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Role of the microbiome and probiotics in the prevention of allergic diseases

Znaczenie mikrobiomu i rola probiotyków w prewencji chorób alergicznych

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Abstract

Microbes are present in many places in our body (the intestines, skin, reproductive organs), but the majority of them, which play the most important role, are those which reside in the gastrointestinal tract. It is known that the digestive tract of a foetus is sterile; however, after birth, the number of microorganisms in the neonate's intestines grows rapidly. The colonisation of the gastrointestinal tract by bacteria is of fundamental importance to one's future life. Particular attention is paid to the so-called health programming. It is believed that during the first 1,000 days of a child's life (including foetal life, infancy and early childhood), it is possible to programme human metabolism through appropriate nutrition. Adequate nutrition during pregnancy, lactation and the first few years of a child's life not only ensures appropriate weight gain and optimal nutritional status, but is also part of long-term health programming. Presumably, health programming also plays a role in the development of allergic diseases. Recent evidence indicates that the risk of atopy may be associated with intestinal dysbiosis; as a result, there has been a growing interest in the role of probiotics in the prevention of allergic diseases. The best documented practice is the preventative administration of probiotics to pregnant and nursing women, and to children in their first 6 months of life in order to reduce the rate of atopic dermatitis. Certain data also point to the role of probiotics in the acquisition of food tolerance. In addition, it is important that the probiotic administered be effective, since not every formulation present on the market guarantees the desired effect. The bacterial strains must be examined for their genome, catalogued in banks and marked with an appropriate identification number. It is only from such catalogued and well-studied strains that colonies for the most effective formulations can be grown. It is not quantity, but quality of the bacteria that ensures their effectiveness.

Keywords: microbiome, probiotics, allergic diseases, children

Streszczenie

Drobnoustroje występują w wielu miejscach naszego organizmu (jelita, skóra, narządy rodne), ale największą grupę stanowią i najważniejszą rolę odgrywają te, które zasiedlają przewód pokarmowy. Wiadomo, że układ pokarmowy płodu jest jałowy, jednak po urodzeniu liczba mikroorganizmów w jelitach noworodka szybko wzrasta. Zasiedlanie przewodu pokarmowego przez bakterie ma fundamentalne znaczenie dla naszego przyszłego życia. Szczególną uwagę zwraca się na tzw. programowanie zdrowotne. Uważa się, że w ciągu 1000 pierwszych dni życia dziecka (obejmujących życie płodowe, okres niemowlęcy i wczesnodziecięcy) mamy możliwość programowania metabolizmu człowieka poprzez odpowiednie żywienie. Prawidłowe żywienie w czasie ciąży, laktacji oraz w pierwszych latach życia dziecka nie tylko zapewnia odpowiednie przyrosty masy ciała i optymalny stan odżywienia, ale również wpływa na odległe – tzw. długofalowe – efekty programowania zdrowotnego. Przypuszczalnie ma też znaczenie w rozwoju chorób alergicznych. Ostatnie dowody wskazują, że ryzyko atopii może być związane z dysbiozą mikrobiomu jelitowego, w związku z tym wzrosło zainteresowanie rolą probiotyków w zapobieganiu zaburzeniom alergicznym. Najlepiej udokumentowane jest podawanie probiotyków kobietom w ciąży, karmiącym oraz dzieciom w pierwszych 6 miesiącach życia jako działanie profilaktyczne zmniejszające częstość atopowego zapalenia skóry. Niektóre dane wskazują także na rolę przyjmowania probiotyków w nabywaniu tolerancji pokarmowej. Dodatkowo istotne jest, by podawany preparat probiotyczny był skuteczny, gdyż nie każdy obecny na rynku gwarantuje pożądane działanie. Szczepy bakterii muszą być przebadane pod kątem ich genomu, skatalogowane w bankach i opatrzone odpowiednim numerem identyfikacyjnym. Tylko z takich skatalogowanych i przebadanych szczepów można hodować kolonie dla najskuteczniejszych preparatów. Gwarantem skuteczności jest nie ilość bakterii, lecz ich jakość.

