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The impact of infant feeding practices on the risk of developing food allergies

Wpływ sposobu żywienia niemowląt na ryzyko rozwoju alergii pokarmowej

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Abstract

Introduction. Food allergy in infants is a major health problem in urbanised countries, the incidence of which is increasing and is a challenge for both parents and doctors. In the first months of life, a child's body is particularly sensitive to allergic reactions, therefore knowing the risk factors is crucial for the prevention and management of this health problem.

Objective. The aim of this study is to examine the impact of infant feeding on the development of food allergies, with particular emphasis on breastfeeding, formula milk, the method of expanding the diet, vitamin D supplementation and probiotics. The potential benefits and limitations of each method be presented.

Brief description of the state of knowledge. In scientific studies, there is a significant indication of the positive impact of breastfeeding on the proper development of the infant's intestinal microbiome, which is associated with a reduced risk of developing food allergies. However, the effect of formula feeding, as well as vitamin D supplementation, remains unclear and depends on many variables. Appropriate supplementation with probiotics may have a beneficial effect on the proper development of the intestinal microbiome, thereby reducing the risk of food allergies. It is not recommended to avoid or delay the introduction of allergenic foods to infants.

Summary. The use of appropriate infant feeding methods may reduce the risk of food allergy in infants. However, further research is needed on the effectiveness of these interventions and their optimal strategies as part of comprehensive infant care.

Key words

breastfeeding, microbiome, probiotic, formula, food allergy in infants, expanding the diet of infants

Streszczenie

Wprowadzenie i cel pracy. W krajach zurbanizowanych alergia pokarmowa u niemowląt jest poważnym problemem zdrowotnym, którego częstość występowania rośnie i który stanowi wyzwanie zarówno dla rodziców, jak i lekarzy. W pierwszych miesiącach życia dziecka jego organizm jest szczególnie wrażliwy na reakcje alergiczne, dlatego znajomość czynników ryzyka jest kluczowa dla zapobiegania alergii i zarządzania tą problematyką zdrowotną. Celem niniejszej pracy jest zbadanie wpływu sposobu karmienia niemowląt na rozwój alergii pokarmowej, ze szczególnym uwzględnieniem karmienia mlekiem kobiecym oraz mlekiem modyfikowanym, a także sposobu rozszerzania diety oraz suplementacji witaminą D i probiotykami. Przedstawia również potencjalne korzyści i ograniczenia poszczególnych metod.

Opis stanu wiedzy. W badaniach naukowych widoczna jest istotna zależność między pozytywnym wpływem karmienia piersią na prawidłowy rozwój mikrobiomu przewodu pokarmowego u niemowląt, co wiąże się ze zmniejszonym ryzykiem rozwoju alergii pokarmowej. Natomiast wpływ karmienia mlekiem modyfikowanym, a także suplementacji witaminą D jest niejasny i jest zależy od wielu zmiennych. Odpowiednia suplementacja probiotykami może mieć korzystny wpływ na prawidłowy rozwój mikrobiomu jelitowego, a tym samym na redukcję ryzyka wystąpienia alergii pokarmowej. Nie należy unikać ani opóźniać wprowadzania produktów w celu prewencji alergii pokarmowej u niemowląt.

Podsumowanie. Zastosowanie odpowiednich metod żywieniowych może zmniejszyć ryzyko wystąpienia alergii pokarmowej u niemowląt. Jednakże potrzebne są dalsze badania nad skutecznością tych działań oraz ich optymalnymi strategiami w ramach kompleksowej opieki nad niemowlętami.

Słowa kluczowe

karmienie piersią, mikrobiom, probiotyk, mleko modyfikowane, alergie pokarmowe u niemowląt, rozszerzanie diety niemowląt

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INTRODUCTION

Food allergy in infants is a major health problem in urbanized countries, the incidence of which is increasing, leading to a challenge for both parents and doctors. Food allergy is an abnormal reaction of the immune system to contact with a potentially harmless antigen present in food. The most common type of allergic reaction is food allergy mediated by immunoglobulin E. Even the smallest amount of allergen can cause life-threatening anaphylaxis [1]. Food allergies are often confused with food intolerance, which manifests itself similarly; however, its mechanism is completely different, as it occurs without the participation of immunological mechanisms. An example of this is lactose intolerance, caused by the absence or deficiency of the enzyme lactase, necessary for the breakdown of lactose. In this case, unlike allergic reactions, small amounts of food may not cause symptoms [2].

