SZEWCZYK, Kamila, SZEWCZYK, Bartłomiej, HOŁOWNIA, Weronika, PYTEL, Paulina, KRZESŁOWSKA, Wiktoria Julia and WIŚNIEWSKI, Szymon. Physical Activity as a Trigger for Anaphylaxis: Understanding Food-Dependent Exercise-Induced Anaphylaxis. Journal of Education, Health and Sport. 2024;74:52562. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.74.52562
https://apcz.umk.pl/JEHS/article/view/52562

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.05.2024. Revised: 25.05.2024. Accepted: 15.06.2024. Published:17.06.2024.

Physical Activity as a Trigger for Anaphylaxis: Understanding Food-Dependent Exercise-Induced Anaphylaxis

Kamila Szewczyk, Regional Specialist Hospital, 26-060 Czerwona Gora, Poland
kamholo97@gmail.com
https://orcid.org/0009-0008-4493-9593

Bartłomiej Szewczyk, St. Lucas Hospital, 26-200 Konskie, Poland
bartek.szewczyk998@gmail.com
https://orcid.org/0000-0001-8743-5186

Weronika Hołownia, Medical University of Warsaw 61 Zwirki i Wigury Street, 02-091 Warsaw, Poland
weronika.holo1@gmail.com
https://orcid.org/0009-0005-5771-6725

Paulina Pytel, Regional Specialist Hospital, 26-060 Czerwona Gora, Poland
paulinapytel079@gmail.com
https://orcid.org/0009-0001-6959-4666

Wiktoria Julia Krzesłowska, Central Clinical Hospital of Medical University of Lodz, ul. Pomorska 251, 92-213 Lodz, Poland
wiktoria.julia.krzeslowska@gmail.com
https://orcid.org/0009-0009-6368-1572

Szymon Wiśniewski, Collegium

Medicum, Jan Kochanowski University of Kielce, aleja IX Wiekow Kielc 19A, 25-317 Kielce, Poland
szymon.wisniewski.med@gmail.com
https://orcid.org/0009-0000-9474-821X

Corresponding author:
Kamila Szewczyk, Regional Specialist Hospital, 26-060 Czerwona Gora, Poland
kamholo97@gmail.com

Abstract

Introduction:

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinctive form of anaphylaxis, a severe and potentially life-threatening allergic reaction, that is triggered by physical activity following the consumption of specific food allergens. Unique in its manifestation, FDEIA embodies a complex interaction between food intake and exercise, making it a condition of noteworthy concern particularly among athletes and active individuals.

Aim of the study:

This article endeavors to explore the multifaceted nature of food-dependent exercise-induced anaphylaxis, beginning with a foundational understanding of anaphylaxis and the specific dynamics involved in exercise-induced reactions.

Material and methods:

Literature available in the PubMed database was reviewed using the following keywords: food-dependent exercise induced anaphylaxis; exercise induced-anaphylaxis; food allergies; pathogenesis of FDEIA; diagnosis of FDEIA; sport and anaphylaxis.

Conclusions:

FDEIA is a unique and complex condition that requires a comprehensive understanding for effective management. By exploring its various aspects, from pathophysiology to diagnosis and treatment, we can better equip individuals with the knowledge and tools to navigate this condition and minimize the risk of potentially life-threatening reactions.

Keywords: food-dependent exercise induced anaphylaxis; exercise induced-anaphylaxis; food allergies; pathogenesis of FDEIA; diagnosis of FDEIA; sport and anaphylaxis;

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinctive form of anaphylaxis, a severe and potentially life-threatening allergic reaction, that is triggered by physical activity following the consumption of specific food allergens. This condition, which is of noteworthy concern particularly among athletes and active individuals, embodies a complex interaction between food intake and exercise. Understanding and recognizing FDEIA is crucial as it has the potential to safeguard individuals from unexpected anaphylactic reactions, which could be catastrophic, especially when occurring during sport or other forms of physical exertion.

This article endeavors to explore the multifaceted nature of food-dependent exercise-induced anaphylaxis, beginning with a foundational understanding of anaphylaxis and the specific dynamics involved in exercise-induced reactions. It further delves into the pathophysiology of FDEIA, identifying critical cofactors such as alcohol, aspirin, and specific food allergens like gluten and nuts that might exacerbate the condition. Diagnostic strategies, including the food challenge test and identification of associated conditions like urticaria, eczema, and asthma, are examined. Management and treatment strategies, alongside anaphylaxis action plans, offer vital information for those living with this condition. Additionally, preventive measures and current research directions provide insight into not only avoiding triggers but also understanding the underlying mechanisms and potential future treatments for FDEIA.

