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Review Article

The role of skin and gut microbiome in atopic dermatitis

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Abstract

In the last decade, there has been an increase case of atopic dermatitis (AD) worldwide. AD is a type of disease with chronic inflammation of the skin characterized by mild to severe itching, recurrent, and mostly occurred in infancy and childhood. There were some substantial data of patients with AD that have been disturbed and less diverse skin and gut microbes than healthy individuals. In the skin microbiome, AD is known to possess a larger percentage of *Staphylococcus aureus (S. aureus)* than healthy individuals. In addition, the population of *Staphylococcus aureus*, *Clostridium difficile*, and *Escherichia coli* in the gastrointestinal tract of patients with AD is higher than normal individuals, whereas the population of *Bifidobacteria*, *Bacteroidetes*, and *Bacteroides* are experiencing a decrease. The AD will be prevented or treated if there is a balance in the skin and gut microbiome. It seems to underlie the benefit of probiotic in AD management.

Key words
Atopic dermatitis, gut microbiota, probiotic, skin microbiota, human & health.

Introduction

Atopic dermatitis (AD) is the most typical chronic inflammatory skin disease occurring in early life, with a 20% prevalence in children.[1] AD is a chronic and recurring inflammation of the skin that affects the economic and social conditions significantly. Because of the increase in incidence, the research on AD has shifted its focus towards epidemiology, prevention, and therapy of AD.[2]

A variety of factors contribute to AD, along with the genetics and the environment influencing disease progression. Although AD exhibits signs of skin barrier dysfunction and immunological aberrations, AD's mechanisms are not understood well.[3] Recently, alterations in the skin and gastrointestinal microbiome have been studied in more depth. It can be suggested that there is an association between the skin microbiome that is disrupted and the AD progression.[4]

The environment for bacterial growth in AD is considerably different from that of normal skin, and this situation might explain the dysbiosis observed in AD fundamentally. A rise in pH on the skin surface is caused by a non-functional skin barrier, supporting the growth of *Staphylococcus aureus* (*S. aureus)*. Changes in the microbial structure of the skin in AD are influenced by immunological response, which plays a role in the skin.[5] Probiotics are live bacteria and yeasts known to have various health benefits. When ingested, probiotics provide

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benefits by interacting with the gut flora, and also, when applied to the skin topically, they work by modulating the skin microbiota.[3]

The microbiome refers to every microbe that inhabits the human body, animals, plants, and other living creatures. According to Joshua Lederberg, the ecological community of symbiotic, commensal, and pathogenic microorganisms that occupy a space in the body is referred to as the microbiome.[6] It is stated that there are approximately 10-100 trillion microbiomes in the human body. Moreover, ten microbial cells are reported living in every 10 billion cells of an individual.[6] Dysfunctional immune system and misregulated inflammation are considered the causes of *non-communicable diseases* (NCDs). It is likely that the dysfunctions of the microbiome can increase the risk of infection.[7] AD is identified as a disease with chronic inflammation of the skin characterized by mild to severe itching, recurrence, and often happened in infancy and childhood.[8] AD is diagnosed clinically based on the patient's medical history, skin lesions' morphology, distribution of lesions, and associated clinical signs and symptoms.[9]

The Skin Microbiome in Atopic Dermatitis

The skin's topological and endogenous factors affect the resident flora, which may be modified by external factors including clothing, cleanliness, topical treatment, and skincare products. It is not equally disseminated in the skin.[4] The colonization of bacteria in particular skin areas depends on the specific skin conditions, such as pH levels, moisture levels, and the keratinocyte adhesion. According to current research, bacteria habitually exist within various skin layers and not merely on the surface of the skin. This finding explicates that bacteria may get through the outer skin barrier and typically interact with a variety of cells in the lower dermis.[10]

Overall, the skin microbiome consists of up to 10^7 microorganisms per cm^2, particularly *Corynebacterium*, *Streptococcus*, *Staphylococcus*, and *Propionibacterium*. Nevertheless, several studies indicate that people with AD have a higher percentage of *S. aureus* in their skin microbiome than normal individuals.[11] Although the understanding of AD's pathophysiology is considered lacking, several studies have shown that the development of AD is accelerated by skin barrier impairment and immunological dysregulation.[12] AD causes the skin to become dry, which is related to the epidermal barrier permeability defect generated by the presence of mutations in the filaggrin gene (FLG).[13]

