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Probiotics and allergic diseases

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Abstract

The prevalence of allergic diseases including atopic dermatitis, asthma, allergic rhinitis (AR) and food allergy is increasing worldwide and they cause a big economic and social burden. Understanding of reasons that contribute to the etiology of allergic diseases as well as new treatment approaches are very important for the follow-up and prevention of these diseases. In recent years, probiotics seem to be promising for allergic diseases. The effect of probiotics in the prevention and treatment of eczema is more extensively studied, but little is known about the association of the microbial flora of the host and allergic airway diseases and the efficacy of probiotics in decreasing the symptoms of patients with asthma and rhinitis. Hitherto, there is no strong evidence for use of probiotics in the treatment of eczema; however, administration of probiotics in breastfeeding mothers in the prenatal period and infants in the postnatal period can be accepted as a safe and helpful option in the prevention of eczema. In contrast, there is not yet reliable evidence or recommendations on use of probiotics for the prevention or treatment of asthma, AR, food allergy, and anaphylaxis currently. More standardized studies should be performed with different strains of probiotics to evaluate the protective and therapeutic effects of probiotics on other allergic diseases as well as eczema. In this review, the relationship between allergy and probiotics is handled in the light of current literature.

Key words: Probiotic; Allergy; Atopic dermatitis; Asthma; Allergic rhinitis

Core tip: The data in recent years concerning probiotics seem to be promising for allergic diseases. In this review, the relationship between allergy and probiotics is handled in the light of current literature.

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INTRODUCTION

Probiotics are beneficial bacteria that have valuable effects on health if taken in sufficient amounts. They are live single cell microorganisms which suppress the growth of harmful bacteria by competition at the adherence sites and by the direct effects of the antimicrobials they secrete. Probiotics secrete several vitamins such as thiamine, vitamin K_2 and folic acid, aid digestion by producing digestive enzymes and help the body absorb the nutrients[1]. Probiotics increase the production of mucin, decrease the permeability of intestinal lining and have effects on both innate and adaptive immunity. Members of *Lactobacillus*, *Bifidobacteria*, *Bacteroides*, *Enterococci generas*, *Streptococcus thermophilicus* and *Saccharomyces boulardii* are used as probiotics[2-4]. In order to have the better utility, probiotics can be used with prebiotics. Prebiotics are non-digestible food ingredients that promote the growth and activity of probiotics. Fermentation of prebiotics by the gut microbiota reveals short chain fatty acids such as acetate propionate and butyrate which serve as the energy sources for the regeneration of the colon epithelium. Some of the prebiotics are inulin, oligofructose, polydextrose, fructooligosaccharides, galactooligosaccharides, xylooligosaccharides, and lactulose[5-7]. Probiotics are used in a variety of diseases such as gastroenteritis, inflammatory bowel diseases, irritable bowel syndrome, celiac disease, peptic ulcers, colon cancer, lactose intolerance, bacterial vaginosis, childhood obesity, hyperlipidemia, anxiety, depression, stress, autism and allergic diseases[8-10].

The prevalence of allergic diseases is increasing worldwide. Asthma, atopic dermatitis (AD), allergic rhinitis (AR) and food allergy are common and important diseases which cause a big economic and social burden. Understanding of reasons that contribute to the etiology of allergic diseases as well as new treatment approaches are very important for the follow-up and prevention of these diseases. The data in recent years concerning probiotics seem to be promising for allergic diseases. The effect of probiotics in prevention and treatment of eczema is more extensively studied, but little is known about the association of the microbial flora of the host and allergic airway diseases and the efficacy of probiotics in alleviating the symptoms of patients with asthma and rhinitis. Although methodologies and results of the studies investigating the protective effects of probiotics in the development and treatment of allergic airway diseases are variable and controversial, they give a promising perspective and offer new insights for further studies[11,12]. In this review, the relationship between allergy and probiotics is handled in the light of current literature.

