

REVIEW

Probiotics and prebiotics in dermatology

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The rapid increase in the medical use of probiotics and prebiotics in recent years has confirmed their excellent safety profile. As immune modulators, they have been used in inflammatory skin conditions, such as atopic dermatitis. We review the literature regarding the use of probiotics and prebiotics in dermatology. Probiotics and prebiotics appear to be effective in reducing the incidence of atopic dermatitis in infants, but their role in atopic dermatitis treatment is controversial. Their role in acne, wound healing, and photoprotection is promising, but larger trials are needed before a final recommendation can be made. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2014.04.050>.)

Key words: acne; atopic dermatitis; dermatology; prebiotics; probiotics; wound healing.

Probiotics are live microorganisms that, when administered in adequate amounts, may confer a health benefit on the host.¹ They have been widely reported to alleviate lactose intolerance, suppress diarrhea, reduce irritable bowel symptoms, and prevent inflammatory bowel disease. The probiotics most commonly used are lactobacilli, bifidobacterium, and enterococci, also part of the intestinal microflora.

Prebiotics are defined as nondigestible carbohydrates that stimulate the growth of probiotic bacteria in the intestine. The most common prebiotics are indigestible oligosaccharides.²

The safety of lactobacilli, bifidobacteria, and enterococcus is well documented even in infants, and they are generally recognized as innocuous substances.³⁻⁷ There is some concern regarding adverse events, mostly in patients with underlying medical conditions,^{8,9} but several randomized studies have shown their safety in infants.¹⁰⁻¹² There are some sporadic cases of *Lactobacillus* infection, usually in elderly populations or infants with underlying medical conditions. For example, the occurrence of a liver abscess, endocarditis in 2 elderly individuals, and sepsis caused by *Lactobacillus* in 3 infants has been reported (one 6-week-old ill infant, and 2 borderline premature infants with short gut syndrome).⁹ There are not

Abbreviations used:

AD:	atopic dermatitis
CDAD:	<i>Clostridium difficile</i> —associated diarrhea
IFN- γ :	interferon gamma
OR:	odds ratio
PAD:	pediatric atopic dermatitis
RR:	relative risk
SCORAD:	SCORing Atopic Dermatitis

many studies of the use of probiotics and prebiotics in dermatology, with the exception of atopic dermatitis (AD), and even in that context their clinical use is controversial. We will discuss the existing clinical and experimental studies exploring this use, in particular in AD, acne, and wound healing.

ATOPIC DERMATITIS

Key points

- Probiotics and prebiotics modulate T helper cytokine activation
- Probiotics upregulate regulatory T cells and accelerate barrier function recovery
- Some probiotics effects may be strain-specific

Research about the use of probiotics and prebiotics in AD has been extensive (Table 1). Their

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effect in the reduction of allergic diseases could be linked to the hygiene hypothesis, which suggests that a lack of exposure to microbes early in life can affect the development of the immune system and increase susceptibility to allergies.¹³ Allergic diseases are associated with an imbalance in T helper (T_H1/T_H2) cytokine activation. Probiotics can inhibit the T_H2 response while stimulating the production of T_H1 cytokines, such as interferon gamma (IFN- γ).¹⁴⁻¹⁷ In addition, decreases in regulatory T cells (Tregs), which are crucial regulators of the immune response, have been reported in patients with AD, and their number is inversely correlated with immunoglobulin E (IgE), eosinophilia, and IFN- γ levels.^{18,19} Probiotics upregulated the generation of Tregs, which migrated to inflammation sites and suppressed disease progression in mice.²⁰

Another mechanism involved in the pathogenesis of AD is dysfunction in the skin barrier. *Lactobacillus paracasei* was found to speed barrier function recovery.²¹ However, filaggrin expression was not altered by probiotics in an atopic dog model.²² Barrier defects in AD also seem to involve the intestinal mucosa,^{23,24} and the composition of the intestinal microflora is different in patients with AD. Infants with eczema^{25,26} and atopic sensitization²⁷ had a reduced proportion of bifidobacteria species and a lower microflora diversity early in life.²⁸ AD patients have decreased barrier function, not only in the skin but also in the intestinal mucosa, permitting the frequent transfer of exogenous antigens with the induction of symptomatic AD.^{24,29} Clinical improvement was found after reversal of this alteration.³⁰

