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Review

Microbiosis in pathogenesis and intervention of atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a chronic, non-contagious, inflammatory skin disorder characterized by relapsing eczematous lesions. Its pathogenesis remains incompletely understood. The current evidence has emerged to show that skin and gut microbiome play critical roles in the pathogenesis and progression of AD. Skin mircrobiome mainly refers to skin commensal organisms that promote normal immune system functions and prevent the colonization of pathogens; while gut microbiome can modulate immunologic, metabolic and neuroendocrine functions. With the current knowledge of microbiome effects on the onset of the disease, there are evolving multifarious interventions targeting microbiome for the treatment of AD. In this report, we have reviewed the critical roles of microbiosis in the pathogenesis of AD, summarized potential mechanisms mediated by microbiosis and aimed to enlighten a theoretical basis for its therapeutic applications in the treatment of AD.

1. Introduction

Atopic dermatitis (AD) (or atopic eczema) is a chronic inflammatory skin disorder, which is characterized by intense itching and recurrent eczematous lesions [1]. The conditions are long lasting and usually show in an exacerbation-then-remission pattern with intermittent treatments and periodical flare-ups [2,3]. The latest studies estimate that the prevalence of persistent or adult-onset disease is higher than previously assumed [4]. Unfortunately, there is still no single accurate explanation on the cause and mechanism of the disease. Recently, the study of microbiome has drawn widespread attentions. In fact, there are about 10 times of microorganisms as of human cells in an individual [5,6]. Therefore, the microbiome effectively adds a huge amount of genes to the human body, which can potentially increase up to 200 times of genetic materials through their close interactions with the host [7,8]. During the interplays, the immune system, in particular adaptive immunity, has formed with a consistent acquisition of complex microbiota. The rapid changes in many external factors such as antibiotics' interventions or working environment cause prominent variations in the microbiome [9]. Microbiome can also influence the immune system, vice versa. It is now believed that microbiome contributes to a rapid increase in chronic inflammatory disorders that have been seen in industrialized countries [1]. Notably, the composition of the human microbiome could be a crucial factor in the state of both health and disease.

Skin and gut microbiomes are two main ecosystems which have been widely studied for their roles in AD. The skin is colonized by a number of microorganisms such as bacteria, fungi, mites and viruses. These microorganisms are generally classified into two groups, resident and transient microbes [10]. Resident microbes are permanently stable groups of microorganisms that are usually commensal. They are not harmful under most conditions and may provide some benefits to the host. Transient microbes only settle themselves down on the surface temporarily. Most of them come from the environment and stay for hours to days [11]. The diversity of these transient and resident microbes is determined by different characteristics of local surface areas (moisture, pH value, salinity and sebum content), internal (age, sex and genotype) and external factors such as career, lifestyle, climate pattern, and cosmetics or antibiotics [12]. Numerous studies about the compositions of microbial communities in healthy volunteers have revealed that resident skin bacteria can mainly be categorized into four different phyla: *Actinobacteria*, *Bacteroidetes*, *Proteobacteria* and *Firmicutes*. Recent 2nd generation DNA sequencing technologies have rendered a comprehensive investigation of microbial communities using culture-independent assay, revealing a considerably greater diversity of microorganisms than that estimated by previous methods [10]. The gut microbiome is a highly complex ecosystem that bacteria play a leading role due to its special intestinal environment. Except the major four phyla of bacteria, it also includes eukaryotic viruses, fungi and some archaea [13]. The gut microbiome is formed in early ages, but its composition is highly dynamic which greatly depends on various factors such as diet, age and environmental conditions [14]. The gut

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Table 1
Relative factors and possible roles in AD.