Understanding Anaphylaxis and Exercise

Definition of Anaphylaxis

Anaphylaxis is defined as a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal. [1] This acute allergic reaction involves multiple systems in the body and can rapidly progress to a life-threatening state. It may occur following exposure to a variety of allergen triggers including food, insect venom, drugs, and vaccines. [2] Recognizing the signs of anaphylaxis, understanding its treatment protocols, and knowing preventive measures are crucial for managing this medical emergency effectively.

Anaphylaxis presents with a range of symptoms that involve multiple body systems. The skin, respiratory system, cardiovascular system, and gastrointestinal system are the primary systems affected. Cutaneous manifestations may include urticaria, angioedema (swelling of the deeper layers of the skin), and flushing. Respiratory symptoms often involve shortness of breath, wheezing, and stridor due to airway constriction. Cardiovascular signs can be severe, such as hypotension (low blood pressure) and tachycardia (rapid heart rate), which may lead to shock. Gastrointestinal symptoms might include nausea, vomiting, abdominal pain, and diarrhea. The rapid identification of these clinical features is crucial for timely intervention and treatment. [2]

The initial treatment typically involves a prompt intramuscular injection of epinephrine (adrenaline) in the mid-outer thigh, positioning the patient supine (semi-reclining if dyspneic or vomiting), and when indicated, providing supplemental oxygen, intravenous fluid resuscitation, and cardiopulmonary resuscitation. For individuals at risk of anaphylaxis, especially those with known triggers, self-management strategies are essential for preventing severe outcomes. Patients are advised to carry epinephrine auto-injectors at all times. These devices are designed for easy use and can be lifesaving when administered promptly during an anaphylactic episode. Personalized emergency action plans should also be developed. These plans provide step-by-step instructions on recognizing symptoms and using the auto-injector, as well as detailing when to seek emergency medical help. [1]

Immediate intramuscular administration of epinephrine into the anterolateral thigh is the first-line therapy, even if the diagnosis is uncertain. [3] Epinephrine, also known as adrenaline, is the first-line treatment for anaphylaxis. It works by reducing throat swelling, opening the airways, and maintaining heart function and blood pressure. The EAACI task force suggests prescribing 0.15 mg adrenaline auto-injectors for children from 7.5 kg to 25–30 kg and 0.3 mg adrenaline autoinjectors for children from 25–30 kg, and at least 0.3 mg adrenaline autoinjectors for adolescents and adults at risk of anaphylaxis. [4] It's important to note that anaphylactic reactions may spontaneously cease at any stage of symptoms, but may also progress in severity despite adequate treatment. This unpredictability makes it difficult to evaluate the efficacy of therapeutic procedures. [5]

The Role of Exercise in Triggering Anaphylaxis

Exercise-Induced Anaphylaxis (EIA) is a rare disorder where anaphylaxis, a severe or life-threatening allergic response, is triggered by physical exertion. The syndrome is broadly grouped into two categories: exercise-induced anaphylaxis and food-dependent, exercise-induced anaphylaxis (FDEIA). This rare disorder is characterized by anaphylactic symptoms that occur after physical activity. The reaction can range from mild to severe, including symptoms such as hives, flushing, wheezing, and gastrointestinal distress. In some cases, continuing the exercise can lead to more severe reactions like angioedema, laryngeal edema, hypotension, and even cardiovascular collapse. It's important to note that while EIA is a rare condition, it can be life-threatening and requires immediate medical attention when symptoms occur. [6], [7]

Difference Between FDEIA and Other Forms of Anaphylaxis

EIA and FDEIA are specific forms of anaphylaxis where symptoms can manifest during or shortly after physical exertion. Anaphylaxis can occur during exercise or soon after. If the occurrence of anaphylaxis is related to pre-exercise food intake (especially a food to which the patient is sensitive), the term FDEIA is used. FDEIA is distinct from typical exercise-induced or food-induced anaphylaxis. In FDEIA, neither food intake nor physical activity alone is sufficient to trigger anaphylaxis; both factors are required. Foods commonly implicated in FDEIA include wheat, shellfish, and nuts. This condition highlights the complex interaction between dietary factors and physical exertion in the pathogenesis of anaphylaxis,

distinguishing it from other forms where a single allergen or activity can independently initiate an anaphylactic reaction. [6]–[8]

