

Probiotics and infantile atopic eczema

Ahmet Zülfikar Akelma¹
Aziz Alper Biten²

¹Pediatric Allergy and Immunology Unit, Ankara Keçioren Teaching and Research Hospital, Ankara, Turkey;

²General Directorate of Management Services, Republic of Turkey Ministry of Health, Ankara, Turkey

Abstract: Pediatric eczema is a common disease which causes economic and social burden. Its incidence differs among the societies, with an incidence reported to reach up to 20% in developed countries. Eczema is the first allergic disease seen in the childhood, and it is recognized as a precursor for the development of atopic diseases such as asthma, allergic rhinitis, and food allergy in the forthcoming years of children. Increased incidence of eczema in recent years has led to new research in epidemiology, prevention, and intervention of this disease. It is no doubt important to treat itching, rash, and excoriation of the skin; however, treatment of pediatric eczema should not be considered only as a treatment of skin lesions. Considering skin treatment as the tip of the iceberg, proper management of the allergic processes can be accepted as the rest of the iceberg. The role of probiotics in the prevention of atopic eczema is yet to be clarified. Evidence presented by existing studies suggesting that probiotics may prevent pediatric eczema is not strong enough. A positive effect, if any, may be related with onset time, dose, duration, and use of specific probiotics. To date, there is no strong evidence for use of probiotics in the treatment of eczema; however, administration of probiotics in breast-feeding mothers in the prenatal period and in infants in the postnatal period can be accepted as a safe and helpful option in the prevention of eczema. Nevertheless, there are still questions to be answered in the future about probiotic administration for eczema. Clinical use of probiotics will gradually become more widespread when these questions are answered. Based on current information, the administration of probiotics for pediatric eczema topic is addressed in this review.

Keywords: probiotic, eczema, prevention, gut

Introduction

Pediatric eczema is a common important disease which causes economic and social burden. Its incidence differs among the societies, with an incidence reported to reach up to 20% in developed countries.¹ Eczema is the first allergic disease seen in the childhood. Infantile eczema usually occurs in the first year of life and majority of cases resolve before 6 years of age. Most of the eczema cases are mild, although up to 30% are seen as moderate-to-severe cases. Eczema is recognized as a precursor for the development of atopic diseases such as asthma, allergic rhinitis, and food allergy in growing children.²⁻⁴ Increased incidence of eczema in recent years has led to new research in epidemiology, prevention, and treatment of this disease.⁵ Given that it is a frequently seen disease, causes substantial proportion of severe cases, and accompanies other allergic diseases, meticulous treatment and follow-up of pediatric eczema has become compulsory.

Correspondence: Ahmet Zülfikar Akelma
Pınarbaşı M, Ardahan S Number 25,
Keçiören, 06380 Ankara, Turkey
Tel +90 312 356 9000
Fax +90 312 356 9002
Email akelma@gmail.com

The treatment of pediatric eczema classically includes skin hydration, topical corticosteroids, antihistamines, topical calcineurin inhibitors (tacrolimus and pimecrolimus), and trigger elimination. Except for a few children with severe eczema, symptoms of the most patients are brought under control and a marked improvement is achieved in their quality of life.⁶ It is no doubt important to treat itching, rash, and excoriation of the skin; however, the treatment of pediatric eczema should not be considered only as a treatment of skin lesions. Correct understanding of the immunologic processes which are involved in pediatric eczema, development of appropriate treatment approaches, and prevention of the other atopic disease processes should also be included among goals of the treatment. Considering skin treatment as the tip of the iceberg, proper management of the allergic processes can be accepted as the rest of the iceberg.

Immunopathologic process

The etiology of pediatric eczema is not exactly known. Genetic predisposition and several prenatal and postnatal environmental factors play a role in the development of eczema. Important mutations having a role in eczema have been demonstrated in the last decade. Eczema can be defined as a skin problem characterized by impaired integrity of the skin barrier, increased inflammatory response against antigens, and decreased antimicrobial response. These pathophysiological changes, by a vicious circle, lead to inflammation in the skin. Identification of the nonsense mutations in filaggrin (*FLG*) gene in the patients with atopic dermatitis (AD) and ichthyosis vulgaris has suggested that *FLG* is of importance in the skin barrier function. Skin symptoms in the patients with *FLG* mutation are severe, and the risk for development of the other atopic diseases such as asthma has been found to be high in these patients.⁷ Additionally, mutations in 1q21, in which epidermal differentiation complex proteins such as involucrin, loricrin, and hornerin are located, have been detected in AD.⁸

Prenatal factors such as maternal diet, stressful life during pregnancy, and gestational diabetes are suggested to influence development of atopic diseases. Among postnatal factors, diet content in the early life, microorganisms, and allergen exposure are potential risk factors and are the target of treatment.⁹ During the past few decades, the hygiene hypothesis has been suggested in order to explain the prominent increase in incidence of atopic diseases. It has been proposed that while incidence of allergic diseases increases in the children growing in smaller families, infections in children living together with their older siblings

prevent allergic diseases. Correlations between allergic diseases and microbial agents have been discussed over time. The idea of existence and proper maintenance of natural flora have positive effects on immune system, and the fact that this could prevent development of allergic or autoimmune inflammation in these people has been promising. Numerous studies have been conducted about the potential role of probiotics in prevention and intervention of asthma, food allergy, and eczema. The promising outcomes obtained from probiotics lead to the intensified interest in this subject.^{10,11}