The development of food allergy is influenced by many factors, including genetic predisposition, exposure to the allergen, immaturity of the gastrointestinal tract and severe atopic dermatitis. In the first months of life, a child's body is particularly sensitive to allergic reactions, which may lead to numerous symptoms: skin, gastrointestinal, as well as respiratory. The older the child, the lower the risk of allergies. Accurately determining the incidence of food allergy in infants is very difficult. This stems from both underestimation (studies based on data from oral challenge tests) and overestimation (data based on parents' reports of the diagnosis or occurrence of allergy symptoms) of this condition [3]. Based on numerous studies, it was estimated that the incidence of food allergy in infants, confirmed by a food challenge test, was over 10%. Although these estimates were based on food provocation tests, they were mostly performed in an open or single-blinded fashion [4]. The multicentre EuroPrevall cohort trial examined the prevalence of food allergy in European children. In the study, 12,049 newborns were enrolled, including 1,513 from Poland. Of all children, 9,336 (1,280 from Poland) were followed up at 2 years of age. In the study, the incidence of food allergy after a double-blind placebo-controlled food challenge (DBPCFC) was: for eggs 0.84% (adjusted value 1.23%) in Europe and 0.6% in Poland, for cow's milk 0.54% (adjusted value 0.74%) in Europe and 0.6% in Poland [5, 6].

Food allergy can significantly affect the quality of life, both for the child and its caregivers, requiring frequent visits to the doctor, often tedious diagnostics and the use of elimination diets, which may lead to deficiencies. The disturbing phenomenon of the rising occurrence of food allergy makes it essential for both paediatricians and parents to sufficiently understand this issue.

OBJECTIVE

The aim of this study is to examine the impact of infant feeding on the development of food allergy, with particular emphasis on breastfeeding, formula feeding, expanding children's diet, and vitamin D and probiotic supplementation. By analyzing available scientific research and current literature, the intention is to identify differences in the risk of food allergy in infants fed using different methods, as well as to understand the mechanisms that may underlie these relationships. Another aim is to present the potential benefits and limitations of individual feeding methods and supplementation in the context of food allergy prevention in infants, which may have significant implications for clinical practice and recommendations regarding infant feeding.

MATERIALS AND METHOD

A review of the current literature was made in the PubMed and Google Scholar databases using the term: 'food allergy' and a combination of the term with key words such as: 'infants', 'breastfeeding', 'formula feeding', 'expanding the diet of infants', 'vitamin D', 'probiotic' and 'microbiome'. Current World Health Organization (WHO) guidelines on breastfeeding, expanding infants' diet, vitamin D, and probiotic supplementation were also reviewed. Finally, 42 original and review articles were included in the analysis.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Breastfeeding. The WHO recommends that infants should be exclusively breastfed for the first 6 months of life. After this period, complementary foods should be introduced and breastfeeding shall be continued until the age of 2 or even longer [7,8]. Recently, there has been a lot of pressure on the promotion of breast milk feeding due to the many beneficial effects of this method for both the child and the mother. Among other things, breastfeeding supports the development of a strong immune system which reduces the risk of acquiring many diseases, including allergies and asthma [9]. Breast milk contains essential nutrients and numerous bioactive substances, including antigen-immunoglobulin G immune complexes. It is suggested that immune complexes transferred from sensitized mothers induce tolerance in the newborn by activating its receptors and inducing antigen-specific regulatory cells. This is one of the many impressive, irreplaceable features of human milk, supporting primary prevention and subsequent proper development of the baby [10]. Breast milk also contains probiotics and prebiotics, which have beneficial effect on the development and maintenance of healthy intestinal microbiome in children. More and more research shows how crucial the proper composition of the gastrointestinal microbiota is for maintaining proper functions of the immune system. Data suggest that breastfeeding may lead to the growth of colonies of specific *Bifidobacterium* species through the prebiotic effects of human milk oligosaccharides (HMO) [11], and breastfeeding-associated bifidobacteria may support proper immune function through the production of aromatic lactic acids [12].

A study published in 2022 examined 135 healthy pregnant women and their newborns, suggested that changes in the microflora of breast milk may influence the development of food allergies. Breast milk and infant stool samples were compared at 5 time points and analyzed by microbial 16s rRNA gene sequencing. As a result, they showed that the microflora of mother's milk was more diverse and numerous in the group of infants without food allergies. A high presence of *Bifidobacterium*, *Akkermansia* and butyrate-producing bacteria was found in this group. However, the food allergy group showed a higher content of *Proteobacteria*,

Acinetobacter and *Pseudomonas* in mother's milk. Analysis of changes in the intestinal microflora in both groups of infants revealed compliance of changes in the number of *Bifidobacterium* with changes in the microflora of mother's milk [13]. Henrick BM et al. examined 347 stool samples taken from 157 of 208 infants born in a hospital in Stockholm, Sweden, showed that the composition of gut bacteria was highly variable at birth, but became more uniform over time. Moreover, this trial showed that the increase of *Bifidobacterium* occurred mainly in breastfed infants [14].