Epidemiology of FDEIA

The occurrence of anaphylaxis in the general population is at least 1.6% and is likely even higher. [9] It is worth noting that five to fifteen percent of anaphylactic episodes are caused by, or associated with, exercise. [10] There is limited information on the prevalence of FDEIA in children; however, Tanaka conducted a questionnaire-based study that found a prevalence rate of 0.0017%. FDEIA may present in both sexes and the age of onset can be extremely variable and can vary anywhere from age 4 to 74 years. [11] Women with EIA have linked its occurrence to various phases of the menstrual cycle. In some patients, a pre-menstrual association with EIA has been consistently observed, necessitating the restriction of exercise to non-critical phases of the cycle. [12], [13]

Pathophysiology of FDEIA

Immune System Response

In the pathophysiology of FDEIA, a critical aspect is the immune system's response to allergens. One theory suggests that immunoglobulin E (IgE) cross-links with specific food allergens, and when combined with exercise, this interaction lowers the threshold for mast cell degranulation. This process releases histamine and other vasoactive mediators, which can lead to anaphylactic reactions. [12] Additionally, exercise is known to induce the release of mediators from mast cells that are IgE-dependent, further lowering the mast cell degranulation threshold. [14] This heightened state of sensitivity in the presence of allergens and physical exertion underscores the complex immune response involved in FDEIA.

Role of Food Allergens

The role of food allergens in FDEIA is particularly significant and deserves further exploration. It has been observed that certain foods, including wheat, shellfish, and nuts, are

commonly implicated in triggering FDEIA. [15] In fact, studies have shown that more than 80% of patients with wheat-induced FDEIA have IgE antibodies that react specifically to omega-5 gliadin, a known trigger for this condition. [16] This specific interaction between food allergens and exercise highlights the intricate relationship between these two factors in the development of anaphylaxis. It is important to note that neither food allergens nor exercise alone would suffice to trigger an anaphylactic reaction, but their combination is necessary for such a response to occur. [6]–[8] This underscores the complex nature of FDEIA and the need for further research in this area.

Impact of Physical Activity on Allergen Absorption

Physical activity influences the absorption and distribution of allergens, which is a key factor in the pathophysiology of FDEIA. Exercise increases blood flow to muscles while decreasing circulation to the gut mucosa, potentially exposing more muscle tissue mast cells to allergens. [15] This redistribution of blood flow can transport recently ingested allergens to different mast cells in the skin or skeletal muscle, increasing the potential for anaphylactic reactions. [16] Additionally, vigorous exercise can disrupt the digestion and absorption of allergenic food, leading to a rise in allergenic proteins in the blood, which then sensitizes IgE-mediated mast cells. [14] Furthermore, exercise may cause changes in the gastrointestinal barrier, such as increased permeability due to tight junction dysfunction. This can be exacerbated by factors such as thermal injury, alcohol ingestion, and the use of non-steroidal anti-inflammatory drugs like aspirin (ASA), which have been shown to increase gliadin absorption in individuals predisposed to FDEIA. [16]

Critical Cofactors in FDEIA

Impact of Environmental Factors

Environmental factors play a significant role as critical cofactors in the manifestation of FDEIA. These factors include extreme temperatures, both hot and cold, which can exacerbate the severity of anaphylactic reactions when combined with exercise and food allergens. [17] Additionally, environmental conditions such as humidity and weather changes have been identified as augmenting factors that can influence the occurrence and intensity of FDEIA. [18], [19] The presence of environmental allergens, such as pollens and dust mites,

also contributes to the complexity of managing FDEIA, as these elements can act as additional triggers or enhance the allergic response. [17]

The Role of NSAIDs and Other Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ASA, are prominent cofactors in FDEIA, significantly lowering the threshold for anaphylactic reactions when combined with specific food allergens and exercise. [17] The ingestion of NSAIDs can increase gastrointestinal permeability, thereby enhancing the absorption of allergens and facilitating more severe reactions. [19] Other medications such as angiotensin-converting enzyme inhibitors, beta-blockers, and even cannabis have been mentioned as potential cofactors that could influence the severity and threshold of allergic responses in FDEIA. [17] It is crucial for individuals susceptible to FDEIA to be aware of the potential risks associated with these medications, especially when taken in proximity to exercise and allergen exposure.

