



# Interaction between foods and nonsteroidal anti-inflammatory drugs and exercise in the induction of anaphylaxis

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## Purpose of review

To assess the studies that focus on the study of food-dependent exercise-induced anaphylaxis (FDEIA) and food-dependent NSAID-induced anaphylaxis (FDNIA).

## Recent findings

Cofactors, as exercise and nonsteroidal anti-inflammatory drugs (NSAIDs), are relevant in up to 30% of episodes of anaphylaxis. Gliadin and lipid transfer proteins are the main allergens involved. The attempts to reproduce FDEIA and FDNIA in a controlled setting have an important failure rate. The cyclooxygenase (COX) pathway could play an important role in the underlying mechanisms: NSAIDs and exercise increase the permeability of the intestinal barrier. This effect is stronger with NSAID that inhibit both isoforms than with preferential COX-2 inhibitor. Basophils obtained from FDNIA patients, showed an increase of its activation with the food allergen with lysine–aspirin compared with the food allergen alone. This potentiating effect was not observed when basophils were stimulated with the food allergen with selective COX-2 inhibitor. Other mechanisms including transient receptor potential superfamily, reactive oxygen species, altered B-cell pathway and increased neutrophil activation markers have been speculated.

## Summary

The frequent implication of cofactors, as exercise and NSAID, in food-induced anaphylaxis highlights the importance of recognizing and including them into diagnostic workup. The understanding of the underlying mechanisms would help in the development of diagnostic and therapeutic strategies.

## Keywords

food allergy, food-dependent exercise-induced anaphylaxis, food-dependent nonsteroidal anti-inflammatory drug-induced anaphylaxis

## INTRODUCTION

Anaphylaxis is an acute, life-threatening, multisystem syndrome resulting from the sudden release of mediators derived from mast cells and basophils [1]. The frequency of hospital admissions for anaphylaxis, including food-induced anaphylaxis, is increasing, although its mortality rate remains stable [2]. Food allergens are consistently the main triggers for anaphylaxis in children and teens [3]. In adults, there is a great variability depending on the series and the geographical area, with series reporting drugs, insects [4,5] but also food [6,7] as main elicitors. The number of food allergy reactions that resulted in anaphylaxis is highly variable and depending on the study ranges from 0.4% to almost 40% [8,9]. Differences in age, food and geographic area found in those studies may account for the important variability. In adults, a recent study shows that food allergy typically begins in the

second and third decade and almost 50% of these patients report anaphylaxis. Interestingly, an older age at time of diagnosis was associated with higher risk for severe reactions [10].

Cofactors are defined by the European Academy of Allergy and Clinical Immunology (EAACI) guidelines as ‘patient-related or external circumstances that are associated with more severe allergic reactions’ and include exercise, alcohol and

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## KEY POINTS

- Food-dependent exercise-induced anaphylaxis (FDEIA) has been considered a subtype of exercise-induced anaphylaxis (EIA) where both allergic sensitization to food and exercise are necessary factors.
- Two phenotypes of FDEIA could be identified; an on/off phenomenon where the exercise may act as a switcher and another one where exercise worsen preexisting symptoms.
- The spectrum of foods involved in FDEIA and FDNIA is wide (wheat, nuts, seeds, vegetables, shellfish, ...). Gliadin and LTP are the main food allergens involved.
- Some of the patients with clinical history of anaphylaxis compatible with NSAID hypersensitivity and negative test with the culprit drug, could be patients with food allergy associated to a NSAID hypersensitivity acting as a cofactor.
- There is no validated protocol for FDEIA and FDNIA diagnosis. Preventive treatments are not available. The underlying mechanisms still are unclear. Thus, further studies focused in FDEIA and FDNIA are needed.