Prenatal factors such as maternal diet, stressful life during pregnancy and gestational diabetes are suggested to be responsible for the development of atopic diseases. In the postnatal period, diet content in the early life, microorganisms and allergen exposure are potential risk factors and are target of treatment[13]. Hygiene hypothesis has been suggested during a few decades in order to explain the prominent increase in the incidence of atopic diseases. Incidence of allergic diseases increases in the children growing in smaller family, while infections experienced in the children living together with their older siblings have been proposed to prevent allergic diseases[11]. Correlations between allergic diseases and microbial agents have begun to be discussed over time. The idea that the existence and proper maintenance of natural flora have positive effects on the immune system and could prevent the development of allergic or autoimmune inflammation in these people has been exciting. Numerous studies have been conducted about the potential role of probiotics in the prevention and intervention of asthma, food allergy and eczema. The promising outcomes obtained from probiotics lead to the interest in this subject intensified in allergic diseases[11,14].

PROBIOTICS AND IMMUNE RESPONSE

Probiotics contribute education of the immune system and appropriate response to the antigen. The beneficial effect of probiotics on allergy is often associated with enhancement of Treg cells. Specific probiotics have been shown to induce an increase in Treg cells as well as to suppress Th17 responses. Th17 cells secrete IL-17 that induces tissue inflammation[15,16]. The pathogenesis of allergic diseases was first described as an imbalance of Th1/Th2 cells. Probiotics inhibit allergic diseases by suppressing the Th2 response[17,18]. The timing of the bacterial colonization in the gut is crucial. The timing of bacterial colonization early in life is important for appropriate immune education and the transmission from mother to the fetus during pregnancy. The early colonization with *Bacteroides* and *Bifidobacterium* species might play a crucial role in the development of immune regulation[15]. Clinical studies evaluating the effects of probiotics in allergic diseases are seen in Table 1.

PROBIOTICS AND AD

AD is a common important disease which causes an economic and social burden. Its incidence differs among the societies with an incidence reported to reach up to 20% in developed countries[19]. AD is the first allergic disease seen in the childhood. Infantile eczema usually occurs in the first year of life and the majority of cases resolve before 6 years of age. Most of AD cases are mild, although up to 30% are seen as moderate to severe cases. AD is recognized as a precursor of the development of atopic diseases such as asthma, AR and food allergy in the forthcoming years of children[12,20,21]. Increased incidence of eczema in recent years has made new research a current issue in epidemiology, prevention and treatment of this disease[22]. Given that it is a frequently seen disease, causes a substantial proportion

Table 1 Clinical studies evaluating the effects of probiotics in allergic diseases

Disease	Ref.	Number of participants	Strains	Age	Results
Atopic dermatitis	Kalliomäki *et al*[54], 2007	159	*Lactobacillus* GG	Prenatal and postnatal	Decreased incidence of eczema
	Taylor *et al*[55], 2007	178	*L. acidophilus* LAVRI- Al	Postnatal	No change in eczema rates
	Kopp *et al*[56], 2008	94	*Lactobacillus* GG	Prenatal and postnatal	No difference
	Griskevicius *et al*[57], 2008	446	Group 1: *L. Rhamnosus* HN001 Group 2: *B. animalis ssp. lactis* HN019	Prenatal and postnatal	Decreased incidence of eczema by the intake of *L. rhamnosus*
	Enomoto *et al*[27], 2014	130	*Bifidobacterium breve* M-16V, *Bifidobacterium longum* BB536	Prenatal and postnatal	Decreased incidence of eczema
	Rautava *et al*[28], 2012	241	*Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999, *Lactobacillus paracasei* ST11 and *Bifidobacterium longum* BL999	Prenatal and postnatal	Decreased incidence of eczema
Atopic sensitization	Huurre *et al*[58], 2008	171	*Lactobacillus* GG, *B. lactis*	Prenatal and postnatal	Decreased incidence of sensitization
Allergic airway diseases	Abrahamsson *et al*[59], 2007	232	*L. reuteri*	Prenatal and postnatal	No difference in wheeze
	Wickens *et al*[60], 2012	425	*B. lactis*, *Lactobacillus* HN001	Prenatal and postnatal	Decreased incidence of rinoconjunctivitis
	Chen *et al*[40], 2010	105	*L. gasseri* A5	School children	Decrease in asthmatic symptoms
	Wassenberg *et al*[41], 2011	31	*Lactobacillus paracasei* ST11	Adults	Decreased cytokine release
Food allergy	Dupont *et al*[47], 2015	119	Probiotic supplemented formula	Infants with cows' milk protein allergy	Decreased incidence in food related symptoms
	Tang *et al*[48], 2015	62	*Lactobacillus rhamnosus* CGMCC 1.3724	Children with peanut allergy	Increased incidence of desensitization
Urticaria	Arslanoğlu *et al*[5], 2008	134	Prebiotic-supplemented hypoallergenic formula	Postnatal	Decreased cumulative incidence of allergic urticaria
Systemic nickel allergy syndrome	Randazzo *et al*[43], 2015	22	*Lactobacillus reuteri* DSM 17938	Adults	Decrease in symptoms