Filaggrin is a protein derived from pro-filaggrin produced by keratinocytes.[14] Filaggrin protein is the main structural protein of the stratum corneum, it is encoded by the filaggrin (FLG) gene which is found on chromosome 1q2. FLG null mutations have been found to affect skin barrier function, thus increase the risk of AD.[12] Patients with AD and deficiency in FLG expression are prone to the decreased stratum corneum hydration, the increase of Transepidermal Water Loss (TEWL), and a higher pH than nonatopic individuals. This skin barrier disorder provokes allergens and microbes to penetrate the skin. *S. aureus* is the most common microbe associated with AD, colonizing approximately 90% of AD patients.[15] Filaggrin also has an inhibitory effect on the growth of *S. aureus*.[14]

Genetic abnormalities in physical (e.g., FLG and SPINK5) and immunological (e.g., IL-4 and IL-13) skin barrier genes can cause further attenuation of the skin barrier. The response of a weakened skin barrier is prone to increase skin susceptibility to allergens. Furthermore, it will

provoke skin dryness and pruritus, causing the compromised skin barrier under even greater physical exertion. On a general thought, a skin barrier that has been compromised might increase the skin pH, alter the keratinocyte adhesion, and also increase the activity of serine protease and inflammation. Likewise, the acute response of Th2 is analysed to depress several peptide antimicrobial (AMP) responses. These conditions influence skin microbiota dysbiosis in AD, leading to the increase colonization of *S. aureus* and a decrease in microbiota diversity as a whole. The *S. aureus* colonization is believed to worsen AD by secreting virulence factors that disrupt the skin barrier and lead to more severe inflammation. There have not been any further studies to determine the other mechanisms of the skin microbiome's role in changing the pathogenesis of AD.[10]

The skin microbiome plays a role in interacting with the immune response has been widely investigated. A common commensal bacterium, *S. epidermidis*, has been revealed to alter the innate inflammatory response via the toll-like receptor (TLR) and the crosstalk. TLR3-mediated keratinocyte inflammation can be suppressed by *S. epidermidis* by stimulating TLR2 with lipoteichoic acid (LTA) as a result of skin damage. Similarly, in germ-free mice models, it can boost T cell recruitment and influence T cell maturation. Moreover, pattern recognition receptors (PRR) expressed by keratinocytes are able to recognize microbial flora on the skin surface. The response of TLR2 protects the skin against bacterial evasion by generating host antimicrobial peptides (AMP), such as beta-defensin 2 and 3 (DEFB-2 / DEFB-3). Additionally, TLR2 activation by microbial flora induces the recruitment of mast cells and enhance the tight junction forming a more stimulating skin barrier. Despite TLR activation and AMP synthesis by keratinocytes, commensal microorganisms persist on the skin's surface. It inhibits inherent immune systems while also allowing commensal microorganisms to help protect the skin from infections.[10]

Endogenous AMPs are essential in inhibiting pathogenic microorganisms from invading the skin. Cathelicidin and defensins (DEF) are two primary classes of AMP. Both have the ability to eliminate *S. aureus* in vitro. Nevertheless, the expression of cathelicidin and beta-defensins 2 and 3 (DEFB-2 and DEFB-3) diminished in AD compared to psoriasis. Furthermore, the keratinocyte model demonstrates that Th2 cytokines associated with DA, such as IL-4, IL-5, and IL-13, can suppress host AMP expression in vitro. Aside from Th2-specific cytokines, IL-10 has also been associated with decreased AMP synthesis. Altogether, the lack of host AMP is another cause for decreased microbiota diversity and increased the growth of *S. aureus* in AD.[10] The list of preceding studies regarding the skin microbiome's effect on AD can be seen in the **Table 1.**

The Gut Microbiome in Atopic Dermatitis

Most colonization of microbiota is located in the gastrointestinal tract, with diverse numbers and compositions.[19] Alterations of the microbiome in the gastrointestinal tract can affect immune balance through metabolites, causing inflammation of the microenvironment and particular gut microbiomes.[20] The combination of gut microbiome dysbiosis and an unbalanced immune system will cause various diseases, such as AD.[11]