Słowa kluczowe: mikrobiom, probiotyki, choroby alergiczne, dzieci

INTRODUCTION

Allergic diseases are becoming an increasingly common social problem despite the progress in knowledge that has taken place over the last few years. In the search of factors which may affect, indirectly or directly, the development of allergic diseases, the type of gastrointestinal microflora is taken into account. In the human body, it is dominated by lactic acid bacilli and is a physiological barrier against the pathomechanisms of many diseases, including allergies. Probiotics play an important role: they have an immunomodulatory action independent from their impact on the maintenance of a physiological flora in the digestive tract.

In the ECAP study (Epidemiologia Chorób Alergicznych w Polsce, Epidemiology of Allergic Diseases in Poland), signs of allergy were reported by as many as 40% of the respondents. Inflammation of the nasal mucosa was found in 35% of the subjects, while allergic rhinitis (AR) was recorded in 22% of individuals living in urban areas and in a much smaller number of those who resided in rural areas. According to current predictions, the incidence of allergic diseases will be constantly increasing; it is estimated that soon they may affect as many as more than half of society[1]. Research results may be accounted for by the "hygiene hypothesis," which links the rapid increase in the incidence of allergic diseases in highly industrialised areas with reduced exposure to environmental antigens, primarily as a result of high antibiotic use, consumption of processed foods and widespread use of chemical cleaning agents (understood as an excessively sterile life)[2,3].

What weapon does our body have in this battle? The first person to draw attention to the important role of microorganisms was Theodor Escherich, an Austrian paediatrician, who in 1880 demonstrated a positive effect of *Escherichia coli* on the intestinal microflora in healthy children and in patients with diarrhoea. Another milestone was a study by the Russian scientist Ilya Mechnikov, who drew particular attention to the important role of *Lactobacillus* bacteria residing in the human gastrointestinal tract in maintaining good health. Over the last decade, a number of studies have been published on the subject.

Initially, in the literature, the term "microflora" (e.g. "intestinal microflora") was used to refer to the bacteria residing in the human body. Currently, two terms are used: **microbiota**, which means all microbes, i.e. bacteria, fungi, viruses and archaea living in the human body and **microbiome**, a set of microbial genomes. The normal qualitative and quantitative composition of the microbiota is referred to as **eubiosis**. The microbiota supports the homoeostasis of the whole body by shaping immunity, metabolism and synthesis of many chemical compounds. It is important that the bacteria which have a beneficial effect on the processes taking place in the intestines and the general health of the body maintain the majority status among other microbes. Any change in the composition, number and function of microorganisms can lead to **dysbiosis**, which can result in many diseases (Tab. 1)[4].

Diseases: • autoimmune • metabolic: type 2 diabetes, obesity • cardiovascular: atherosclerosis • neurological: stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease • neoplastic • psychiatric: anxiety, depression • allergic: AD, AR, asthma
Autism
Coeliac disease
Ageing process
Chronic inflammation, e.g. Crohn's disease, irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), ulcerative colitis
Behavioural changes: professional burnout, stress exacerbation, decreased cognitive abilities, asocial behaviour
Infections

Tab. 1. Potential consequences of dysbiosis (authors' original work)

Microorganisms are present in numerous places in our body (the intestines, skin, reproductive organs), but the majority of them, which play the most important role, are those residing in the gastrointestinal tract. It has been established that there are approximately 2 kg of microbes in the human intestine which support the eubiosis of the gastrointestinal tract. These include approximately 10^{14} bacteria representing approximately 500 strains. Nearly 80% are bacteria that cannot be grown using traditional microbiological methods. In the case of 30% of microbiota species, it is possible to establish fixed numerical ranges; these species constitute a universal and stable **core** group of microorganisms, present in the majority of people. The rest of the microbiota is modified by physiological processes, including the immune system, genotype, lifestyle (diet, physical exertion) and the host's living environment. The dominant microorganisms in this group are those that are beneficial to the host, primarily those producing lactic acid (belonging to the genera *Bacteroides*, *Firmicutes*, *Proteobacteria* and *Actinobacteria*), although the potentially pathogenic microorganisms are also present. In this rich intestinal ecosystem, symbiotic, commensal and pathogenic microbes compete with one another both for the site of adhesion to the intestinal epithelium and for nutrients[4].