of severe cases and accompanies other allergic diseases, meticulous treatment and follow-up of pediatric eczema have become compulsory.

There is a correlation between the development of AD and gut microbiota though it is not exactly clear[23]. A randomized double blind study conducted with administered bacterial lysate shown a correlation between gut microbiota and AD[24]. A greater number of elder siblings were found to be correlated with an increase in lactobacilli and bacteroides colonization and a decrease in clostridia in the gut. Risk for development of AD increased in the infant aged 5-13 mo with a higher gut concentration of clostridia[24]. This study demonstrated that gut microbiota is one of the reasons underlying the development of AD. A more diverse intestinal microbiota in the first week of life is associated with a reduced risk of subsequent eczema in infants at an increased risk of allergic disease[25]. This study suggested that interventions that enhance microbial diversity in early life may provide an effective means for the prevention of eczema in high-risk infants.

The knowledge about whether probiotics prevent the development of AD is increasing day by day. In a cohort from Norway with a wide population, the potential association was investigated between the intake of probiotics during pregnancy and infancy periods and the development of questionnaire-reported atopic eczema, rhinoconjunctivitis and asthma. The intake of probiotic milk products was found to be correlated with a decreased incidence of atopic eczema and rhinoconjunctivitis; however, this was not correlated with the incidence of asthma in the 36-mo follow-up[26]. Probiotics used by pregnant women or breast-feeding mothers and/or given to infants reduced the risk of eczema in infants; however, the certainty in the evidence is low. No effect was observed for the prevention of other allergic conditions[14]. Enomoto *et al*[27] examined the effect of the intake of *Bifidobacterium breve* (*B. breve*) M-16V and *Bifidobacterium longum* (*B. longum*) BB536 over prenatal 1 mo and postnatal 6 mo on the development of allergic disease. They found that the incidence of eczema was lower in the probiotic group than in control in a short follow-up period of 18 mo. Rautava *et al*[28] investigated the role of probiotic intervention regimens in reducing the risk of eczema in infants. Mothers with a history of allergic disease and atopic sensitization were randomly assigned to the *Lactobacillus rhamnosus* LPR and *B. longum* BL999 (LPR1BL999) group, the *Lactobacillus paracasei* (LP), ST11 and *B. longum* BL999 (ST111BL999) group, or the placebo group during 2 mo before and after the expected date of delivery. They found that infants whose

mothers received any of the probiotic supplements developed significantly less episodes of eczema when compared with the placebo group. However, skin prick test results were similar between the groups. It is noteworthy in the mentioned study that, probiotics did not prevent atopic sensitization and prevented only non-atopic eczema[29]. Based on this result, long-term effects of the use of probiotics may be limited. It has been noted in a recent meta-analysis that, additionally administered probiotics in the early life prevented AD in long term compared to placebo[30]. There are several studies suggesting *Lactobacillus rhamnosus GG* (LGG), a mix of specific probiotic strains and prebiotic + prebiotic mixtures have a positive effect in the prevention of the incidence or decrease of the severity of AD. Nevertheless, these studies are not enough for use of probiotic with this purpose[31].