Influence of Alcohol and Stress

Alcohol consumption is another significant cofactor in FDEIA, affecting the absorption of allergens and potentially lowering the threshold for anaphylactic reactions. [17], [18] The impact of alcohol may vary depending on the amount consumed and its timing relative to exercise and food intake. Psychosocial stress is also a critical factor, as it can exacerbate allergic diseases such as asthma and atopic dermatitis, which in turn can influence the severity of food allergy outcomes. The release of neuropeptides and neurotransmitters during stress-related responses plays a role in activating the allergic inflammatory pathways, thereby increasing the risk of adverse reactions in individuals with FDEIA. [18] Understanding these critical cofactors in FDEIA is essential for managing and preventing severe allergic reactions, particularly in individuals who are active or engage in regular physical exercise. By recognizing and mitigating these cofactors, individuals can better manage their condition and reduce the risk of experiencing anaphylaxis.

Diagnosis of FDEIA

The diagnosis of FDEIA typically begins with a detailed clinical history and physical examination. Physicians assess the temporal relationship between food intake, exercise, and the onset of symptoms. It is crucial to determine whether symptoms occur exclusively during exercise following the ingestion of specific foods or if they can occur independently. [20] The importance of historical details surrounding the episodes is noted, as a clinical diagnosis is often made based on the consistency of anaphylactic reactions occurring during or within an hour of exercise, which are preceded by food ingestion [17]

Laboratory Tests and Biomarkers

Several laboratory tests are employed to confirm the diagnosis of FDEIA. Skin prick tests (SPT) and specific IgE immunoassays are standard methods to detect specific food allergens. A negative SPT result might rule out a particular food as the culprit, whereas a positive result with the suspected food aligns with patient history and supports the diagnosis. [16] Moreover, the detection of serum immunoglobulin E (IgE) specific to recombinant ω-5 gliadin has been acknowledged as a reliable diagnostic method, with certain cut-off values recommended for confirming the presence of this allergen. [19] SPT can help identify potentially implicated foods, which can then be confirmed through a challenge test. However, a negative skin test does not rule out the diagnosis, as specific tissue sensitization has been documented. [12]

Food-Exercise Challenge Test

The Food-Exercise Challenge Test is a critical diagnostic tool for FDEIA. This test involves an Oral Food Challenge (OFC) followed by physical exercise under controlled conditions, often with additional cofactors like ASA or alcohol to provoke a reaction. The challenge is meticulously planned over several days, starting with a provocation test for hypersensitivity to ASA, followed by exercise and specific food challenges. An augmented Oral Food Challenge (OFCPE) includes the ingestion of the suspected allergen, followed by exercise and, if no reactions occur, the introduction of other cofactors one at a time. [17] This comprehensive approach helps to confirm the diagnosis by replicating the conditions under which symptoms typically manifest.

The integration of clinical history, laboratory tests, and challenge tests provides a robust framework for diagnosing FDEIA, ensuring that patients receive accurate and effective management for their condition.

Differential Diagnosis

Differential diagnosis of FDEIA involves considering various conditions with similar presentations to ensure accurate diagnosis and appropriate management. EIA without food dependency is characterized by anaphylactic reactions triggered solely by physical exertion, independent of food ingestion. Non-exercise-dependent food allergies entail allergic reactions to specific foods occurring without the involvement of exercise. [6], [7] Idiopathic anaphylaxis presents with anaphylactic episodes without identifiable triggers, including food or exercise. The exact frequency of idiopathic anaphylaxis remains unclear, but most patients require daily treatment with systemic steroids and antihistamines. Since even minimal physical activity, like walking, can trigger EIA and FDEIA, it is essential to take a detailed history from patients with idiopathic anaphylaxis to rule out this possibility. [21]

Mastocytosis or mast cell activation syndrome (MCAS) involves abnormal mast cell activation leading to anaphylaxis-like symptoms, requiring consideration in the differential diagnosis. Many patients witch MCAS show signs of skin involvement, like urticaria pigmentosa, and report symptoms such as dyspepsia, abdominal cramps, diarrhea, and bloating. While bronchospasm is rare in mastocytosis, patients may still present with sudden anaphylactic episodes that are initially deemed idiopathic. Nevertheless, a detailed history and clinical examination often point to a diagnosis of mastocytosis. This diagnosis can be confirmed by finding anatomical evidence of mast cell hyperplasia and elevated biochemical markers, such as alpha-tryptase. [22]

What is more vasovagal syncope leads to a sudden drop in heart rate and blood pressure, often resulting in fainting, and can be mistaken for anaphylactic shock. [23] Cardiovascular conditions such as arrhythmias or myocardial infarction may present with symptoms resembling anaphylaxis, necessitating careful differentiation. [24] Asthma, particularly exercise-induced bronchoconstriction, can manifest with respiratory symptoms similar to anaphylaxis, adding complexity to the diagnostic process. [25] Panic attacks and

anxiety disorders may exhibit symptoms such as rapid heart rate and chest tightness, mimicking anaphylaxis. [26] Heat-related illnesses such as heat exhaustion or heat stroke can present with symptoms resembling anaphylaxis, posing diagnostic challenges in certain situations. [27] Hereditary angioedema may cause recurrent episodes of severe swelling mimicking anaphylaxis, necessitating thorough evaluation. [28] Hypoglycemia resulting in low blood sugar levels can cause symptoms similar to anaphylactic reactions, further complicating the diagnostic process. [29] Many conditions can present with symptoms similar to FDEIA and EIA, necessitating careful differential diagnosis.