nonsteroidal anti-inflammatory drugs (NSAIDs) among others [11]. Cofactors, also known as augmenting factors, could explain why patients sometimes could tolerate some foods and some others not, and why the same food could induce allergic reactions of different severity at different moments. Although the exact underlying mechanisms is poorly understood, in the presence of these cofactors, allergic reactions may be amplified or triggered at lower doses of allergen (from two to six times depending on the series) [9,12–14]. Cofactors are relevant in up to 30% of episodes of anaphylaxis [12] and some of them, as alcohol or exercise, have been suggested as a risks factors for fatal anaphylaxis [2,15]. Most of the evidence related to cofactors arises from studies in adult patients and it has not yet been optimally studied in pediatric population. The frequent implication of cofactors in food-induced anaphylaxis highlights the importance of recognizing and including them into diagnostic workup. Furthermore, the better understanding of the underlying mechanisms would help in the development of therapeutic and prophylactic strategies.

## EXERCISE AND FOOD-INDUCED ANAPHYLAXIS

Exercise-induced anaphylaxis (EIA) is a rare syndrome including two different anaphylaxis phenotypes in which exercise or physical activity are

common triggers. Food-dependent exercise-induced anaphylaxis (FDEIA) has been considered a subtype of EIA where both allergic sensitizations to food and exercise are necessary factors [16]. Conversely, pure EIA patients are not sensitized to food. The exact underlying mechanisms in all of EIA phenotypes are still unknown. Interestingly, all suggested hypothesis have been proposed for FDEIA, where the exercise somehow modulates the IgE-mediated response induced by the food. For this reason, this review will focus in FDEIA.

No hypothesis for pure EIA has been proposed. Exercise-induced asthma is a similar phenomenon where bronchospasm is triggered by exercise and (supposedly) no allergens are required. Similarly, the underlying mechanisms are not clear but some hypotheses suggest that the airway rewarming associated to exercise may stimulate mast cells. Therefore, the mediators released from mast cells through thermal stimuli would be responsible for bronchial obstruction [17,18]. In the same way, as a hypothesis, exercise would increase the temperature in most other tissues inducing a massive release of mediators from mast cells in multiple organs, triggering a systemic reaction, in our case, an EIA.

FDEIA have been described mostly in adolescents and young adults, but also in preadolescent children and older adults. The female-to-male ratio observed in most studies is 1:1, although a great heterogeneity can be found. Interestingly, a Japanese study showed an important change of this ratio, from 2:11 to 1:1, in two different studies performed 14 years apart in similar populations of high school students [19].

There is almost no data regarding its prevalence and incidence because it has been reported as an individual cases or short series. One of the few attempts to establish FDEIA prevalence is a Japanese study performed in high school students in 2012. After evaluating 76 534 students (39 767 boys) they found a prevalence of 0.018%, with no differences between boys and girls. The major causative food were crustaceans and wheat [19]. Previously, the same authors performed a study in the same population and did not observe changes in FDEIA prevalence or culprit foods [20]. A similar work, this time in 170 146 elementary school children, found significantly lower prevalence (0.0047%), although the food triggers were similar (wheat, crustaceans and soy) [21].

Wheat, particularly  $\omega$ 5-gliadin, is the best characterized food allergen involved in FDEIA in Japan and European countries [22,23]. However, several foods have been also related, as seafood, seeds, nuts, vegetables, milk, eggs and meat in  $\alpha$ -gal allergic patients [24–28]. In the Mediterranean area, where

lipid transfer protein (LTP) sensitization is a common cause of food allergy, several plant-derived foods (legumes, nuts, vegetables, fruits) have been related to FDEIAN, including wheat because of *Tri a 14* sensitization [29–31]. Interestingly, aeroallergens have been also described as FDEIAN triggers; dust mites contaminating flour have been suggested as an elicitor of anaphylaxis in dust mite allergic patients [32].