Factors	Possible roles in AD	Refs.
Increased PH	Conducive to the growth of *S. aureus*	[28,29]
AMPs	Including cathelicidin and defensins, being produced by commensal bacteria or host cell to kill *S. aureus*	[31,32]
Integrin α5β1	Conserved mechanism for *S. aureus* invasion of human cells	[40,41]
Fibronectin-binding proteins	Adhesion to fibronectin that is present at high levels in the upper strata of epidermis and stratum corneum of AD skin	[40,41]
SAgs	Promoting excessive production of T cell cytokines which causes cytotoxicity; acting as allergens and generating an IgE response	[36]
α-Toxin	Membrane damage/lysis of keratinocytes	[37]
δ-Toxin	Mast cell degranulation. Synergy with IgE. Allergic skin inflammation	[46]
Protein A	Proinflammatory. Binding to TNFR-1 on keratinocytes	[47]
S. epidermidis	Amplifying the function of AMPs	[41]

microbiome executes many important functions in the host including colonization resistance of pathogenic bacteria. The indigenous gut microbiota can compete against pathogenic bacteria for nutrients and adhesion sites. It can suppress the colonization of pathogenic bacteria by producing antibacterial substances (bacteriocins). There are many other important functions of the gut microbiome including the fermentation of residues and endogenous mucus, salvage of energy as short-chain fatty acids, and so on [15].

Based on the current understanding of both skin and gut microbiomes and their roles in AD, multifarious therapeutic interventions targeting microbiomes on AD have been emerging, including petrolatum/emollient, topical steroids, bleach bath, antibiotics, probiotic therapy, topical ozonated oil, ozonated water therapy and ultraviolet B (UVB). In this review, we will discuss the possible mechanisms underlying the onset of AD that is mediated by microbiomes and the current development of clinical interventions targeting microbiomes.

2. Critical roles of microbiosis in AD

2.1. Skin microbiome alterations in AD

Recent studies have shown that there is a strong correlation between the disease severity and skin bacterial diversity [16]. In AD, changes in the balance of the microbiome and the host's cutaneous immune response can cause to aggravate AD, thus leading to a secondary skin infection. For example, there have long been thought a relation between AD's aggravation and infection or colonization by the pathogen *Staphylococcus aureus* (*S. aureus*) [17,18]. When skin microbiome is altered, it may create an increase in proportion of *S. aureus* colonization but a subsequent decrease in proportion of *Staphylococcus epidermidis* (*S. epidermidis*) colonization. When AD patients are treated continuously or intermittently using anti-inflammatory and antimicrobial medications, the diversity of the microbiome shows an alteration with a particular elevation of the populations of *Streptococcus*, *Corynebacterium* and *Propionibacterium* [17]. After adequate therapy, regeneration and restoration of the healthy skin microbiome occur [17]. It has been postulated that both endogenous (*e.g.* genetic polymorphisms in antimicrobial peptides of the native immune system) and exogenous (*e.g.* excessive hand washing and irritation) factors are accounted for these deviations in the skin microbiome [19,20].

2.2. Gut microbiome alterations in AD

Gut microbial compositions and profiles can be affected by various environmental factors, such as stress, diet and pollutants, particularly in early life [21]. The gut microbiome plays an important role in the onset and natural course of AD. The association between gut microbiome diversity and AD development remains obscure [22–24]. Some studies have shown that the gut microbiome in early life was associated with age of onset, severity, remission, flares and even phenotype of AD [25]. However, others suggested that gut microbiome diversity is inversely related to the development of AD [22]. It is easy to speculate that the development of AD might be closely associated with microbiome diversity since the interaction and relationship between specific gut microbiome and host immune systems are so important. Indeed, compared with healthy people, the proportions of *Clostridia*, *Clostridium difficile*, *Escherichia coli* (*E. coli*) and *S. aureus* in the gut microbiome from AD patients are increased; whereas those of *Bifidobacteria*, *Bacteroidetes* and *Bacteroides* are decreased [22–24,26,27]. There is a higher proportion of butyrate-producing bacteria, such as *Coprococcuseutactus*, in healthy or infants with a mild AD than those with a severe AD [27]. It is still unclear whether changes in the gut microbiome's compositions can promote the onset of AD, cause immune system shift and disrupt the gut epithelial barrier, ultimately resulting in the development of AD.

3. Possible microbial mechanisms of microbiosis in AD

3.1. Skin microbial mechanism (Table 1)

3.1.1. Physical changes to the skin barrier

The changes of bacterial habitation environment from normal skin to AD lesions have been speculated the fundamental causes to the dysbiosis observed in AD. Abnormal physical skin barrier results in an increase in pH on the skin surface, which is conducive to the growth of *S. aureus* [28,29]. Keratinocytes in the epidermis have differentiated as a result of direct exposures to microbes, thus pathologically altered expressions of their surface markers. In particular, an increase in expression of both fibronectin and fibrinogen in keratinocytes has been found in AD lesions and these markers can directly bind to *S. aureus in vitro*. Fibronectin-binding proteins (FnBPs) promote invasion of *S. aureus* and integrin alpha5 beta1 serves as host cell receptor which interacts with staphylococcal FnBPs through the cellular or soluble fibronectin [30].