A study by Fujimura et al. analyzing stool samples using 16s rRNA gene sequencing in a group of 298 infants aged 1–11 months from a US birth cohort, demonstrated that the neonatal gut microbiota influences susceptibility to allergic asthma in children. happens through changes in the gut microenvironment that affect the population and function of CD4 + T cells. The group of newborns with the highest risk of developing IgE antibodies in response to allergens showed a lower relative abundance of certain bacteria (e.g. *Bifidobacterium*, *Akkermansia* and *Faecalibacterium)*, and a higher relative abundance of individual fungi (*Candida* and *Rhodotorula)* in the intestinal microbiome [15].

The presented information suggests that the composition of breast milk microflora may reduce the risk of developing food allergy in infants by influencing the colonization of intestinal microflora and butyrate production. However, this topic is still under research and many factors, such as genetics, environment and the mother's diet, may also play a role in this process.

Formula feeding. The issue of what effect supplementing with formula milk has on the intestinal microbiome and thus on the risk of allergy should also be discussed. There is no clear evidence that formula feeding compared to breastfeeding increases the risk of food allergy. However, formula milk (although its composition is similar to mother's milk) does not contain all bioactive ingredients. Research suggests that formula-fed babies may have a different gut microbiome composition compared to exclusively breastfed babies. In the United States, 16s RNA gene sequencing was performed on stool samples from 10 healthy, exclusively breast-fed premature infants and 10 healthy formula-fed premature infants. *Propionibacterium*, *Veillonella,* and *Escherichia* were found to be abundant in the gut microbiome of breastfed infants, followed by *Staphylococcus*, *Enterococcus*, *Clostridium*, *Streptococcus,* and *Klebsiella*. However, in infants fed with formula milk, the intestines were colonized mainly by *Streptococcus* and *Klebsiella* and much less numerous *Propionibacterium* [16]. Similar results were obtained in a study on 20 Korean newborns. In the case of formula-fed infants, the microbiome may be more diverse, additionally containing numerous strains of *Escherichia coli, Enterococcus faecalis and Veillonella atypical,* and a much smaller group of *Bifidocbacterium longum* [17].

In recent years, technological developments have enabled the inclusion of 2′-fucosyllactose (2′FL), the most common naturally occurring HMO, in infant formulas. Interestingly, emerging research suggests formulas enriched with HMOs have led to infants having a similar microbiome composition to that of exclusively breastfed infants [18, 19].

In the last 2 decades, access to formula milk and its consumption has increased significantly. As previously mentioned, the incidence of food allergies in infants has increased in recent years, and one of the most common causes is cow's milk allergy (CMA) [20]. Despite the available partially hydrolyzed formula (pHF) and extensively hydrolyzed formula (eHF) used prophylactically in infants with documented family history, the problem is still growing. Amino Acid-Based Formula (AAF) is also available, which is intended for infants with severe symptoms of CMA, especially those whose symptoms persisted despite the use of eHF, or with an episode of anaphylactic shock. A recent prospective, randomized, double-blind, controlled clinical study was conducted at 20 sites in 6 countries, demonstrated the effectiveness of an elimination diet with AAF in the treatment of CMA. The trial included 169 infants with confirmed IgE-mediated CMA who were randomly assigned to 2 groups to receive AAF and AAF with a specific synbiotic blend for 12 months. Symptoms disappeared in children after 12 months of using AAF, and tolerance to cow's milk protein was achieved after 36 months of therapy in 75% of the patients. This study confirmed the effectiveness of the AAF intervention, regardless of whether it is used with or without the specific symbiotic blend, and proves that lack of exposure to cow's milk protein antigens does not slow down the development of tolerance [21].

It should be added that the European Academy of Allergy and Clinical Immunology (EAACI) guidelines suggest avoiding the administration of CMA-containing formula in the first week of life to prevent cow's milk allergy in infants and young children. However, for infants who need a breast milk substitute, there are no recommendations for or against the use of regular formula after 1 week of age to prevent food allergy [22]. Therefore, the impact of formula feeding on the intestinal ecosystem is complex and may vary depending on many factors, such as the type of formula, feeding method, family burdens, and the overall health of the child.

Expanding the diet of infants. Many parents are concerned about introducing new food products into their infant's diet, especially those that are most likely to cause allergies. This is often related to the fear of developing violent symptoms of allergic reactions, including life-threatening anaphylaxis.

