

Prebiotics and probiotics in atopic dermatitis (Review)

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Abstract. Recent years have brought additional data on the benefits of prebiotics and probiotics treatment in patients with atopic dermatitis. This review includes all the articles published in PubMed, Scopus, Embase and Cochrane databases until 05.06.2018. The terms used for the search were 'prebiotic', 'probiotic', 'atopic dermatitis', 'Severity Scoring of Atopic Dermatitis', and 'SCORAD'. There was an increase of the intestinal permeability reported in patients with atopic dermatitis and a reduction of the cutaneous microbiome diversity. Probiotics modulate the general microbiome and immune status by improving the intestinal barrier; these effects can be responsible for reducing allergic phenomenon and atopic dermatitis severity. We have structured the results by age groups as infants, 1-18 years, adults, and also pregnancy and lactation. Literature does not offer yet answers on the issues such as the optimal dosing, duration needed to see beneficial effects, the optimal time to start the treatment; the personalized use of probiotics according to colonic

dysbiosis may be associated with better results. However, most randomized controlled trials and meta-analyses support the administration of probiotics for at least 8 weeks in order to obtain beneficial effects in improving severity scoring of atopic dermatitis.

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1. Introduction

Food can have therapeutic benefits; as early as 2500 years ago the parent of medicine, Hippocrates said: 'Let food be thy medicine and medicine be thy food'.

Atopic dermatitis (AD) is a chronic, inflammatory skin disease, characterized by dry skin, intense pruritus, eczematous cutaneous lesions that occurs in people with atopic terrain. It is manifested by intense pruritic papules with evolution towards lichenification. Patients with AD may associate other atopy (allergic rhinitis, bronchial asthma). AD prevalence is increasing, reaching 10-20% in the pediatric population and up to 3% of adults, commonly the onset occurs during the first year of life (1).

Etiopathogeny of AD is complex and multifactorial involving genetic factors, environmental factors and immunological factors. The composition of the intestinal and cutaneous microbiome, the maternal diet during pregnancy, the mode of delivery, antibiotic treatment during pregnancy and early infancy, westernized lifestyle with chronic exposure to allergens increase the risk of allergic diseases and AD.

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Abbreviations: AD, atopic dermatitis; CD14, cluster of differentiation 14; GM, gut microbiome; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; IgA, immunoglobulin A; IL, interleukin; INF, interferon; IR, insulin resistance; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; SCORAD, severity scoring of atopic dermatitis; Th1, T-helper cell type-1; Th2, T-helper cell type-2; Treg, regulatory T cell; TLR4, Toll-like receptor 4; TGF- β , transforming growth factor- β ; TNF- α , tumor necrosis factor- α ; WAO, World Allergy Organisation

Key words: prebiotic, probiotic, atopic dermatitis, SCORAD

The severity of AD can be assessed using the SCORAD severity score (Severity Scoring of Atopic Dermatitis) (2).

2. Definition of terms

Prebiotics are non-digestible ingredients that beneficially affect the host by selectively stimulating growth or limiting some species of intestinal bacteria, such as *Bifidobacterium* and *Lactobacilli* that have the potential to improve the health of the host (3).

Probiotics are living microorganisms that confer a health benefit on the host when there are administered in adequate amounts (4).

The most known microorganism used as probiotics are the bacteria from the Lactobacillus family (*acidophilus*, *sporogenes*, *lactis*, *reuteri* RC-14, GG, *L. plantarum* 299v), *Bifidobacterium* (*bifidum*, *longum*, *infantis*), *Streptococcus* group (*thermophilus*, *lactis*, *fecalis*), but there are also non-bacterial organisms (non-pathogenic yeast *Saccharomyces boulardii*). *Lactobacillus* and *Bifidobacteria* belong to normal microbial flora; they are Gram-positive, anaerobic bacteria, and several types produce not only lactic acid but also other antimicrobial substances such as hydrogen peroxide and bacteriocins (small proteins that may have a bactericidal effect) (5).