Some probiotic effects may be strain-specific, mediated through Toll-like receptors, and expressed by enterocytes.³¹ For example, different strains of *Lactobacillus salivarius* induce differing modulation on cytokine release; the strain LDR0723 modulates a T_H1 response, and strains BNL1059 and RGS1746 favor a T_H2 response.³² It has recently been shown that prebiotics, like probiotics, can significantly decrease the generation of toxic fermentation products³³ and modulate immune parameters, including the T_H1/T_H2 balance that could be beneficial to AD patients.^{34,35}

Probiotics in the prevention of pediatric atopic dermatitis

Key points

- Metaanalysis data show a 20% to 24% reduction in the incidence of pediatric atopic dermatitis by using probiotics
- The long-term effects in the prevention of pediatric atopic dermatitis are controversial

CAPSULE SUMMARY

- Probiotic and prebiotic use has increased in recent years.
- Probiotics and prebiotics have a role in the inflammatory response and barrier function in addition to antimicrobial properties.
- Understanding the mechanisms of action of probiotics and prebiotics in dermatologic conditions may stimulate the development of new effective therapies.

Consolidated data have been published as 5 meta-analyses (Table II). While both Lee et al³⁶ and Doege et al³⁷ found a significant risk reduction of pediatric atopic dermatitis (PAD) with the use of prenatal and/or postnatal probiotics, Osborn and Sinn³⁸ did not find this relationship, although they did find a

significant reduction in eczema. The 2 latest metaanalyses, by Pelucchi et al³⁹ and Panduru et al,⁴⁰ analyzed 18 articles (14 trials) and 16 trials, respectively. The global relative risk (RR) of PAD was 0.79 and for IgE-associated PAD was 0.80 according to Pelucchi et al,³⁹ and the odds ratios (ORs) for general and high-risk populations were 0.76 and 0.54, respectively. Overall prenatal followed by postnatal administration of probiotics, especially with *Lactobacillus* and *Bifidobacterium*, are protective against the development of PAD.

The long-term effects of the prevention of PAD have been evaluated in 4 trials.⁴¹⁻⁴⁴ *Lactobacillus rhamnosus* during prenatal and postnatal periods provided persistent protection in the development of PAD and atopic sensitization at 4, 6,⁴⁴ and 7 years of age.⁴¹ However, Kuitunen et al⁴² found that a probiotic/prebiotic mix reduced the incidence of PAD by 5 years of age only in children who were delivered by cesarean section. More recently, West et al⁴³ did not find any long-term effects of the prevention of PAD in 8- and 9-year-olds in the cohort receiving *L. paracasei* after weaning, despite a protective effect at 13 months.⁴⁵

Given the 20% to 24% reduction of incidence of AD in the latest metaanalyses and their good safety profile, we believe that the addition of probiotics, especially *Lactobacillus* strains, starting during the last 2 weeks of pregnancy and continuing for the first 3 months of life, are a good option in preventing PAD.

Table 1. Possible mechanisms of action of probiotics strains in atopic dermatitis

Mechanism of action
Inhibition of T _H 2 response ^{14,15,33-35}
Stimulation of T _H 1 response ^{14,15,33-35}
Upregulation of regulatory T cells ²⁰
Acceleration of skin and mucosa barrier function ^{21,30,69}
Increase in intestinal microflora diversity ³⁰
Reduction of fermentation products ³³⁻³⁵
Inhibition of <i>Staphylococcus aureus</i> attachment ⁷⁹

Prebiotics in the prevention of pediatric atopic dermatitis

Key point

- **Metaanalysis data show a reduction of 32% in the incidence of pediatric atopic dermatitis after using prebiotics**

A recent metaanalysis by Osborn and Sinn⁴⁶ analyzed 4 studies (1218 infants) exploring the effect of specific prebiotics in the prevention of allergy. They found a significant reduction in eczema (RR, 0.68) using a galactooligosaccharide and fructooligosaccharide combination. Because of the short duration of follow-up in these studies, it was unclear if prebiotic benefits persist beyond infancy. However, Arslanoglu et al⁴⁷ found that infants who were at risk of atopy and who were fed with a prebiotic-supplemented formula during the first 6 months of life had a significantly lower 5-year cumulative incidence of PAD.

