 %	*0*	0,0%	*4*	0,3%	*2*	0,2%
Vit v 1 (nsLTP)	*28*	2,3%	*23*	1,9 %	*99*	8,2%	*130*	10,8 %	*63*	5,2%
Xip g 1 (β-Parvalbumin)	*11*	0,9%	*1*	0,1 %	*17*	1,4%	*28*	2,3%	*11*	0,9%
Zea m 14 (nsLTP)	*36*	3,0%	*29*	2,4 %	*135*	11,2 %	*182*	15,1 %	*84*	7,0%

Legend to Figure 1: Forest diagram depicting the correlation between sensitization to various food allergens and Food-Dependent Exercise-Induced Allergic Reactions. The association is present for various Lipid Transfer Proteins (LTPs) such as Ara h 9, Can s 3, Cor a 8, Jug r 3, Mal d 3, Pru p 3, Tri a 14, and Zea m 14 as well as with Tri a 19 (omega-5-gliadin).



Legend to Figure 2: Mean specific IgE levels to Lipid Transfer Protein (LTP) in patients who sensitized but tolerant to plant-derived foods or experiencing allergic reactions of varying severity, with or without exercise as a cofactor. Individuals with a history of Food-Dependent Exercise-Induced allergic reactions (FDEIAR) or Anaphylaxis (FDEIA) exhibit reduced IgE levels compared to those experiencing food anaphylaxis at rest.



T-Test		Ara h 9	Can s 3	Cor a 8	Jug r 3	Mal d 3	Pru p 3	Tri a 14	Vit v 1	Zea m 14
FDEIAR *vs*	***Tolerant***	P = 0.02	P = 0.03	P = 0.02	P = 0,01	P = 0,001	P = 0,0001	*ns*	*ns*	*ns*
	Oral allergy Syndrome	*ns*	*ns*	*ns*	P = 0,04	P = 0,005	*ns*	*ns*	*ns*	*ns*
	Urticaria - Angioedema	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	Anapylaxys	P = 0,01	*ns*	*ns*	P = 0.03	P = 0,03	P = 0,006	*ns*	*ns*	P = 0,01