Management and Treatment Strategies

Acute Management of Anaphylactic Reactions

Immediate treatment of acute allergic reactions in FDEIA includes administering epinephrine as the first-line treatment, followed by antihistamines, H1 and H2 blockers, inhaled bronchodilators, and steroids as needed. [20], [30], [31] It is essential for any patient who has self-administered epinephrine to seek immediate medical care for further monitoring and treatment, as the anaphylactic reaction might have ongoing life-threatening effects. [30] Immediate termination of physical effort at the earliest warning manifestation is crucial to avoid potentially life-threatening cardiovascular symptoms. [20]

Long-term Management

For long-term management, avoidance of known triggers is key. This includes refraining from exercise for 4 to 6 hours after ingesting the known food trigger and avoiding exercise in extreme weather conditions. [20], [30] Patients are advised to carry an epinephrine autoinjector during exercise and consider the impact of environmental factors such as very cold, hot, or humid weather, or during the pollen season. [19], [20] Additionally, some case studies suggest the use of prophylactic treatments such as omalizumab, a monoclonal antibody that binds to IgE, or misoprostol, a prostaglandin analogue, which have shown to reduce anaphylactic reactions in some patients. [30]

Dietary and Lifestyle Modifications

Dietary and lifestyle modifications play a significant role in managing FDEIA. Patients should avoid the implicated food 4 to 6 hours before and 1 to 4 hours after exercise or other cofactors like aspirin and alcohol. [19] Some evidence suggests that pre-treatment with agents that inhibit cell degranulation, such as sodium cromoglycate or ketotifen before ingestion of the causative food and exercise, may prevent symptoms of anaphylaxis. [20] Additionally, patients are encouraged to engage in regular physical activities safely and carry an anaphylaxis identification card at all times. [19]

Prevention of FDEIA

Educating Patients and Caregivers

An essential part of preventing FDEIA involves educating patients and their caregivers about the condition. It is crucial for them to understand the signs and symptoms of anaphylaxis and the importance of carrying an epinephrine autoinjector at all times. This education is vital in ensuring the safety and well-being of individuals with FDEIA. Patients should be provided with clear and concise written instructions on how to correctly use the autoinjector, emphasizing the importance of proper administration in the event of an anaphylactic reaction. Furthermore, it is essential to have a well-documented anaphylaxis treatment plan in place, outlining the necessary steps to be taken in case of an emergency. This plan should be easily accessible and regularly reviewed to ensure its effectiveness. [31] Additionally, education should extend beyond the individual and include schools, camps, and other organizations where patients may engage in physical activities. It is crucial that supervising adults in these settings are also well-informed about recognizing and managing anaphylaxis, as their prompt action can be life-saving. By disseminating knowledge and raising awareness about FDEIA, we can create a safer environment for those affected by this condition. [32]

Strategies for Safe Exercise

To safely engage in physical activities, individuals with FDEIA should strictly avoid exercising for 4 to 6 hours after consuming known food triggers. The intensity and type of exercise should be carefully considered, as aerobic activities like running or cycling might pose higher risks. [30] Patients are advised to modify their exercise routines by choosing less vigorous activities and ensuring they do not exercise alone. Carrying necessary medications, including antihistamines, corticosteroids, and an epinephrine autoinjector, is recommended during exercise. Pre-treatment with medications such as ketotifen, which stabilizes mast cells and prevents the release of histamine, can also be beneficial. [33]

Avoidance of Known Triggers

Avoiding known triggers is the cornerstone of preventing FDEIA. This includes not only the avoidance of specific foods known to cause reactions but also other potential triggers like NSAIDs and aspirin before exercising. [14], [33] Patients should be vigilant about their diet, avoiding causative foods at least 4 to 6 hours before any physical activity. It is also advisable to monitor and possibly adjust the environment in which exercise takes place, avoiding extreme temperatures and high pollen conditions which could exacerbate symptoms. Continuous monitoring and adjustments based on individual experiences and reactions are necessary to effectively manage and prevent FDEIA. [30]