"NATURAL HISTORY" OF THE INTESTINAL MICROBIOME

In the human body, there is a unique set of microorganisms responding to changes in the diet, lifestyle and medication taken (Tab. 2). The microbiome is constantly changing

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Basic factors	Environmental factors	Individual factors
• Age • Sex • Stress • Diseases	• Geographical (region, climate) • Demographic • Cultural habits • Socioeconomic conditions • Technological development • Rapid lifestyle changes • Diet • Foreign microbes • Hormones • Antibiotics and other medication • Cleaning agents • Preservatives	• Genetic status • Pregnancy • Type of birth • Immune system • Intestinal epithelium • Pancreatin and other digestive juices • Enzymes • Bile acids • Intestinal peristalsis • Intestinal pH • Oxidation-reduction potential

Tab. 2. Factors affecting the intestinal microflora (authors' original work)

during the course of one's life and differs between individuals, even monozygotic twins[5].

It is known that the digestive tract of a foetus is sterile, but after birth the number of microorganisms in the neonate's intestines grows rapidly. Already towards the end of the first week of life, there are approximately 100 cells in one millilitre of intestinal content. The dominant strains in this period include aerobic bacteria such as: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, *Streptococcus faecium*, non-haemolytic *Streptococcus*, *Enterobacteriaceae* bacilli (*Escherichia coli*, *Klebsiella aerogenes*, *Proteus mirabilis*, *Serratia*) and *Pseudomonas aeruginosa*. Following a decrease in the oxidation-reduction potential of the intestine, anaerobic bacteria appear (*Bifidobacterium*, *Clostridium*, *Bacteroides* and *Lactobacillus*).

Currently, particular attention is paid to the so-called health programming. It is believed that during the first 1,000 days of a child's life (including foetal life, infancy and early childhood), it is possible to programme human metabolism through appropriate nutrition[6]. Adequate nutrition during pregnancy, lactation and the first few years of a child's life not only ensures appropriate weight gain and optimal nutritional status, but is also part of long-term health programming. Breastfeeding is very beneficial for the development of the intestinal microbiota of a child. Human breast milk contains healthy bacteria (*Bifidobacterium*, *Lactobacillus*, *Enterobacteriaceae*) and substances that stimulate bacterial growth (prebiotics), including the most important human milk oligosaccharides (HMO). In breastfed infants, protective bacteria of the genus *Bifidobacterium* dominate and there is a small number of the genus *Lactobacillus*; there are also much fewer bacteria of the genera *Clostridium* and *Escherichia*. The type of birth also significantly affects the composition of the original microflora. In neonates born by natural delivery, the composition of the gastrointestinal microflora is very similar to that present in the mother's reproductive and digestive tracts. In children born by caesarean section, the situation is different: the predominant genera are *Klebsiella*, *Clostridium* and *Enterobacteriaceae* (except for *Escherichia coli*); it is only later that the gastrointestinal tract is colonised by *Escherichia coli*, *Bacteroides* and *Bifidobacterium*.

Intestinal microflora in children is constantly changing and with time it becomes similar to that of adults. The composition of bacteria in a 2-year-old child is probably very similar to the adult microflora. Currently, it is believed that intestinal microflora composition is affected by many environmental factors, which sometimes results in an increased risk of allergic diseases. The relationship between caesarean delivery and the symptoms of atopic dermatitis (AD), allergic rhinitis and even asthma is particularly emphasised[7].

ROLE OF BACTERIA IN THE IMMUNE RESPONSE

One of the most important functions of the body is to establish a protective barrier against pathogenic factors and ensure physiological readiness to induce an immune response against a health threat. The gut-associated lymphoid tissue (GALT) reaches maturity in a child in a gradual fashion. The element which is fundamental for these processes is indeed the microbiome, or, more specifically, its interaction with intestinal dendritic cells. Bacteria, i.e. lactic acid bacilli, have a beneficial effect on a child's health, which is associated with the nature of the mechanisms induced during the stimulation of pattern-recognition receptors (PRR), primarily toll-like receptors (TLR). Their site of action is the surface of enterocytes and dendritic cells. They recognise microbial-associated molecular patterns (MAMP) typical for probiotic microorganisms. Stimulating them leads to a chain of reactions, including intracellular transmission. Through this route, mechanisms are activated which are responsible for intestinal barrier integrity and the control of microbes in the intestinal lumen[7–9].