FDEIAN generally occurs following submaximal exercise of a relatively short duration, although a huge variety of physical activities have been related, as brisk walking or yard work. Jogging has been identified as the most frequent exercise related to those reactions, although almost no studies with long series of patients have been published since Shadick *et al.* [33]. These authors conducted a cross-sectional analysis of 279 individuals with EIAN for more than a decade using a validated questionnaire. They found that 218 (78%) patients referred symptoms associated to jogging, 42% to walking and around 25% when playing tennis, dancing or bicycling. Recently, the analysis of the European Anaphylaxis Registry has shown that vigorous exercise reported by the patients seems to be linked to a higher risk of developing severe anaphylaxis, independent from the trigger food. Actually, the registry identified exercise as a significant factor increasing the risk for severe drug-induced anaphylaxis too. When the analysis was restricted to food anaphylaxis, the intensity of the exercise correlated with the risk of developing more severe reactions [34]. Interestingly, although the number of persons exercising has increased, and fitness is more fast-paced and intense than ever (spinning, zumba, ...), it does not have apparently changed the prevalence of FDEIAN.

In most cases of FDEIAN, symptoms occur when the food is ingested within minutes to 2 hours before exercise, although it has been reported reactions with food ingested up to 6 h before exercise. A study with 54 patients performed in Italy by Romano *et al.* [35], found that the time elapsed between meal and exercise ranged from 30 to 120 min, and the duration of exercise before the onset of symptoms ranged from 10 to 50 min. Shadick *et al.* [33] showed that 90% of patients develop symptoms within 30 min after initiating exercise. Only a few reports suggest that patients can develop an anaphylaxis when consuming the culprit food shortly after exercising [36]. However, considering that these patients develop severe reactions, the routine recommendations of food avoidance must be extended also after exercise.

It is well defined that FDEIAN patients develop anaphylaxis symptoms when exercising after/before

consuming the culprit allergen but have no symptoms when consuming the food without concomitant exercise. Actually, it has been proposed that patients with mild symptoms in absence of exercise that develop anaphylaxis when exercising must be diagnosed of food allergy exacerbated by exercise [37]. However, in several studies with supposedly FDEIAN patients, some of those had mild symptoms such as mild urticaria or oral allergic syndrome with the culprit food [35,38]. As suggested previously by other authors, it is possible that FDEIAN is actually a subtype of food allergy. In that way, two phenotypes of FDEIAN could be identified; an on/off phenomenon where the exercise may act as a switcher and another one where exercise worsen preexisting symptoms.

There is no validated protocol for exercise challenge, with or without food, to evaluate FDEIAN. Therefore, diagnosis is mainly clinical, based on compatible symptoms and allergy tests [23,39]. The attempts to reproduce FDEIAN in a controlled setting have an important failure rate, variable depending on the study from 96 to 34% [13,35,40], and frequently a great amount of allergen and the combination of several cofactors as NSAIDs are needed [13,14]. Several variables may account for the limited reproducibility of challenge tests in FDEIAN. The characteristics of the exercise such as intensity or duration that are necessary to induce an allergic reaction in each individual are not clear. Indeed, it is also unknown whether the dose of allergen required may vary at different times for the same individual or the cumulative dose is also an important factor [13,14].

The underlying mechanisms in FDEIAN are still unclear and several hypotheses have been proposed. In this regard, the EAACI published in 2015 a position statement [16] where four different hypotheses are reviewed; exercise increases gastrointestinal permeability, increases activity of tissue transglutaminase in the gut mucosa, induces blood flow redistribution, and finally, exercise increases histamine release from basophils because of an increase of plasma osmolarity.

Summarizing the analysis published by the EAACI, there is not sufficient evidence in the context of the current studies supporting that the exercise per se is sufficient to induce alterations in gastrointestinal permeability and enhance the absorption of food allergens [16]. However, the combination of exercise and other substances with capability to damage the gut mucosa may increase the risk of allergic reaction [41,42].

It has been proposed that tissue transglutaminase may create large complexes together with w5-gliadin in response to exercise because of IL-6

production. However, there is no direct evidence of tissue transglutaminase activation in response to exercise and the presence of complex allergen-transglutaminase in patients with FDEIA [43]. In the same way, the increase of IL-6 production during exercise is, at most, moderate. Robson-Asley *et al.* demonstrated that after 90 min of running, only a three-fold increase was observed [39]. Considering that FDEIA is usually related with submaximal exercise of short duration, the increase of IL-6 in those patients may not be relevant.