Probiotics have been used to investigate the gut microbiome as a significant causative factor in the immunological pathway of AD. Orally administered probiotics can interact with the mucosal lining of gastrointestinal and intestinal lymphoid tissue (GALT), which contains more than 70% of immune cells.[21]

Table 1 Previous studies on skin microbiome and atopic dermatitis

Author	*Research Design*	*Population*	*Intervention*	*Control*	*Outcome*
Kong et al, 2012[16].	Case control	12 pediatric patients aged 2-15 years with moderate to severe AD	-	11 healthy controls aged 2-15 years	In lesions of AD: *S. aureus* and *S. epidermidis* increased, no association between the number of *S. aureus* colonies in nasal samples and the severity of AD
Oh et al, 2013 [17].	Case control	13 patients with AD	-	49 healthy controls	In AD: *S. aureus* lesions increased, positive correlation with the severity of AD
Nakatsuji et al 2017[18].	Case review	49 adults with AD	-	30 normal adults	Increase in *S. epidermidis,S. hominis:strain-specific* AMP increased and selectively eliminated *S.aureus*
Kim et al, 2017[18].	Case control	27 patients with AD	10 applied skin wash before and after AD treatment	6 healthy controls	In lesions of AD: *Staphylococcus*, *Pseudomonas*, and *Streptococcus* increased

Complex interaction can occur between probiotics and macrophages, epithelial and mucosal dendritic cells. Probiotics can stimulate the signalling of immune activation by creating IL-12, IL-18, and tumor necrosis factor (TNF-), or they can stimulate tolerance signalling by boosting anti-inflammatory cytokines like IL-10 and TGF-, depending on their strains. In a cytokine environment enriched by IL-10 or TGF-β, dendritic cells and macrophages can increase T cells (Tregs) induced, which play an important role in sustaining peripheral immunity to tolerance by keeping a balanced ratio of effectors and Treg cells. Other than probiotics, changes in gut microbiome genes can alter the development of host immune cell function, primarily in infants with AD.[11]

Butyric, propionic, and acetic, kinds of short-chain fatty acids, possess anti-inflammatory and immunomodulatory effects generated by the gut microbiome, including *Akkermansia muciniphila*. Its key role in AD and other inflammation diseases may describe the relationship between feeding, microbiome, and skin immunity. Based on the previous studies in laboratory mice, it can be suggested that linoleic acid and 10-hydroxy-cis-12-octadecenoic acid could lessen the symptom of AD and regulate the gut microbiome. Moreover, a different research suggests that administering the probiotic *Bifidobacterium animalis* subsp. *lactis* (LKM512) could increase kynurenic metabolite acids' levels, which reduce the scratching behavior of mice with AD.[11] Various studies have demonstrated the influence of the gastrointestinal microbiota on AD, which is listed on the **Table 2.**

Alterations of the skin microbiome and gut microbiome of AD patients offer to show the potential of microbiome modulation as therapy for AD. One aspect that has been examined is the benefits of probiotics and prebiotics. Several studies have analyzed the variations in clinical and laboratory parameters of AD patients after the administration of probiotics.[2]

Probiotics are live bacteria and yeast that are known to provide numerous health benefits. Probiotics offer beneficial effects by interacting with gut flora when ingested, and they modulate