Probiotics in the treatment of atopic dermatitis

Key points

- **The use of probiotics in the treatment of atopic dermatitis has been evaluated in small and heterogeneous trials**
- **Although a promising role has been found in individual trials, metaanalyses have not shown efficacy in the treatment of pediatric atopic dermatitis**

Although data exist showing the protective effect of probiotics in the incidence of PAD, there is less convincing information about their effects as treatment. Two metaanalyses, by Lee et al³⁶ and Michail et al,⁴⁸ failed to find clinically significant changes in the severity of PAD with the use of probiotics. However, treatment trials tend to be smaller and more heterogeneous than their preventive counterparts, so they are less likely to show significance.³⁶ Lately, *Lactobacillus plantarum* for 12 weeks in 83 children with PAD showed a reduction of 9.1 in

SCORing Atopic Dermatitis (SCORAD) scores at week 14, compared with a 1.8 reduction in SCORAD scores in the placebo group.⁴⁹ Although this difference reached statistical significance, it is probably not clinically relevant.

There are even fewer data about the role of probiotics in adult AD. Lactobacilli were found useful in decreasing itch and burning scores in 10 patients with intractable AD,³⁰ and *L paracasei* K71 decreased skin severity scores at weeks 8 and 12 in 34 AD patients.⁵⁰ Drago et al³² found that a probiotic mixture reduced SCORAD scores of 38 patients with moderate to severe AD, and Iemoli et al⁵¹ found similar results in 48 AD patients.⁵¹ Although these studies are promising, however, the small number of subjects prevents generalization of the results.

ACNE

Key points

- **Small trials have shown up to 80% clinical improvement in acne patients using probiotics**
- **Probiotics may reduce inflammation in acne by decreasing the release of inflammatory cytokines and recruitment of CD8 cells, and by activating regulatory T cells**
- **The increase in ceramide production may strengthen barrier function in acne patients**

The pathophysiology of acne involves excess sebum production, follicular hyperkeratinization, *Propionibacterium acnes* hypercolonization, and inflammation.⁵² These factors may be aggravated with stress. Stress can also alter the intestinal lining, by encouraging bacterial overgrowth, stagnating intestinal transit time, and thereby compromising the intestinal barrier.⁵³⁻⁵⁵ Fifty-four percent of acne vulgaris patients have marked alterations to intestinal microflora.⁵⁶ Constipation is more frequent in adolescents with sebaceous gland diseases, including acne,⁵⁷ and concentrations of lactobacilli and bifidobacterium are significantly lower in constipated patients.^{57,58}

One of the potential benefits that systemic probiotics may offer is the reduction of inflammation in acne,^{59,60} probably caused by the downregulation of gene expression related to the release of inflammatory cytokines and the recruitment of pathogenic CD8 T cells while activating Treg cells.^{59,61} Probiotics may also decrease sebum content, which can lead to lower follicular colonization by *P acnes* and therefore decrease inflammation.^{62,63} These were primarily short-term studies, indicating the need for investigations studying the long-term effects of lactobacillus extract in acne lesions.

Table II. Metaanalyses of the use of probiotics in prevention of atopic dermatitis