Current Research and Future Directions

Recent Advances in Understanding FDEIA

FDEIA continues to reveal significant insights, albeit the complexity of its mechanisms presents ongoing challenges. Recent studies focus on the peculiar interaction between specific food allergens and exercise, which lowers the threshold for mast cell degranulation, thereby triggering anaphylactic reactions. The identification of specific biomarkers like recombinant ω-5 gliadin has been pivotal, as these markers are crucial for diagnosing and understanding the pathophysiology of wheat-dependent FDEIA. Additionally, innovative therapies such as the use of omalizumab, a monoclonal antibody that targets IgE, have shown promise in preventing severe reactions in refractory cases. [30]

Gaps in Knowledge

Despite advancements, considerable gaps remain in the understanding of FDEIA. One of the primary challenges is the unpredictable manifestation of symptoms, which can occur during periods of rest or routine activities, not just during exercise. This unpredictability suggests that current models do not fully capture the underlying pathomechanisms of FDEIA. Moreover, the natural history and prognosis of FDEIA are not well-documented due to the lack of standardized methods for confirming "natural tolerance". This is critical as FDEIA generally presents a higher threshold for reactions compared to other IgE-mediated food allergies, necessitating stringent criteria for research and clinical evaluations. [19]

Emerging Therapies and Interventions

The therapeutic landscape for FDEIA is evolving, with several emerging interventions aimed at mitigating its development. The use of misoprostol, a prostaglandin E1 analogue, has demonstrated potential in reducing anaphylactic reactions by enhancing gastrointestinal breakdown of allergenic proteins before exercise. [30] However, the absence of a defined treatment protocol or preventive strategy for FDEIA underscores a significant clinical challenge. Addressing this gap is crucial, as the recurrent nature of severe allergic reactions in FDEIA imposes a substantial burden on affected individuals and healthcare systems. [19] The ongoing research and clinical trials are essential for developing effective management strategies that improve patient outcomes and quality of life.

Conclusion

Through the exploration of food-dependent exercise-induced anaphylaxis, this article has delved into the complexities surrounding this rare but significant condition. Highlighting its unique triggers, diagnosis, management, and the critical role of dietary and environmental factors. The interplay between specific food allergens and physical activity, alongside cofactors like NSAIDs, alcohol, and environmental conditions, underscores the intricate nature of FDEIA. It reminds healthcare professionals and patients alike of the importance of a comprehensive approach to its management - ranging from acute intervention strategies to long-term preventive measures that aim to safeguard individuals from potentially life-threatening anaphylactic reactions.

The ongoing research and emerging therapies for FDEIA point to an optimistic future where more effective treatment and management strategies could significantly improve patient outcomes. Nevertheless, the gaps in knowledge and the unpredictability of symptom manifestation necessitate continuous scientific inquiry and education. As the understanding of FDEIA evolves, it remains crucial for individuals at risk and their healthcare providers to remain vigilant, adopting an informed and proactive stance toward managing this challenging condition. In doing so, they harness the collective advancements in medical science to not only manage but also potentially mitigate the risks associated with food-dependent exercise-induced anaphylaxis.

Author's contribution

Conceptualization, Wiktoria Julia Krzesłowska and Kamila Szewczyk; methodology, Weronika Hołownia, Kamila Szewczyk, Paulina Pytel; software, Szymon Wiśniewski, Bartłomiej Szewczyk; check, Weronika Hołownia, Szymon Wiśniewski; formal analysis, Wiktoria Julia Krzesłowska and Paulina Pytel; investigation, Bartlomiej Szewczyk; resources, Szymon Wiśniewski, Bartłomiej Szewczyk, Weronika Hołownia; data curation, Weronika Hołownia, Szymon Wiśniewski; writing - rough preparation, Kamila Szewczyk; writing - review and editing, Kamila Szewczyk; project administration, Wiktoria Julia Krzesłowska, Bartłomiej Szewczyk.visualization, Kamila Szewczyk, Weronika Hołownia; supervision, Kamila Szewczyk, Paulina Pytel;All authors have read and agreed with the published version of the manuscript.

Funding Statement

Study did not receive special funding.

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Data Availability Statement

Not applicable

Acknowledgments

Not applicable

Conflict of Interest Statement

The authors of the paper report no conflicts of interest.

References

[1] F. E. R. Simons *et al.*, "International consensus on (ICON) anaphylaxis," *World Allergy Organ. J.*, vol. 7, no. 1, pp. 1–19, 2014, doi: 10.1186/1939-4551-7-9.