According to the recommendations ESPHGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition), the introduction of complementary products can be started no earlier than 17 weeks of age and no later than 26 weeks of age, preferably when the infant demonstrates the developmental skills necessary to consume them [23]. However, according to WHO recommendations, expanding the diet should start from the end of 6th month of life. Until recently, there were guidelines in force indicating the exact order in which foods should be introduced. However, scientific studies conducted on large groups of children have shown that delayed introduction of potentially allergenic foods does not reduce the risk of food allergy [24]. Therefore, the current guidelines allow parents great freedom in choosing when and what food to introduce. It is recommended to introduce foods gradually, in small amounts at first, and monitor the child's reaction [25].

When examining food allergies in infants, scientists often focus on 3 main allergens: eggs, nuts and cow's milk protein, which are the most frequently reported allergy triggers in this age group [26, 27]. However, it is important to remember that any food can sensitize. Recently, several studies focused on the relationship between the moment

of introducing potentially allergenic products and the risk of allergic diseases. A meta-analysis of 5 studies (1,915 participants) conducted by Ierodiakonou et al., showed that early introduction of eggs at 4–6 months of age was correlated with a reduced risk of egg allergy. The above systematic review was presented in accordance with the PRISMA guidelines [28]. Furthermore, scientific data from two studies proved that introducing peanuts into the diet of a child aged 4–11 months was associated with a reduced risk of peanut allergy, compared to introducing them later. The Learning Early about Peanut Allergy (LEAP) Study was a randomized, controlled trial conducted in the United Kingdom that included 640 infants aged 4–11 months with severe eczema or egg allergy, then randomly assigned them to eat or avoid peanuts until age 60 months. The study showed that among infants who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group [29].

Another randomized trial conducted in the UK by Michael R. et al. recruited 1,303 exclusively breastfed infants at 3 months of age and randomly assigned them to 2 groups: early introduction of 6 allergens or exclusive breastfeeding until 6 months of age. In a per-protocol analysis, the incidence of any food allergy was significantly lower in the early introduction group (2.4%) compared with the exclusively breastfed infant group (7.3%), as was the incidence of peanut allergy (0% vs. 5%) and egg allergy (1.4% vs. 5.5%) [30].

In general, expanding the diet in infants may increase the risk of food allergy, especially if food allergens are introduced too late. Therefore, parents should not avoid or delay introducing strong allergens into their children's diet.

Vitamin D supplementation. This vitamin, known mainly for its role in calcium and bone physiology, also plays an important role in the functioning of the immune system by reducing excessive inflammatory responses and promoting immune tolerance [31]. In recent years, there has been increasing interest in the possible relationship between vitamin D deficiency and the risk of food allergy in infants.

A meta-analysis conducted by Psaroulaki showed that vitamin D deficiency in mothers and infants was associated with a higher risk of food allergy, especially in the second year of life. The disease risk was 68% higher for children who did not have optimal level blood serum concentration of 25-hydroxyvitamin D [25(OH)D] [32]. The Australian randomized controlled trial examined the effects of vitamin D supplementation in early childhood on the risk of developing food allergies: it involved 195 infants with positive family history of allergic disease and adequate 25(OH)D levels at birth. Each mother supplemented vitamin D during pregnancy, reaching its serum norm in the last weeks before delivery. The study did not show any effects of vitamin D supplementation on the risk of allergy in the first months of life. It should be taken into account that 95% of the examined infants were exclusively breastfed, therefore in the placebo group, the demand for vitamin D could be partially covered by the supply of mother's milk. This may suggest that the correct level of the vitamin in the prenatal period may be crucial in the prevention of food allergy [33].

Other studies have examined the effect of prenatal vitamin D supplementation on the risk of asthma in children. In the American randomized, double-blind trial 9268 pregnant women were assessed for eligibility and 806 had children who were included in the analysis. Children born to mothers supplementing vitamin D suffered from asthma much less often [34]. The same conclusion was reached by other American scientists who conducted randomized, double-blind, placebo-controlled trial of 806 mother-offspring pairs [35]. A similar correlation between prenatal vitamin D supplementation and the risk of food allergy was expected. A literature review from 2023 demonstrated that many research results are contradictory and no effect of vitamin D supplementation on reducing the risk of food allergy has been demonstrated. Moreover, it has been shown that both low and too-high concentrations of 25(OH)D in the prenatal period are risk factors for the occurrence of food allergy in early life [36].