Metaanalysis (year)	Population	No. of trials	No. of subjects	Endpoint	Effects	Comments
Lee et al ³⁶ (2008)	Pregnant mothers and/or infants ≤ 6 months old	6	1581	Incidence of AD ≤ 4 years	RR = 0.69 (95% CI, 0.57-0.83); if excluding only postnatal intervention, RR = 0.61 (95% CI, 0.49-0.75)	<i>Lactobacillus rhamnosus</i> GG, <i>Lactobacillus acidophilus</i> LVA-R1-A1, and a combination of probiotics with a prebiotic showed a decrease in the incidence of pediatric AD; <i>Lactobacillus reuteri</i> showed a paradoxical increase in sensitization to allergens; excluding 1 purely postnatal protocol, revealed a lower relative risk
Osborn et al ³⁸ (2009)	Pregnant mothers and/or infants ≤ 12 months old	5	1584	Incidence infant eczema and AD ≤ 4 years	RR of infant eczema = 0.82, (95% CI, 0.70-0.95); RR of AD = 0.80 (95% CI, 0.62-1.02)	No subanalysis for time of supplement (prenatal, postnatal, or both)
Doege et al ³⁷ (2012)	Pregnant mothers and infants ≤ 12 months old	7	2843	Incidence of AD ≤ 5 years	RR of lactobacilli = 0.67 (95% CI, 0.52-0.86); RR of mixed prebiotics = 0.86 (95% CI, 0.70-1.06)	Lactobacilli showed a significant reduction of the development of atopic eczema (4 studies); no effect with strain mixtures (3 studies)
Pelucchi et al ³⁹ (2012)	Pregnant mothers and infants ≤ 24 months old	14	3092	Incidence of AD and IgE-associated AD ≤ 7 years	RR of AD = 0.79 (95% CI, 0.71-0.88); RR of IgE-associated AD = 0.80 (95% CI, 0.66-0.96)	The RR of AD was lower in infants/young children with no family history of allergic diseases; global 20% reduction in the incidence of AD and IgE-associated AD
Panduru et al ⁴⁰ (2014)	Pregnant mother and infants ≤ 13 months old	16	3495	AD development in children ≤ 9 years of age	OR in the general population, 0.56; OR in high-risk populations, 0.76	Prenatal administration followed by postnatal administration was protective (OR, 0.54; $P = .001$), unlike exclusive postnatal administration (OR, 0.89; $P = .59$); <i>Lactobacillus</i> alone and <i>Lactobacillus</i> with <i>Bifidobacterium</i> are protective against AD

AD, Atopic dermatitis; CI, confidence interval; IgE, immunoglobulin E; OR, odds ratio; RR, relative risk.

A trial of probiotics showed an 80% clinical improvement in acne patients after oral supplementation of *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*.⁶⁴ A recent study (n = 36) showed statistically significant improvement in inflammatory lesion count, total lesion count, and clinical grade of acne after daily consumption of *Lactobacillus* for 12 weeks compared to fermented milk (placebo) consumption.⁶³ When used as an adjuvant to minocycline in subjects with mild to moderate acne, a significantly lower total lesion count ($P < .001$) was found after 8 weeks compared to groups given only probiotic supplementation or only minocycline treatment.⁶⁵

A decrease in ceramides in the stratum corneum causes water loss and barrier dysfunction in the epidermis.⁶⁶ Sphingolipids, which have antimicrobial properties against *P. acnes*, are low in patients with acne.^{62,67} The application of topical probiotics, such as *Streptococcus thermophilus*, increased ceramide production when applied for 7 days as a cream.⁶⁸ Probiotics may accelerate the recovery of skin barrier function,²¹ especially at higher doses.⁶⁹ A topical lactobacillus increased skin barrier strength, although this was not statistically significant; triclosan, an antibiotic, worsened barrier repair after 2 months of use.⁵⁹ Triclosan also led to a marked increase in bacterial counts after 2 months of use, despite an initial reduction, indicating possible resistance development.⁵⁹

Systemic antibiotics are commonly prescribed for the treatment of acne, and *Clostridium difficile*—associated diarrhea (CDAD) is one of the most severe adverse events associated with their use. A recent metaanalysis of the use of probiotics in pediatric and adult populations receiving antibiotics found a 66% reduction in the incidence of CDAD, which means that the use of probiotics would prevent 33 episodes of CDAD per 1000 persons.^{70,71} Although none of the studies included studied populations with acne, it is reasonable to extrapolate these results to patients receiving chronic antibiotic therapy for acne.

WOUND HEALING

Key points

- Probiotics have been shown to decrease the bacterial load and promote wound healing in burn patients
- Probiotics have been shown to significantly reduce the area of chronic leg ulcers and decrease bacterial load

The failure of antibiotics to treat biofilms has led scientists to search for modalities based on the principle of probiotics displacing pathogens.