There are also studies demonstrating that probiotic support is ineffective in the prevention of the development of AD. In a study by Allen *et al*[32] with women from 36 wk gestation and their infants to the age of 6 mo, the incidence of eczema was investigated in the 2nd year of age in infants who received daily either the probiotic (*Lactobacillus salivarius* CUL61, LP CUL08, *B. animalis* subspecies lactis CUL34 and *Bifidobacterium bifidum* CUL20) or placebo. Use of probiotics was found not to prevent the development of eczema during the study. In that study, probiotics were found to decrease the incidence of food allergy in early childhood as an indirect effect. There are interesting results in the evaluations carried out according to the type of probiotics. For example, according to a meta-analysis use of lactobacilli during pregnancy was stated to prevent atopic eczema in children between 2 and 7 years old, but a mixture of various bacterial strains did not affect the development of eczema[33].

The role of probiotics in the prevention of atopic eczema is yet to be clarified. Evidence presented by the studies suggesting that probiotics may prevent pediatric eczema is not enough strong. A positive effect, if any, may be related with onset time, dose, duration and use of specific probiotics. Support of this issue with further and longer research would be helpful in elimination of the limited uncertainties in the use of probiotics. Another question is that can probiotics be used for the treatment of pediatric eczema? Evidence about the use of probiotics in the treatment of eczema is not enough good as their use in the prevention. It is suggested in a limited number of studies that probiotics decrease the severity of eczema. In a randomized double-blind placebo-controlled study examining the effect of the use of *Lactobacillus plantarum* (*L. plantarum*) CJLP133 for 12 wk in children with AD aged 12 mo and 12 years, an improvement in SCOring of Atopic Dermatitis (SCORAD) scores was noted, while levels of eosinophil counts, interferon-gamma (IFN-γ) and IL-4 were decreased. However, no significant reduction was observed in total use of topical corticosteroids[34]. Wang *et al*[35] compared children who received LP, *Lactobacillus fermentum* (LF) and LP + LF with those who received placebo in a double-blind, prospective, randomized study. SCORAD index was lower in the probiotic groups compared to placebo until 4 mo after probiotics were discontinued. In brief, the use of LP and LF mix probiotics was found to be correlated with clinical improvements in the children having AD. In another study, Niccoli *et al*[1] showed that the use of *L. salivarius* LS01 led to improvements in quality of life in the children having AD.

Consequently, numerous studies investigating the role of probiotics in the prevention or intervention of AD present clinical suggestions for the use of probiotics. Even if the evidence is not strong enough, use of probiotics for the prevention of eczema is recognized by a considerable number of clinicians. Another difficult-to-answer question about the use of probiotics is that "when should probiotics be initiated?" Factors that can influence early-life colonization include antibiotic treatment, method of delivery, maternal and infant diet, and biodiversity in the home, surrounding environment and in family members. Initiation of probitocis in the early life is a better option in order to prevent eczema, a result that we want to obtain. Early initiation of probiotics is of key importance, if a benefit would be obtained. Even if possible, administration of probiotics to mothers in the prenatal period can be helpful in the infant under risk of eczema. Considering all critical outcomes, because there is a net benefit resulting primarily from prevention of eczema, World Allergy Organization (WAO)-McMaster University Guidelines for Allergic Disease Prevention suggest using probiotics in pregnant women and women who breastfeed infant at a high risk for allergy in their children. Similarly, the WAO guideline panel suggests using probiotics in infants at a high risk of developing allergies[36]. However, there are still questions to be answered in the future about probiotic administration for eczema and other allergic diseases: Which probiotic, at what dose, when, how long, and to whom? Clinical use of probiotics will gradually become more widespread as these questions find their answers[23].

PROBIOTICS AND ALLERGIC AIRWAY DISEASES

The prevalence of asthma as well as other allergic diseases is increasing worldwide. Maturation of the immune system in the first years of life may play a role in this increase and this may be related to hygiene hypothesis and imbalances in lymphocyte T-helper 1 (Th1)/lymphocyte T-helper 2 (Th2) balance and activation of Th2 cytokines such as IL-4, IL-5, and IL-13[11].