PROBIOTIC BACTERIA

Based on the knowledge on the impact of intestinal microbiota on future health, researchers have been focusing to an increasing extent on the modulation of its programming by the use of probiotics. According to a definition by the Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO), probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host"[10]. In order for a given bacterial strain to be considered probiotic, it should meet certain criteria on *in vitro* and *in vivo* studies, including:

- precisely identified origin and species;
- human microbiome origin;
- absence of pathogenic action;

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- resistance to low pH and bile salts;
- ability to adhere to the host's intestinal epithelium;
- antagonistic activity against pathogenic microorganisms.

Probiotic bacteria include lactic-acid-producing bacteria of the genera *Lactobacillus* (e.g. *L. acidophilus*, *L. casei*, *L. reuteri*, *L. rhamnosus*) and *Bifidobacterium* (*B. animalis*, *B. breve*). Probiotics also include saccharomycetes *Saccharomyces boulardii*.

Probiotics support the processes ensuring intestinal homoeostasis, mainly in the mucosa, through the repair and maintenance of intestinal barrier integrity and by increasing the amount of mucus. This stimulates enterocytes to produce transforming growth factor β (TGF-β) and prostaglandin E2 (PGE2), and B-cells to secrete immunoglobulin A (IgA); probiotics also improve the efficacy of defence mechanisms by acting on local dendritic cells[7].

It is important that the probiotic administered be effective, since not every formulation present on the market guarantees the desired effect. The bacterial strains must be examined for their genome, catalogued in banks and marked with an appropriate identification number. It is only from such catalogued and well-studied strains that colonies for the most effective formulations can be grown. It is not quantity, but quality of the bacteria that ensures their effectiveness. Considering the fact that the action of probiotics begins in the small intestine, probiotics must be characterised by adequate protection against the pH of gastric juices and resistance to bile salts.

WHEN TO USE PROBIOTICS?

Probiotics have many properties that can be used clinically. It is believed that a probiotic formulation should be used in the following cases[11]:

- to boost body immunity;
- in respiratory tract infections in children;
- to prevent bacterial and fungal infections;
- in allergy, particularly AD;
- in dysbacteriosis of various origin;
- in irritable bowel syndrome;
- in acute gastroenteritis;
- in diarrhoea caused by rotaviruses and other viruses, in other types of acute diarrhoea and in travellers' diarrhoea;
- to prevent and treat genitourinary tract infections;
- in anxiety and depressive disorders in pregnant women during the perinatal period;
- in anxiety and depressive disorders in nursing women;
- in mild to moderate depressive symptoms.

ROLE OF PROBIOTICS IN THE PREVENTION OF ALLERGIES

In 1989, a hypothesis was proposed whereby a decreased exposure to microbes is the cause of an immune system imbalance contributing to the development of an allergic reaction (so-called hygiene hypothesis)[12]. This hypothesis was based on the observation that the prevalence of AR and AD was lower in children living with older siblings in large families (resulting in an increased exposure to microbes). In recent years, it has been demonstrated that intestinal dysbiosis may be associated with an increased risk of atopy[13]. It is suggested that probiotics can prevent an allergic reaction due to their anti-inflammatory action[14]. Many mechanisms have been discovered whereby probiotics reduce atopy and shift the balance in the Th1/Th2 response towards Th1 by inhibiting Th2 cytokines or by indirectly increasing the production of IL-10 cells and regulatory T-cells by dendritic cells.

The best documented practice is the preventative administration of probiotics to pregnant women, nursing mothers and children in their first 6 months of life in order to reduce the rate of AD. Recently published literature reviews indicate a beneficial effect of probiotics in the prevention of AD; however, they emphasise the fact that further research is necessary since the current diversity in probiotics (different bacterial strains, inconsistent endpoints etc.) does not help to acquire firm evidence[15].