Blood flow redistribution induced by exercise has been related with oxidative cell damage [44] and the transport of allergens away from the gut mucosa to other tissues as skin to skeletal muscles [39,45]. Mast cells in the gut mucosa would be tolerant to those particular allergens, explaining the absence of symptoms without exercise. However, allergens would redistribute through the blood flow after exercising, allowing the stimulation of phenotypically different mast cells (not tolerant) in tissues away from the gut mucosa, and therefore inducing the allergic reaction. Although an interesting hypothesis and biologically plausible, there is no experimental evidence.

Basophil and mast cell activation because of an increase of plasma osmolarity has been demonstrated only in a few *in-vitro* studies [36,46,47]. However, the osmolarity achieved *in vitro* would be pathological *in vivo*, so the conclusions extrapolated from these studies are limited. Indeed, most studies are based in cell lines [47] or single cell models [36], limiting the extrapolation of the results to complex organisms as humans where the allergic reactions are the result of multiple cell interaction. Interestingly, although the unrealistic osmolarity and the limited extrapolation, in one study, the authors showed that the increase in basophil activation was only observed in FDEIA patients and not in healthy individuals, suggesting that basophil from FDEIA patients may be more sensitive to osmolarity changes [48].

The transient receptor potential (TRP) superfamily acts as polymodal sensors and ion channels. They regulate several cellular processes and are critical in several metabolic activities. There is an increasing amount of evidence suggesting that many of the inflammatory mediators released in allergic reaction involve two of this channels, particularly TRPV1 and TRPA1 [49]; and it may also be true in EIA. Several products released during exercise as bradykinin or hydroxyl radicals, and also heat or acidic status can activate those channels. Again, although an interesting hypothesis and is biologically plausible, there is no experimental evidence so far.

## NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND FOOD-INDUCED ANAPHYLAXIS

NSAIDs are involved in up to 25% of food-induced anaphylaxis, representing a risk factor with an odds ratio higher than 11 [50]. NSAIDs have also been demonstrated to exacerbate food allergy in patients diagnosed with FDEIA [51], although NSAIDs were not originally involved in the reactions. In this way, it has been suggested that the term 'augmentation factor-triggered food allergy,' might be more appropriate [14]. However, in the food-dependent NSAID-induced anaphylaxis (FDNIA), NSAID is the only cofactor required to enhance the allergic reaction [30,52–54]. The number of foods involved in FDEIA, when NSAID is involved as well, and FDNIA is wide (wheat, nuts, seeds, shellfish) [30,51–58].

NSAIDs are considered the most commonly implicated drugs in hypersensitivity reactions in susceptible individuals [59,60]. It is well known that atopy is a risk factor for hypersensitivity reactions to NSAIDs [61–64]. One subgroup with typical symptoms includes patients in the first and second decade of life with respiratory allergy who are sensitized to house dust mites and develop periorbital angioedema after administration of NSAIDs [63]. Moreover, some of these patients can develop anaphylaxis after ingestion of wheat flour contaminated with mites [32,65].

Diagnosis of hypersensitivity reactions to NSAIDs is based on carefully obtained information of patient history on symptom description, timing of reaction and previous episodes potentially related to NSAIDs. According to the results of Blanca-Lopez *et al.* study [66], the value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance should be taken into account as a valid diagnostic tool. In some cases, clinical history is not enough to identify the culprit drug or the underlying mechanisms and drug provocation test with the suspected drug remains the gold standard to confirm the diagnosis of NSAID hypersensitivity in patients with equivocal clinical history [59,60]. However, provocation tests are not recommended in case of severe anaphylaxis. Interestingly, according to the result of some studies, only 20–30% of patients with a previous history suggesting a NSAID-induced hypersensitivity reaction are finally classified according to the ENDA work-up approach, in the remaining 70–80%, the involvement of NSAIDs in the clinical reaction is ruled out [67–72]. It could be possible that the clinical history did not collect factors other than NSAIDs that contribute to the reaction. This may well be the case in patients with food-dependent NSAID-induced anaphylaxis. In these patients, tests