[2] W. H. Organization, *Brief overview of anaphylaxis as an adverse event following immunization (AEFI) and practical guidance on its identification, case management and response in a primary care setting*. Geneva PP - Geneva: World Health Organization.

[3] D. Fischer, T. K. Vander Leek, A. K. Ellis, and H. Kim, "Anaphylaxis," *Allergy, Asthma Clin. Immunol.*, vol. 14, no. 2, p. 54, 2018, doi: 10.1186/s13223-018-0283-4.

[4] A. Muraro *et al.*, "EAACI guidelines: Anaphylaxis (2021 update).," *Allergy*, vol. 77, no. 2, pp. 357–377, Feb. 2022, doi: 10.1111/all.15032.

[5] J. Ring *et al.*, "Guideline (S2k) on acute therapy and management of anaphylaxis: 2021 update," *Allergo J. Int.*, vol. 30, no. 1, pp. 1–25, 2021, doi: 10.1007/s40629-020-00158-y.

[6] A. M. Feldweg, "Exercise-Induced Anaphylaxis," *Immunol. Allergy Clin. North Am.*, vol. 35, no. 2, pp. 261–275, 2015, doi: https://doi.org/10.1016/j.iac.2015.01.005.

[7] M. P. Giannetti, "Exercise-Induced Anaphylaxis: Literature Review and Recent Updates," *Curr. Allergy Asthma Rep.*, vol. 18, no. 12, p. 72, 2018, doi: 10.1007/s11882-018-0830-6.

[8] N. Sayaca, "Exercise-Induced Anaphylaxis," D. Kaya Utlu, Ed. Cham: Springer International Publishing, 2023, pp. 561–572.

[9] R. A. Wood *et al.*, "Anaphylaxis in America: the prevalence and characteristics of anaphylaxis in the United States.," *J. Allergy Clin. Immunol.*, vol. 133, no. 2, pp. 461–467, Feb. 2014, doi: 10.1016/j.jaci.2013.08.016.

[10] G. Du Toit, "Food-dependent exercise-induced anaphylaxis in childhood," *Pediatr. Allergy Immunol.*, vol. 18, no. 5, pp. 455–463, Aug. 2007, doi: https://doi.org/10.1111/j.1399-3038.2007.00599.x.

[11] Y. Aihara *et al.*, "Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students," *J. Allergy Clin. Immunol.*, vol. 108, no. 6, pp. 1035–1039, Dec. 2001, doi: 10.1067/mai.2001.119914.

[12] M. C. Castells, R. F. Horan, and A. L. Sheffer, “Exercise-induced anaphylaxis,” *Curr. Allergy Asthma Rep.*, vol. 3, no. 1, pp. 15–21, 2003, doi: 10.1007/s11882-003-0005-x.

[13] J. P. Wade, M. H. Liang, and A. L. Sheffer, “Exercise-induced anaphylaxis: epidemiologic observations.,” *Prog. Clin. Biol. Res.*, vol. 297, pp. 175–182, 1989.

[14] C. W. Kim *et al.*, “Combined effects of food and exercise on anaphylaxis.,” *Nutr. Res. Pract.*, vol. 7, no. 5, pp. 347–351, Oct. 2013, doi: 10.4162/nrp.2013.7.5.347.

[15] C. Povesi Dascola and C. Caffarelli, “Exercise-induced anaphylaxis: A clinical view.,” *Ital. J. Pediatr.*, vol. 38, p. 43, Sep. 2012, doi: 10.1186/1824-7288-38-43.

[16] D. Zogaj, A. Ibranji, and M. Hoxha, “Exercise-induced Anaphylaxis: the Role of Cofactors.,” *Mater. Sociomed.*, vol. 26, no. 6, pp. 401–404, Dec. 2014, doi: 10.5455/msm.2014.26.401-404.

[17] S. Miceli Sopo, M. Gelsomino, E. Del Vescovo, and G. Bersani, “Food Dependent Exercise-Induced Anaphylaxis in pediatric age. Can we trust the oral food challenge with exercise and acetylsalicylic acid?,” *Acta Biomed.*, vol. 92, no. 1, p. e2021068, Dec. 2020, doi: 10.23750/abm.v92i1.10093.

[18] M. Shin, “Food allergies and food-induced anaphylaxis: role of cofactors.,” *Clin. Exp. Pediatr.*, vol. 64, no. 8, pp. 393–399, Aug. 2021, doi: 10.3345/cep.2020.01088.