In a meta-analysis of nine different studies in which a total of 3,257 children were examined, the risk ratio (RR) for asthma in children who received probiotics was 0.99 (95% confidence interval: 0.81–1.21)[16]. Thus, currently, there is no evidence that probiotics have a preventative effect against asthma in children, although it may be due to a lower rate of asthma than atopic dermatitis in small children. The ultimate conclusions will be possible to make after large studies have been conducted involving large groups of patients. No beneficial effects of probiotics have been demonstrated for other allergic diseases either (AR, food allergy), although the data are not consistent.

However, a recently published study clearly shows that the use of probiotics contributes to beneficial immunomodulation and reduces clinical symptoms of food allergy[17].

In conclusion, current clinical trial data do not provide a basis for routine probiotic use as an intervention to prevent any form of allergic disease, except for atopic dermatitis in high-risk infants. The optimal probiotic strains, doses and duration of treatment remain unknown. However, research in the field is under way and can be expected to provide a better insight into how probiotics may contribute to the prevention or treatment of atopic diseases.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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References

1. Samoliński B, Raciborski F, Lipiec A et al.: Epidemiologia Chorób Alergicznych w Polsce (ECAP). Alergol Pol 2014; 1: 10–18.
2. Krzych-Fałta E, Furmańczyk K, Piekarska B et al.: Allergies in urban versus countryside settings in Poland as part of the Epidemiology of the Allergic Diseases in Poland (ECAP) study – challenge the early differential diagnosis. Adv Dermatol Alergol 2016; 33: 359–368.
3. Sybilski AJ, Doboszynska A, Samolinski B: Prediction of atopy in the first year of life using cord blood IgE levels and family history. Eur J Med Res 2009; 14 Suppl 4: 227–232.
4. Gałecka M, Basińska AM, Bartnicka A: Znaczenie mikrobioty jelitowej w kształtowaniu zdrowia człowieka – implikacje w praktyce lekarza rodzinnego. Forum Med Rodz 2018; 12: 50–59.
5. Mitsuoka T: Intestinal flora and human health. Asia Pac J Clin Nutr 1996; 5: 2–9.
6. Selma-Royo M, Tarrazó M, García-Mantrana I et al.: Shaping microbiota during the first 1000 days of life. Adv Exp Med Biol 2019; 1125: 3–24.
7. Roży A, Jaguś P, Chorostowska-Wynimko J: Rola probiotyków w profilaktyce i leczeniu chorób alergicznych. Pneumonol Alergol Pol 2012; 80: 65–76.
8. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M et al.: Mechanisms of action of probiotics. Adv Nutr 2019; 10 (suppl_1): S49–S66.
9. Bilotta AJ, Cong Y: Gut microbiota metabolite regulation of host defenses at mucosal surfaces: implication in precision medicine. Precis Clin Med 2019; 2: 110–119.
10. Food and Agriculture Organization of the United Nations, World Health Organization: Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Cordoba, Argentina, 1–4 October 2001.
11. Szajewska H: Zastosowanie probiotyków w pediatrii. Stand Med Pediatr 2008; 5: 380–392.
12. Strachan DP: Hay fever, hygiene, and household size. BMJ 1989; 299: 1259–1260.
13. Lambrecht BN, Hammad H: The immunology of the allergy epidemic and the hygiene hypothesis. Nat Immunol 2017; 18: 1076–1083.
14. Nowak-Węgrzyn A, Chatchatee P: Mechanisms of tolerance induction. Ann Nutr Metab 2017; 70 Suppl 2: 7–24.
15. Wang HT, Anvari S, Anagnostou K: The role of probiotics in preventing allergic disease. Children (Basel) 2019; 6. pii: E24.
16. Azad MB, Coneys JG, Kozyrskyj AL et al.: Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis. BMJ 2013; 347: f6471.
17. Santos SCD, Konstantyner T, Cocco RR: Effects of probiotics in the treatment of food hypersensitivity in children: a systematic review. Allergol Immunopathol (Madr) 2020; 48: 95–104.