Table 2. Previous studies on gut microbiome and atopic dermatitis

Author	*Research Design*	*Population*	*Intervention*	*Control*	*Outcome*
Watanabe et al, 2003 [22].	Case Control	957 infants aged 1 month	-	68 normal subjects	The colony of *Bifidobacterium* decreased and S. *aureus* increased. Gut microbiome dysbiosis might play a part in the occurrence of AD and increase of skin symptoms
Penders et al, 2006 [23].	Case Control	28 infants with AD	-	52 non-sensitized and non-eczematous infants	Neither the total bacterial profile nor the type and proportion of *bifidobacteria* in the stool sample were associated with atopic eczema development.
Penders et al, 2007 [24].	Case Cohort	184 infants born in 1998-2003 in Goteborg, Sweden	-	-	*E. coli*: increased the risk rate of eczema C. *difficile*: increased the development of eczema, recurrent wheezing, allergic sensitization
Nylund et al, 2015. [25]	Case Control	12 infants with AD	-	11 normal infants	Severity of eczema: inversely correlated with the diversity of microbiota and abundant butyrate-producing bacteria
Nowrouzian et al, 2016.[26]	Case Cohort	19 patients aged 0-6 years with AD	-	-	*S. aureus* intestinal colonization carried the combinations of superantigen and certain adhesins had not been associated with the development of atopic eczema
Lee et al, 2016.[27]	Cross Sectional	957 infants aged 1 month	-	12 normal infants	There was no significant difference in gut microbiota diversity between the two groups, an increase in *Clostridia* was associated with the subsequent development of AD
Reddel et al, 2019.[1]	Clinical Trial	28 infants with AD	Mixed probiotic (*B. breve* BR03 and *L. salivarius* LS01) 2x/day (1×10^9 CFU) for 20 days	18 normal controls	Less diverse microbes in the gut in infants with AD

the skin microbiota when applied to the skin topically.[6] Probiotics prevent pathogens adhesion and invasion by obstructing the surfaces of intestine's epithelium and mucosal. They also contribute in regulating hypersensitive allergic reactions by reducing the Th2-mediated response and enhancing the Treg-mediated immune response, which helps in balancing the T helper 1 (Th1) or T helper 2 (Th2) immune response.[2]

Several studies on *Lactobacillus rhamnosus GG* (LGG) have shown a positive effect in AD prevention by combining probiotic strains and prebiotic mixtures.[2] However, a systematic review of 12 studies conducted by Boyle *et al.* showed different things. A *post hoc* subgroup analysis revealed that participants supplemented with LGG had higher SCORAD scores compared to placebo, while another group given other *Lactobacillus* strains had lower SCORAD

scores compared to placebo.[28] A randomized controlled trial of *Lactobacillus plantarum* IS-10506 in pediatric and adult AD patients in Indonesia demonstrated improvement in clinical severity as measured by the SCORAD value, while also suppressing the levels of IL-4 and IL-17 cytokines. This study showed that probiotics can activate Treg cells, thereby assisting in the balance of Th2 and Th1 cells in AD. This is demonstrated by the increased levels of Foxp3, a marker of Treg cell expression, and IL-10, a regulatory cytokine, following probiotic supplementation.[29,30]

Along with oral probiotics, several studies on topical probiotics have been conducted, though the number of these studies is still limited. Blanchete-Rethore *et al.* found that administering a lotion containing 0.3% heat-treated *Lactobacillus johnsonii* NCC 533 (HT La1) to adult patients with AD showed beneficial effect. The results showed that the AD lesions treated with HT La1 lotion twice daily had significantly lower *S. aureus* counts when compared to contralateral lesions that were not given HT La1 lotion after 3 weeks of application ($p<0.001$). Control to *S. aureus* colonization had shown a clinically and statistically significant recovery on the skin lesions treated in AD patients.[31] Another study conducted by Butler *et al.* found that administering a topical ointment containing *Lactobacillus reuteri* DSM 17938 to AD patients resulted in a higher percentage of symptom improvement than the control group, but the result was not statistically significant.[32]

However, it is difficult to find reliable data to support probiotic administration's therapeutic efficacy at the clinical level. The efficacy of probiotic administration in preventing and treating AD seems inconsistent. Although numerous studies have shown a significant improvement in SCORAD, the numbers are still similar to studies that present no significant difference from placebo. Hence, many questions remain to be unanswered regarding its future clinical application.[2]

Conclusion

The skin and gut microbiome are suggested to have a role in the occurrence of AD. Previous research has shown an increase of *S. aureus* in AD lesions, although large-scale studies are required to support its AD association. Compared to control, it is noted that there is a gut microbiome dysbiosis in AD. Studies also discuss the increase of *S. aureus* in the gastrointestinal tract of AD patients. Nevertheless, the effect of these conditions on the onset and severity of AD also requires further study. It is shown the potential for microbiome modulation in AD management.

The use of probiotics has been extensively studied for their benefits on the clinical condition of AD, though the results remain inconsistent. Hence, their use as therapy in AD in regular practice still requires further research.

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