3. Modulating the human microbiome by pre- and probiotics

Gut microbiome (GM) is the genetic material of all microbes, for example bacteria, fungi, protozoa and viruses living on and inside the digestive tract of humans and other animals, including insects. The composition of human microbiome varies depending on age, sex, and exposure to antibiotics.

Bacteria are the dominant microorganisms in the colon (over 1,014 belonging to ~500-1,000 distinct species). The predominant bacteria in the gut microbiome in adult population in Europe are *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*. Human intestinal microbiome is closely related to the host and there are no two human beings with identical intestinal microbiome.

The functions of the intestinal microbiome. Gut microbiome provides numerous biological and metabolic functions; the alteration of the intestinal bacteria balance may initiate inflammation through the activity of lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria that triggers the inflammatory process by binding to the CD14/Toll-like receptor 4 (TLR-4) complex. GM may influence the metabolism of the host by modulating the tissue composition of fatty acids; the species of *Lactobacilli* and *Bifidobacteria* produce bioactive isomers of conjugated linoleic acid with immunomodulating properties, reducing the proinflammatory cytokines. Additionally, intestinal microbiome synthesizes a significant amount of glycosidic hydrolases that decompose plant complexes into monosaccharides and short chain fatty acids (SCFAs) (acetate, propionate, butyrate). SCFAs play an important role in energy metabolism; butyrate provides energy for colonic epithelial cells; propionate affects lipogenesis and hepatic gluconeogenesis, while acetate, at the peripheral level, functions as a substrate for cholesterol synthesis. The

mucosal colon depends on the presence of butyrate as a source of energy on the lumen level, and the lack of these SCFAs is considered to play an important role in the pathogenesis of intestinal disease and inflammatory bowel disease.

Probiotics modulate the intestinal microbiome and immune status by improving the intestinal barrier; these effects are responsible for reducing allergic phenomenon and AD severity (6).

Intestinal permeability is increased in AD patients (7). In addition, babies born by caesarean section have a lower colonization with *Bacteroides* and higher with *Clostridium* (8). Also, early colonization with *Escherichia coli* has a protective role for AD (9).

The skin microbiome and atopic dermatitis. There are 4 strains prevailing on the skin surface: Firmicutes (*Staphylococcus*, *Streptococcus*, *Anaerococcus*, *Finegoldia*, *Veillonella*, *Lactobacillus*, *Peptoniphilus*), Actinobacteria (*Propionibacterium*, *Corynebacterium*, *Micrococcus*, *Kocuria*, *Actinomyces*, *Rothia*), Proteobacteria (*Acinetobacter*, *Haemophilus*, *Enhydrobacter*, *Neisseria*, *Microvirgula*), and Bacteroidetes (*Prevotella*, *Chryseobacterium*, *Fusobacteria*, *Leptotrichia*). The most common genus is *Staphylococcus*; within the *Staphylococcus* genus, the most common species in healthy skin is *Staphylococcus epidermidis* (10-12).

A reduction of the cutaneous microbiome diversity was reported in AD patients (13), AD being associated with early colonization with *Staphylococcus aureus*. The cutaneous presence of *Staphylococcus epidermidis* and *Staphylococcus cohnii* (11) has proven a protective effect against AD in children. Increased colonies of *S. aureus*, *S. epidermidis*, *Propionibacteria*, *Corynebacteria* and *Streptococcus* (11) were isolated in the atopic dermatitis lesions. Another study has found an association between AD severity and the abundance of the genus *Corynebacterium* and the phylum *Proteobacteria*. The presence and chronicity of eczema appear to be more important determinants of skin microbiome configuration (14,15).