[19] W. Srisuwatchari, K. Kanchanaphoomi, J. Nawiboonwong, T. Thongngarm, and M. Sompornrattanaphan, “Food-Dependent Exercise-Induced Anaphylaxis: A Distinct Form of Food Allergy-An Updated Review of Diagnostic Approaches and Treatments.,” *Foods (Basel, Switzerland)*, vol. 12, no. 20, Oct. 2023, doi: 10.3390/foods12203768.

[20] W. Barg, W. Medrala, and A. Wolanczyk-Medrala, “Exercise-induced anaphylaxis: an update on diagnosis and treatment.,” *Curr. Allergy Asthma Rep.*, vol. 11, no. 1, pp. 45–51, Feb. 2011, doi: 10.1007/s11882-010-0150-y.

[21] B. I. Nwaru, S. Dhami, and A. Sheikh, “Idiopathic Anaphylaxis.,” *Curr. Treat. options allergy*, vol. 4, no. 3, pp. 312–319, 2017, doi: 10.1007/s40521-017-0136-2.

[22] C. R. Weiler, “Mast Cell Activation Syndrome: Tools for Diagnosis and Differential Diagnosis.,” *J. allergy Clin. Immunol. Pract.*, vol. 8, no. 2, pp. 498–506, Feb. 2020, doi: 10.1016/j.jaip.2019.08.022.

[23] S. Longo, J. M. Legramante, S. Rizza, and M. Federici, “Vasovagal syncope: An overview of pathophysiological mechanisms.,” *Eur. J. Intern. Med.*, vol. 112, pp. 6–14, Jun. 2023, doi: 10.1016/j.ejim.2023.03.025.

[24] S. Vaina *et al.*, “Anaphylactic cardiovascular collapse manifesting as myocardial infarction following salad consumption. A case of Kounis variant type I syndrome.,” *Acta Biomed.*, vol. 91, no. 1, pp. 134–138, Mar. 2020, doi: 10.23750/abm.v91i1.8176.

[25] C. R. Hildebrand K, Przybyłowski T, Maskey-Warzęchowska M, “Przydatność wybranych testów w rozpoznawaniu powysiłkowego skurczu oskrzeli [Usefulness of selected tests in the diagnosis of exercise induced bronchoconstriction],” *Pneumonol. Alergol. Pol.*, vol. 79, no. 6, pp. 397–406, 2011.

[26] C. D. Friesen and R. J. M. Engler, “Recurrent Panic/Anxiety Attacks: Masquerader of Anaphylaxis and Challenge to Comprehensive History Taking,” *J. Allergy Clin. Immunol.*, vol. 119, no. 1, p. S34, Jan. 2007, doi: 10.1016/j.jaci.2006.11.152.

[27] R. Gauer and B. K. Meyers, “Heat-Related Illnesses.,” *Am. Fam. Physician*, vol. 99, no. 8, pp. 482–489, Apr. 2019.

[28] S. Bhivgade, S. Melkote, S. Ghate, and H. R. Jerajani, “Hereditary angioedema: not an allergy.,” *Indian J. Dermatol.*, vol. 57, no. 6, p. 503, Nov. 2012, doi: 10.4103/0019-5154.103081.

[29] T. E. Dribin, M. S. Motosue, and R. L. Campbell, “Overview of Allergy and Anaphylaxis.,” *Emerg. Med. Clin. North Am.*, vol. 40, no. 1, pp. 1–17, Feb. 2022, doi: 10.1016/j.emc.2021.08.007.

[30] B. Minty, “Food-dependent exercise-induced anaphylaxis.,” *Can. Fam. Physician*, vol. 63, no. 1, pp. 42–43, Jan. 2017.

[31] A. F. Whyte, J. Soar, A. Dodd, A. Hughes, N. Sargant, and P. J. Turner, “Emergency treatment of anaphylaxis: concise clinical guidance.,” *Clin. Med.*, vol. 22, no. 4, pp. 332–339, Jul. 2022, doi: 10.7861/clinmed.2022-0073.

[32] K. M. Järvinen and J. Celestin, “Anaphylaxis avoidance and management: educating patients and their caregivers.,” *J. Asthma Allergy*, vol. 7, pp. 95–104, 2014, doi: 10.2147/JAA.S48611.

[33] J. H. Choi, H. B. Lee, I. S. Ahn, C. W. Park, and C. H. Lee, “Wheat-dependent, Exercise-induced Anaphylaxis: A Successful Case of Prevention with Ketotifen.,” *Annals of dermatology*, vol. 21, no. 2. Korea (South), pp. 203–205, May 2009, doi: 10.5021/ad.2009.21.2.203.