Thus, although evidence indicates that 25(OH)D deficiency both prenatally and in early childhood is a risk factor for food allergy, there are no clear studies demonstrating the preventive effects of vitamin D supplementation on reducing the incidence of food allergy in infants and young children. Despite this, current recommendations state that vitamin D supplementation is necessary from the first days of life, regardless of prenatal supplementation. This is due to its proven numerous benefits for the development of the body and common deficiencies.

Probiotic supplementation. One of the key aspects of allergy research is the analysis of the intestinal microbiome and its impact on the functioning of the immune system. It is a complex community of microorganisms responsible not only for digestive processes but also for the immune system's functioning. The gastrointestinal microbiota influences the maturation of naive and regulatory T lymphocytes and the production of anti-inflammatory cytokines, contributing to the development of immunological tolerance and maintaining immune homeostasis [39]. Disturbing this balance, for example, through antibiotics or excessive hygiene, may increase the risk of allergies.

As previously noted, the hypothesis regarding the intestinal microbiome suggests that changes in its composition, especially in early life, may be associated with the increasing number of cases of food allergy. With the modernization of

Table 1. Recommended daily intake of vitamin D according to the Polish Guidelines and National Institutes of Health (NIH) [35, 36]

	Recommended Dietary Allowances for Vitamin D (Polish Guidelines)	Recommended Dietary Allowances for Vitamin D (NIH)
Premature babies until they reach the corrected age (according to the doctor›s decision)	10–20 mcg (400–800 IU)	10 mcg (400 IU)
0–6 months	10 mcg (400 IU)	10 mcg (400 IU)
6–12 months	10–15 mcg (400–600 IU)	10 mcg (400 IU)
1–10 years	15–25 mcg (600–1000 IU)	15 mcg (600 IU)
Pregnant women throughout pregnancy	50 mcg (2000 IU)	15 mcg (600 IU)

our lifestyle, reduced exposure to the natural environment, limited contact with animals, as well as excessive hygiene, changes in our microbiome may have occurred. It is believed that the higher number of allergies is due to the loss of commensal connections with parasites and bacteria – those that previously had a beneficial impact on human evolution [40, 41]. From this perspective, the use of probiotics may be a promising strategy in the prevention and treatment of allergic diseases [42].

A meta-analysis by Zhang et al. showed that the combined administration of probiotics to pregnant women and later to infants, reduced the risk of food allergy in children. However, this relationship was not found when the probiotic was used only in the prenatal period or only after delivery [43]. Australian researchers performed a double-blind, placebo-controlled randomized trial to evaluate the effectiveness of oral immunotherapy with probiotics and peanuts in children diagnosed with peanut allergy. Sixty-two patients were randomly assigned to 2 groups and underwent treatment for 18 months. At the end of the study, it was shown that 89.7% of children receiving the therapy were desensitized, compared to 7.1% of those receiving placebo. A follow-up study conducted 4 years after cessation of treatment showed that the children in the probiotic immunotherapy group were significantly more likely to be able to safely continue eating peanuts than the participants in the placebo group [44].

Currently, research confirming the effectiveness of probiotics as a preventive or therapeutic agent in the case of food allergy looks promising, but requires further efforts. The routine use of probiotics in preventing food allergy is not currently recommended.

CONCLUSIONS

Proper infant feeding practices and supplementation are important for developing the immune system. Understanding the risk factors for infant food allergies is crucial, especially in preventing and managing this health condition in children. Education of parents about the proper way of feeding infants, including the key role of breastfeeding in the development of the intestinal microbiome, and thus the immune system, and many other beneficial properties resulting from it, is essential. However, if for some reason breastfeeding is not possible, parents should be aware of the availability of different types of formula milk and also have the opportunity to get help in choosing it. Currently, due to an abundance of information, it is very difficult for parents to find reliable materials on the proper way of feeding infants, not to mention ways of preventing allergic diseases. Education on the impact of infant feeding methods on food allergy prevention can be implemented at many levels. Effective information on the differences between breast milk and formula milk, its types, as well as the advantages and consequences of its use, that is provided by midwives during antenatal classes and postnatal visits, could influence parents' decisions. During preventive appointments paediatricians monitoring the development of infants could present individually adapted methods and instructions on expanding the diet, recommend appropriate supplementation, and could also provide a brochure with crucial information. Moreover, parents could receive reliable answers to their pressing questions. Comprehensive and organized Health Protection activities can significantly reduce the incidence of food allergies in children and improve the quality of life of their families.

Further research is needed on methods of preventing and treating food allergies with probiotics, as well as research on formula milk to modify its composition to make it as close to mother's milk as possible. Continuous improvement of guidelines and standards of care for newborns and infants is essential for upgrading the life quality of children and their families, and is therefore required for the development of a healthy and strong society.

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