Other studies have shown that there is also an increase in fungal diversity, as *Malassezia restricta*, *Malassezia globosa* and *Malassezia dermatis* have been isolated in ~90% of patients with atopic dermatitis (16). Several studies have described *M. sympodialis* as the most abundant in patients with atopic dermatitis and the possibility of its coexistence with a non-*Malassezia* species called *Cryptococcus diffluens* (17). In addition, many patients with AD have associated IgE mediated sensitization to *Malassezia* species, with positive skin prick tests (18,19). The rate of IgE mediated *Malassezia* sensitization correlates with disease severity (18,20).

The presence of Demodex mites (*Demodex folliculorum* and *Demodex brevis*) was not associated with an increased prevalence of AD (21).

Changes in skin microbiome composition were also observed in other dermatological conditions such as rosacea, acne, psoriasis, or seborrheic dermatitis; *Demodex folliculorum*, *Bacillus oleronius*, *Helicobacter pylori*, *Staphylococcus epidermidis* and *Chlamydomphila pneumonia* were associated with rosacea (14,22-24). In adolescence and adults with acne in the affected areas there were mostly lipophilic *Propionibacterium* (15).

4. Prebiotic and probiotic in atopic dermatitis

In the past few years, more ongoing studies evaluated the administration of pre- and probiotics in patients with atopic dermatitis.

Prebiotics and probiotics in pregnancy and lactation. Preventive/prophylactic avoidance of major allergens during pregnancy and lactation does not protect against AD development during the first 18 months of life (results from a systematic review that included 5 clinical trials, 952 participants) (25).

World Allergy Organisation (WAO) does not recommend the use of prebiotics neither during pregnancy nor during lactation as a preventive measure against atopic dermatitis for lack of solid scientific evidence (26).

In a meta-analysis led by Pelucchi *et al* (1,619 patients treated/1,475 placebo), there was a modest role of diet supplementation with probiotics in pregnancy to prevent AD in infants (27).

In another meta-analysis published in 2012, conducted by Doege *et al* (28), that included seven randomised, double-blind, placebo-controlled trials, only the supplementing with *Lactobacilli* during pregnancy prevented AD in children aged 2-7 years; other probiotic supplements, with or without *Lactobacilli*, have proven no favorable results (28).

The beneficial effects of the administration of probiotics during pregnancy have been reconfirmed by a recent meta-analysis; this meta-analysis that included over 19 trials (4,076 persons exposed to probiotics/3,700 control group) reported the effect of probiotic consumption during the last part of pregnancy and during the lactation period to decrease AD incidence in children under five years (29).

In some studies, the administration of probiotics started during the first trimester, or after the 36th week of gestation, and continued during breastfeeding (27-29).

Prebiotics and probiotics in infants. Prebiotics administered in the first year of life reduce the risk of asthma or food allergy but the results on atopic dermatitis were inconclusive (26,30).

A systematic review of a meta-analysis that included 8 clinical trials totaling 741 infants, demonstrated the beneficial effect of *Lactobacillus*-containing probiotics on AD severity reduction (31). Probiotics with *Bifidobacterium* (3 studies, 73 infants) did not prove beneficial effects; this result should be interpreted with caution due to the small number of subjects included and the heterogeneity of the studies. Most studies included in meta-analysis followed patients for a limited time (under 8 weeks). Data previously published revealed a smaller number of *Bifidobacteria* strains in the children's feces with atopic dermatitis (32,33). However, the conclusion of this article was that infants with moderate and severe AD presented a protective effect of probiotics (28).

Prebiotics and probiotics in children (1-18 years). In a recent meta-analysis (568 children, 1-18 years; intervention group, 296; control group, 272), there was an improvement in SCORAD reported in children (1-18 years) with AD given probiotics (34). *Lactobacillus fermentum*, *Lactobacillus* and a mixture of different strains (*Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei* and *Lactobacillus salivarius*)

improved significantly the SCORAD values in children (34). These data reconfirm the results of the previously published studies (35).