performed only with NSAIDs in the hospital setting do not reliably reproduce the events occurring in real life, where food allergens play a complementary role to the NSAID-induced hypersensitivity reaction. It could be hypothesized that some of the patients with clinical history of NSAID hypersensitivity and negative test with the culprit drug, are patients with food allergy associated to a NSAID hypersensitivity acting as a cofactor. In this way, and according to the results of Asero study [58], Romano speculated that taking into account the differential diagnosis of FDNIA in patients with suspected diagnosis of NSAID hypersensitivity reactions, it would be possible to reduce the number of individuals falsely labelled as sensitive to NSAIDs [73] in areas with a predominant LTP allergy. However, there are no methodologically well designed studies that address this issue.

Few studies have demonstrated the synergistic effect of NSAIDs and food allergen in FDNIA. Two main hypotheses have been postulated. One theory suggests that NSAIDs increase the permeability of the intestinal barrier causing a major absorption of the allergen [56]. This effect is stronger with NSAID that inhibit both isoforms of Cyclooxygenase (COX) than with preferential COX-2 inhibitor, such as meloxicam [74]. Another theory suggests that NSAIDs have a direct effect on the effector cells (mast cells and basophils) increasing their degranulation and/or activation [75,76,77]. The mechanism underlying food allergy induced by NSAID is under focus of research. The study performed by Pascal *et al.* [77] suggested that it might be related to an alteration of the COX pathway. Basophils were obtained from peach LTP allergic patients, and its activation with Pru p 3 (peach allergen) was enhanced after the addition of Lysine acetylsalicylate (L-ASA). This synergic effect was not observed when the basophils were stimulated with Pru p 3 and valdecoxib. In this same way, previous reports did not show potentiation effect of preferential COX2- inhibitors such as nimesulide and etodolac [52,75] in FDNIA patients. The probable relevance of COX in this synergic effect is also showed by the study of Wojnar *et al.* [78] who demonstrated that the enhancement of the IgE response was a NSAID class effect. Additionally, it has been demonstrated a correlation between both the dose of ASA and the degree of COX inhibition, and the enhancement of the reaction [78–80]. Over and above that, prostaglandin E is a known bioactive lipid produced from arachidonic acid by COX [81] and has shown a protective effect as a preventive treatment in the development of anaphylaxis in food allergy enhanced by NSAID [82].

Other mechanisms apart from COX pathway could also be involved in FDNIA. Supporting this

idea, a recent study [83] has demonstrated differences in the transcriptome of patients with FDNIA compared with patients who develop anaphylaxis without the intake of NSAID, suggesting that these two different phenotypes of food allergy differ in the underlying pathological mechanisms. Those included altered B-cell pathways, increased neutrophil activation markers and increased reactive oxygen species levels. These relevant results should be deeply addressed in further studies.

## CONCLUSION

Considering that new food allergens may still to be discovered, diagnostic tools in food allergy are limited even for known allergens and pure EIA diagnosis is made after ruling out food allergic sensitization. Pure EIA patients may be sensitized to a new allergen or to a known allergen that cannot be detected using the current techniques. Therefore, in all EIA phenotypes, we suggest that exercise is acting as a cofactor. Some of the patients with clinical history compatible with NSAID hypersensitivity and negative test with the culprit drug, could be patients with food allergy associated to a NSAID hypersensitivity acting as a cofactor. More research is needed in order to understand the underlying mechanism of FDEIA and FDNIA with the goal to develop diagnostic tools and effective treatments.

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## Conflicts of interest

There are no conflicts of interest.

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