Asthma is a chronic airway disease characterized by airway inflammation and hyperresponsiveness. Although asthma is a heterogeneous disease with different phenotypes and endotypes, Th2 mediated inflammation is central to the pathogenesis in most of the patients[4]. Therapeutic effects of probiotics in the prevention and

treatment of eczema are more extensively studied, but little is known about the association of the microbial flora of the host and allergic airway diseases and the efficacy of probiotics in alleviating the symptoms of patients with asthma and rhinitis. Methodologies and results of the studies investigating the protective effects of probiotics in the development and treatment of allergic airway diseases are variable and controversial, but they give a promising perspective and offer new insights for further studies[11].

The heterogeneity of gut microbiota is required for the development of mucosal tolerance. The composition of the gut microbiota differs in children with asthma. Some species of *Clostridium difficile* were found in higher amounts whereas *Bifidobacterium* amounts were lower in the intestinal microbiota of asthmatic children[4]. Probiotics modulate immune responses through toll-like receptors, activation of dendritic cells, maintaining a Th1 response and thereby suppressing Th2 response[4,11,12].

Evidence from ovalbumin (OVA)-sensitized murine asthma models showed significant reductions in the number of inflammatory cells in bronchoalveolar lavage fluid and airway hyperreactivity and an increase in the levels of regulatory T cells after administration of *Lactobacillus reuteri* ATCC 23272, LGG or *Bifidobacterium lactis* in single challenges. However, *Lactobacillus salivarius* has not been shown to slow down allergic airway responses or reduce the number of inflammatory cytokines and cells[4,37]. In another study, OVA-sensitized mice were given *B. breve* M-16V, *Bifidobacterium infantis* NumRes251, *Bifidobacterium animalis* (*B. animalis*) NumRes252 and NumRes253, *L. plantarum* NumRes 8 and *Lactobacillus rhamnosus* NumRes6. After challenge with OVA, airway reactivity response to metacholine and numbers of inflammatory cells in bronchoalveolar fluid were measured. Of the 6 strains, only *B. Breve* M16V and *L. plantarum* NumRes8 were found to inhibit the metacholine response, reduce the number of inflammatory cells in bronchoalveolar lavage and reduce OVA-specific IgE and IgG1. These outcomes indicate that the immunomodulatory effects of probiotics can be strain specific[38].

A meta-analysis of randomized, placebo-controlled trials that evaluated the effect of probiotics given prenatally or postnatally within the first year and were published between 2001 and 2012 revealed statistically significant reductions of total IgE levels and the risk of atopic sensitization, but a significant decrease in asthma/wheeze development was not seen. Atopic sensitization risk was decreased significantly when probiotics were given prenatally and postnatally, but the same effect was not seen when given only postnatally[11]. In another meta-analysis of randomized controlled trials of 17 studies enrolling 4755 children, asthma, rhinitis and wheezing development was not changed significantly after prenatal and postnatal probiotic supplementation[39]. In a double-blind, randomized, placebo-controlled study, 105 asthmatic children aged 6-12 years with a history of mild to moderate persistent asthma and persistent AR were enrolled. *Lactobacillus gasseri* A5 was given to the study group (n = 49). Study outcomes revealed decreases in the severity of asthmatic symptoms, improvements in the CACT score ($P < 0.05$) and decreases in bronchial hyperreactivity ($P < 0.001$) and significant improvements in the FEV1, FVC, FEV1/FVC and MEF25-75 levels in the study group[40].

Rhinitis plays an important role in the life quality of the host because of the frequent co-occurrence of AR and asthma and the united airway disease hypothesis[2]. Sinus bacterial diversity is important in the healthy functioning of upper airways and decrease in sinus inflammation[6]. In a study, 31 adults with AR received LP ST11 for 8 wk. IL-5, IL-8 and IL-10 levels from peripheral blood mononuclear cells decreased after the probiotic supplementation[41]. Peripheral blood eosinophils and IFN-γ levels as well as the need for medication were reported to be decreased in patients with Japanese cedar pollinosis after supplementation with *B. longum*[42].

The probiotics used must be resistant to acid and bile for enough efficacy and they should be taken regularly. At least 9 d of probiotic application was reported to be essential for significant inhibition of airway eosinophilia and airway hyperreactivity in mice[11,37]. But experimental animals such as mice have a gut microbial flora which has less than 50% DNA identity to the human microbiota. Therefore, interpretation of the results should be cautiously made[4].