A recent randomized, double-blind, placebo-controlled intervention trial, that included 50 children aged between 4-17 years, reported that the mixture of probiotics (*Bifidobacterium lactis* CECT 8145, *Bifidobacterium longum* CECT 7347, and *Lactobacillus casei* CECT 9104) was effective in reducing SCORAD index (36). The probiotic was administered between 4-12 weeks.

Prebiotics and probiotics in adult. We found several randomized clinical trials and one meta-analysis that have reported beneficial effects of probiotics in AD adult patients (35).

Roessler *et al* (37) in a double-blind, placebo-controlled, randomized cross-over study, using a combination of the probiotics (*Lactobacillus paracasei* Lpc-37, *Lactobacillus acidophilus* 74-2, and *Bifidobacterium animalis* subsp. *lactis* DGCC 420) for 8 weeks, observed that the SCORAD tended to decrease. There was an increased number of *L. paracasei* and *B. lactis* isolated in AD patient's faeces after supplementation.

Another study conducted by Yoshida *et al* that used *Bifidobacterium breve* for 8 weeks in AD patients reported that the severity scoring for atopic dermatitis significantly improved and the proportion of *B. breve* in intestinal microflora was increased in the probiotic group (38).

Drago *et al* using *L. salivarius* for 16 weeks in 38 patients with moderate to severe AD reported an improvement in SCORAD and a significant decrease of T-helper cell type-1 (Th1) cytokines [interleukin-12 (IL-12), interferon (INF)- γ] and Th1/Th2 (IL-12, IFN- γ /IL-4, IL-5) ratio (39); they also reported a significant reduction of staphylococci in faeces in the probiotic treated group.

Iemoli *et al* (40) using a specific mixture of probiotics (*L. salivarius* LS01/*B. breve* BR03) for 12 weeks in 48 adults suffering from moderate to severe AD reported an improvement in SCORAD and of the immunological profile [Th1/Th2 ratio, T-helper cell 17/regulatory T cell (Treg) ratio] and a reduced microbial translocation.

Matsumoto *et al* (41) reported that oral intake of *Bifidobacterium animalis* subsp. *lactis* LKM512 may exert antipruritic effects in adults with atopic dermatitis.

Although these studies are promising, the small number of subjects is limiting the generalization of the results.

5. The type of probiotics used in clinical trials

Probiotic micro-organisms must be appropriate (non-pathogenic and non-toxic) for human consumption. Toxicity tests are conducted as for pharmaceuticals. They must not affect taste, texture, and they must survive in the probiotic food in a sufficiently large concentration until they are consumed.

Various studies conducted in patients with atopic dermatitis evaluated the probiotics such as lactobacilli, bifidobacteria or combinations (Table I).

6. Probiotics - mechanism of action

Probiotics enhance the production of SCFAs (acetate, propionate, and butyrate) which have anti-inflammatory effects (42),

Table I. Species of probiotic bacteria used in atopic dermatitis (adapted after refs. 36,37,49).

<i>Lactobacillus</i>	<i>Bifidobacterium</i>	<i>Saccharomyces</i>
<i>L. rhamnosus</i> GG	<i>B. longum reuter</i>	<i>Saccharomyces boulardii</i>
<i>L. rhamnosus</i> LC705	<i>B. longum infantis</i>	
<i>L. fermentum</i> VRI-033	<i>B. breve</i>	
<i>L. paracasei</i>	<i>B. lactis</i> UABLA-12	
<i>L. plantarum</i>		
<i>L. salivarius</i>		
<i>L. acidophilus</i>		

reduce the generation of toxic fermentation products (43) and improve the Th1/Th2 ratio (44,45), increased lymphocyte and/or leucocyte numbers in gut-associated lymphoid tissues (44), increased intestinal IgA secretion (44).