Topical *L. plantarum* inhibited *Pseudomonas aeruginosa* colonization, improved tissue repair, and enhanced phagocytosis in burn wounds in mice.⁷² Clinical studies on patients with second- and third-degree burns found that the application of *L. plantarum* was as effective as silver sulfadiazine in decreasing bacterial load, promoting the appearance of granulation tissue, and wound healing.⁷³

Probiotics may also disrupt biofilms by regulating the levels of interleukin-8, a neutrophil chemoattractant, and thereby modulating the activity of neutrophils. A reduction of >90% of the area of chronic leg ulcers was observed in 43% of diabetics and 50% of nondiabetic patients after 30 days of topical treatment with *L. plantarum*, as well as a significant decrease in colony-forming units after 5 days.⁷⁴ In addition, a decrease in necrosis and apoptosis of neutrophils in the wound may allow for more effective phagocytosis to debride the wound and decrease the bacterial load, facilitating tissue repair. Finally, the use of a nitric oxide-producing probiotic patch accelerated healing and decreased bacterial load in infected full-thickness wounds in white rabbits.⁷⁵

FUTURE DEVELOPMENTS

Key points

- Probiotics produce bacteriocins and organic acids with antimicrobial properties
- Probiotics also compete with *Staphylococcus aureus* for attachment to keratinocytes
- Probiotics prevent the increase of elastase activity, interleukins-1B and -10, and the decrease of Langerhans cells induced by ultraviolet radiation
- Probiotics have been associated with healthier skin and hair in mice; this mechanism is dependent on interleukin-10

Although there are little human data available, some animal and in vitro models have given us insights about the possible role of probiotics as antimicrobials, in photoprotection, and in hair and skin appearance. We will briefly discuss these preliminary results.

Antimicrobial properties

Probiotics produce peptides known as bacteriocins, or organic acids that possess antimicrobial activity against pathogenic bacteria.⁷⁶⁻⁷⁸ In addition, *Lactobacillus ruteri* inhibits the attachment of *S. aureus* to human epidermal keratinocytes by competitive exclusion rather than through bacteriocins to inhibit colonization.⁷⁹

Photoprotection

Bifidobacterium breve supplementation to hairless mice prevented ultraviolet radiation–induced changes in skin elasticity and appearance⁸⁰ and prevented the increase in elastase activity and interleukin-1 β levels. *Lactobacillus johnsonii* led to protection against ultraviolet radiation–induced immunosuppression by preventing increases of interleukin-10 levels and decreases of epidermal Langerhans cells.^{81,82}

The oral administration of *L. johnsonii* in a randomized, placebo-controlled clinical trial showed that ultraviolet radiation–sensitive subjects who received 6 weeks of probiotics showed early recovery of Langerhans cells allostimulation.⁸³

Hair and skin appearance

Mice eating probiotic yogurt or purified *Lactobacillus reuteri* had a significantly thicker dermis, more anagen hair follicles, and more sebocytes leading to hair gloss. Interleukin-10 was found to be required in order to reproduce these benefits.⁸⁴

Rosacea

Although no data are available about the use of probiotics for rosacea, these patients have significantly higher levels of small intestinal bacterial overgrowth compared to controls, and normalization of the intestinal flora with the use of rifaximin led to sustained improvement of symptoms for >9 months.^{85,86} Also, *Helicobacter pylori* infection is believed to play a role in the pathogenesis of rosacea.⁸⁷ Reduction in bacterial colonization and *H. pylori*–associated symptoms have been reported in several trials.⁸⁸ It remains to be elucidated if the use of probiotics can improve symptoms in rosacea patients by replacing pathogenic bacteria with probiotic strains.

CONCLUSION

Normalization of intestinal microflora with the use of probiotics and prebiotics has a positive effect on several skin conditions. While convincing data show that probiotics and prebiotics decrease the incidence of AD in infants, more research is needed to determine their role in the treatment of AD, acne, photoprotection, and wound healing. Experimental data also suggest their use in microbial management and in hair and skin appearance. We hope that physicians and scientists find this article useful in providing a review on the use of probiotics in various areas of medicine, specifically in AD, acne, and wound healing.

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