More studies done with different strains of probiotics and standardization of methodologies will offer advances in the understanding of microbial flora of patients with asthma and rhinitis and the therapeutic effects of probiotics for these patients. Also the duration of therapy, selection of probiotics in different situations and patients and the dosage of the probiotics need to be considered in the future studies.

PROBIOTICS AND OTHER ALLERGIC DISEASES

There are few studies about the effects of probiotics on urticaria. In a prospective, randomized, double-blind, placebo-controlled study, 134 infants (68 in placebo, 66 in study group) received either a placebo-supplemented hypoallergenic formula or a prebiotic-supplemented (8 g/L scGOS/lcFOS) hypoallergenic formula during the first 6 mo of life. Cumulative incidence of allergic urticaria at 2 years of age was 1.5% in the study and 10.3% in the placebo group ($P < 0.05$)[5]. In patients with systemic nickel allergy syndrome, after 2 wk of *Lactobacillus reuteri* DSM 17938 strain supplementation, a significant improvement was seen in cutaneous symptoms such as urticaria, presence of itch and eczema in both the study and control groups. Gastrointestinal symptoms improved only in the patients supplemented with *Lactobacillus reuteri*[43]. In a case study, probiotic supplementation and antihistamines

were given to a 17-mo-old boy with urticaira pigmentosa and a decrease in pruritus, and improvement of appetite and sleeping was reported[44].

Food allergy is seen early in the course of atopic march and is a known aggravating factor of AD. Food induced anaphylaxis is the most common cause of anaphylaxis in outpatients especially in children and can be fatal. In a study, LP L9 was given to β-lactoglobulin (BLG)-sensitized mice. Levels of $CD4^+CD25^+Foxp3^+$ Treg cells in mesenteric lymph nodes increased by 51.85% after the supplementation[45]. Among the probiotic strains, LGG was reported to be the most studied probiotic in the prevention of food allergy, especially cow milk allergy[46]. In a study, 119 infants with cow milk protein allergy were given a probiotic supplemented extensively hydrolysed casein-based formula. Food related symptoms and SORAD index were improved[47]. A double-blind, placebo-controlled randomized trial of 62 children with peanut allergy on oral immunotherapy *Lactobacillus rhamnosus* CGMCC 1.3724 supplementation was given. In the study group 89.7% and in the placebo group 7.1% of children were desensitized ($P < 0.001$) at the trial end[48]. Probiotic-supplemented peanut sensitized mice have been shown to have increased splenic naturally occurring T regulatory cell populations and reduced gene expression IL-13 compared to controls[49]. In spite of these encouraging results, a meta-analysis of 10 trials did not show preventive effects of prenatal and postnatal usage of probiotics on food allergy[50].

In a murine model of food allergy induced systemic anaphylaxis, VSL3 probiotic was reported to suppress TH2 mediated reactions and anaphylactic reactions[51]. Probiotics can contribute to decreases in the allergic symptoms as well as anaphylactic reactions through induction of Treg cells, suppression of Th2 responses, inhibition of mast cell membrane potassium (IKCa) current and degranulation[52,53]. Clinical studies evaluating the effects of probiotics in allergic diseases are seen in Table 1.

The formation and maintenance of gut flora in a proper way in the early life are crucial especially for AD and other allergic diseases. Although there is partial debate over the prevention of the development of AD, here it is worth noting to mention some recommendations. Although it alone does not prevent eczema yet, breast-feeding of infants should be promoted. Normal vaginal delivery which is quite important for gut microbiota of the infant should be promoted except medical contraindications. Unnecessary use of antibiotics which impair gut flora should be avoided in early life. To the date of this study, there is no strong evidence for use of probiotics in the treatment of eczema; however, administration of probiotics in breastfeeding mothers in the prenatal period and infants in the postnatal period can be accepted as a safe and helpful option in the prevention of eczema. In contrast, there is not yet reliable evidence or recommendations on use of probiotics for the prevention or treatment of asthma, AR, food allergy, and anaphylaxis currently. More standardized studies should be performed with different strains of probiotics to evaluate the protective and therapeutic effects of probiotics on other allergic diseases as well as eczema.

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