7. Probiotics - mechanism of action

Immunomodulatory effect. Probiotics can reduce the severity of AD by inhibiting the T-helper cell type-2 (Th2) mediated response and improving the Th1/Th2 ratio (46); inhibiting Th2 cell response, cytokines such as IL-4, IL-5, IL-6 and IL-13 are no longer released (47-49), INF- γ decrease (cytokine released by Th1 cells), phagocytosis is stimulated, serum IgA is increased (50). Probiotics also stimulate the secretion of IL-10 and transforming growth factor- β (TGF- β) (22). Probiotics can reduce inflammation by reducing proinflammatory cytokines, IL-4, IL-6, tumor necrosis factor- α (TNF- α), INF- γ and high sensitivity C reactive protein (hsCRP) (51) and by increasing expression of IL-10 and Treg-related cytokines at mesenteric lymph nodes. A new mechanism proposed to demonstrate the effectiveness of probiotics is the inhibition of the mature dendritic cell differentiation and transformation of naive T cells into Th2 (52). Immunomodulation decreases the susceptibility to inflammatory and allergic factors modulating the intestine-skin axis. Probiotics also modulate brain function including stress response on the intestine-brain axis (53).

Normalization of microbial composition provides protection against pathogens at the mucosal surface. In newborns, the distribution of different *Bifidobacterium* species in the faeces influences the prevalence of allergic diseases. In a study that proposed to detect differences in levels of different *Bifidobacterium* species in faeces of children with allergies compared to healthy ones, significantly higher levels of *Bifidobacterium longum* were isolated in healthy children, suggesting the role of this strain in preventing the occurrence of bronchial asthma and allergic dermatitis (54).

Metabolic effects. Medical nutrition therapy plays an important role in modulation of the intestinal microflora. The use of 'functional food' as prebiotics, probiotics, natural antioxidant (55,56) was associated with good metabolic effects such as improving digestion and absorption of food ingredients and minerals, vitamin synthesis, and thereby improving overall nutritional status and health.

Probiotic consumption can be associated with reduction of blood glucose, insulinemia and insulin resistance (IR) (57). Some probiotic strains have antioxidant effects (58). A recent meta-analysis has shown favorable effects of alanine aminotransferase decrease and IR reduction in patients with non-alcoholic fatty liver disease (59).

In another meta-analysis, the administration of probiotics was associated with a decrease in total cholesterol, triglycerides and low-density lipoprotein (LDL)-cholesterol and increase in high-density lipoprotein (HDL)-cholesterol (60); beneficial effects on the lipid profile are secondary to reducing intestinal absorption of dietary cholesterol and suppressing bile acid reabsorption.

In a systematic review and meta-analysis, Zhang and Silverberg concluded that patients with overweight and obesity had a higher risk of AD; the association was significant in North America and Asia but not Europe (61). The major limitations of this meta-analysis are related to the cross-sectional design of the included studies. A study published in Germany, did not observe an increase in prevalence of AD in patients with metabolic syndrome (obesity, diabetes, hypertension and hyperlipidemia) (62).

The relationship between metabolic disorders (obesity, dyslipidemia) and atopic dermatitis can be mediated by chronic systemic inflammation, proinflammatory cytokines (IL-6, TNF- α and CRP), increased oxidative stress and consequent change in expression of inflammatory genes.

8. Conclusion

Improving nutritional status, nutrient digestion, specific and non-specific immune response, beneficial effects on the gastrointestinal tract and skin, are arguments for supporting the use of pre- and probiotics in patients with AD. Still, there is not enough data in the literature to respond to questions regarding optimal dosing, optimal time to start treatment and duration necessary to show beneficial effects; the personalized use of probiotics according to colonic dysbiosis can be associated with best results. However, most randomized controlled trials and meta-analyses, support the administration of probiotics for at least 8 weeks with beneficial effects in improving severity scoring of atopic dermatitis.

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Authors' contributions

ER and GR designed the study; ER, GE, RC, AA, RR, OO, TC, FR, MP, MJ and GR performed the literature search and article selection, and drafted the manuscript. The final version of the manuscript read and approved by all authors.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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