Eczema and gut microbiota

There is a correlation between development of eczema and gut microbiota, although it is not exactly clear. A randomized double-blind study conducted with administered bacterial lysate showed a correlation between gut microbiota and AD. It has been found that a larger number of elder siblings was correlated with an increase in Lactobacilli and Bacteroides colonization and a decrease in Clostridia in the gut. Risk for development of AD increased in infants aged 5–13 months with higher gut concentration of Clostridia.¹² This study demonstrated that gut microbiota is one of the reasons for the underlying 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 increased risk of allergic disease. 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.¹³

Probiotics and allergy

Probiotics contribute to the education of the immune system and generation of appropriate response to the antigen. The beneficial effect of probiotics 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.^{14,15} The pathogenesis of allergic diseases was first described as an imbalance of Th1/Th2 cells. Probiotics inhibit allergic diseases by suppressing the Th2 response.^{16,17} 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.¹⁴

Probiotics for the prevention of pediatric eczema

Our knowledge on the prevention of the development of eczema by probiotics is increasing day by day. In a large cohort from Norway, the potential association between the intake of probiotic milk products during pregnancy and infancy periods and the development of questionnaire-reported atopic eczema, rhinoconjunctivitis, and asthma was investigated. The intake of probiotic milk products was found to be correlated with decreased incidence of atopic eczema and rhinoconjunctivitis; however, this was not correlated with the incidence of asthma in the 36-month follow-up.¹⁸ Probiotics used by pregnant women or breastfeeding 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.¹⁰ Enomoto et al¹⁹ examined effect of the intake of *Bifidobacterium breve* M-16V and *Bifidobacterium longum* BB536 over 1 month prenatally and 6 months postnatally on the development of allergic disease. They found that incidence of eczema was lower in the probiotic group than in the controls in a short follow-up period of 18 months. Rautava et al²⁰ 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* ST11, and *B. longum* BL999 (ST111BL999) group or to the placebo group during 2 months before and after the expected date of delivery. They found that infants of mothers receiving 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 that in the mentioned study probiotics did not prevent atopic sensitization and prevented only nonatopic eczema.²¹ 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 the long term compared to placebo.²² There are several studies suggesting that *Lactobacillus rhamnosus* GG, a mix of specific probiotic strains, and prebiotic + prebiotic mixtures have a positive effect in preventing the incidence of or decreasing the severity of AD. Nevertheless, even these studies do not provide enough evidence for the use of probiotic for this purpose.²³

There are also studies demonstrating that probiotic support is ineffective in prevention of the development of eczema.

In a study by Allen et al²⁴ with women at 36 weeks gestation and their children (infants to age 6 months), incidence of eczema was investigated at 2 years in infants who had received the probiotic (*Lactobacillus salivarius* CUL61, *Lactobacillus paracasei* CUL08, *Bifidobacterium animalis* subspecies lactis CUL34, and *Bifidobacterium bifidum* CUL20) daily and in those who received placebo. Use of probiotics was found not to prevent the development of eczema during the study. In that study, probiotics were found to decrease 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.²⁵

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 strong enough. A positive effect, if any, may be related with onset time, dose, duration, and use of specific probiotics. Support for this result with further research would be helpful in elimination of the limited uncertainties in the use of probiotics.

Probiotics for the treatment of pediatric eczema

Another question is: can probiotics be used for treatment of pediatric eczema? Evidence about the use of probiotics in the treatment of eczema is not as good enough as that for their use in prevention. It has been suggested in a limited number of studies that probiotics decrease the severity of eczema. In a randomized, double-blind placebo-controlled study, examining effect of the use of *Lactobacillus plantarum* CJLP133 for 12 weeks in children with AD aged 12 months and 12 years; it was found that there was an improvement in SCORing of Atopic Dermatitis scores, while levels of eosinophil counts, IFN- γ and IL-4, were decreased. However, no significant reduction was observed in total use of topical corticosteroids.²⁶ Wang and Wang²⁷ compared children who received *L. paracasei* (LP), *Lactobacillus fermentum* (LF), and LP+LF with those who received placebo in a double-blind, prospective, randomized study. SCORing of Atopic Dermatitis index was lower in the probiotic groups compared to placebo until 4 months after probiotics were discontinued. In brief, the use of LP and LF mix probiotic was found to be correlated with clinical improvements in the children having AD. In another study, Niccoli et al²⁸ showed that the use of

L. salivarius LS01 led to improvements in quality of life in the children having AD.

Current insights

Numerous studies investigating the role of probiotics in the prevention or intervention of pediatric eczema present limited 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: 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 probiotics 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 is to be obtained. When possible, administration of probiotics to mothers in the prenatal period can be helpful in the infant at risk of eczema. Considering all critical outcomes and because there is a net benefit resulting primarily from prevention of eczema, World Allergy Organization–McMaster University Guidelines for Allergic Disease Prevention suggests using probiotics in pregnant women as well as in women who breastfed infant at high risk for allergy. Similarly, the World Allergy Organization guideline panel suggests using probiotics in infants at high risk of developing allergies.²⁹ However, these are conditional recommendations and very low quality evidence.

The formation and maintenance of gut flora in a proper way in the early life is crucial, especially for eczema and the other allergic diseases. Although there is partial debate on prevention of the development of eczema, it is worth noting some recommendations here. 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 when medical contraindications exist. Unnecessary use of antibiotics which impair gut flora should be avoided in early life.

Conclusion

To the date of this study, there is no reliable evidence for use of probiotics in the treatment of eczema; however, administration of probiotics in breast-feeding mothers in prenatal period and infants in postnatal period can be accepted as a safe and helpful option in the prevention of eczema. However, there are still questions to be answered in the future about probiotic administration for eczema

and the other allergic diseases: Which probiotic? In which dose? When? For how long? and To whom? Clinical use of probiotics will gradually become more widespread as these questions are answered.

Disclosure

The authors report no conflicts of interest in this work.

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