3.1.2. The role of antimicrobial peptides in skin microbiome dysbiosis

During AD, the immunological factors also affect the skin microbial compositions. Endogenous antimicrobial peptides (AMPs) have an important role in preventing pathogenic microbes from infecting the skin. There are two main classes of AMPs in the skin, cathelicidin and beta-defensins (DEFBs) [31,32]. They both can kill *S. aureus in vitro*. Compared with similarly inflamed psoriatic skin, the expressions of cathelicidin, DEFB-2 and 3 are decreased in AD lesions [33]. Furthermore, AD-associated T helper cells2 (Th2) cytokines, such as IL-4, IL-5 and IL-13, can reduce the expressions of host AMPs *in vitro* [34]. IL-10, another Th2-specific cytokine, has also been shown to be associated with the decreased expression of AMPs [35]. Overall, the lack of host AMPs will enhance the growth of *S. aureus* and result in a reduction of microbial diversity in AD lesions.

3.1.3. The pathogenic role of S. aureus in AD disease

It has been hypothesized that *S. aureus* can increase the severity of AD by secreting a variety of virulence factors. One of well-studied factors is the superantigens (SAgs). SAgs bind to major histocompatibility class II (MHCII) molecules on the surface of antigen-presenting

cells (APCs) and T cell receptors on T cells, allowing cells to interact without the constraint of an antigenic peptide presented by MHCII molecules. This results in excessive production of T cell cytokines which causes cytotoxicity. SAgs are also allergens and stimulate an Immunoglobulin-E (IgE) response [36]. Another factor is α-toxin that has been proposed to increase AD severity. The α-toxin monomers form a heterodimer complex on the cell membrane that creates a porous channel leading to cell lysis. It has been shown that α-toxin is severely toxic to keratinocytes [37,38]. In AD, high levels of Th2 cytokines reduce expressions of filaggrin and sphingomyelinase, making keratinocytes more susceptible to α-toxin. This can result in loss of barrier function, increase in penetration of irritants and allergens and development of AD.

3.1.4. Effects of other bacterial strains on AD pathogenesis

Besides the increased colonization of *S. aureus* in AD, 16S rRNA DNA sequencing has indicated an increase in *S. epidermidis* colonization. The presence of *S. epidermidis* seems to protect the skin against infection [39]. Studies have shown that the *S. epidermidis* on the skin of germ-free mice can increase T cell effector function in an IL-1 dependent manner [39]. In both murine and keratinocyte models, *S. epidermidis* has shown a protective role in the amplification of endogenous AMPs [40,41]. Furthermore, *S. epidermidis* has shown to prevent formation of *S. aureus* biofilm in the nasal cavities as well as produce its own AMPs to prevent colonization of other pathogens on the skin [42,43]. Xia et al. have found that *S. epidermidis* can inhibit *Propionibacterium acnes* (*P. acnes*)-induced inflammation in skin. *P. acnes* induces the expression of interleukin-6 and tumor necrosis factor-α (TNF-α) *via* the activation of toll-like receptor (TLR) 2 in both keratinocytes and mouse ears [44]. Therefore, increased *S. epidermidis* colonization in AD lesions can be regarded as a protective role against pathogenic bacteria. However, the exact protective role of *S. epidermidis* in AD remains obscure since these effects are strain dependent and it is unclear if these beneficial strains are active in AD. The application of species-specific bacterial sequencing and metagenomics may help understand the role of *S. epidermidis* in AD skin. Recently, it has been reported an increase in *Corynebacterium bovis* (*C. bovis*) colonization in a disintegrin and metalloproteinase 17 (ADAM17) knockout mouse model of AD [45]. Increased colonization of *C. bovis* leads to a strong Th2 response in the skin, a key feature of acute AD. However, the role of *C. bovis* in development of AD is yet to be determined, since increased *C. bovis* has only revealed in high IgE syndrome (HIES) but not in AD skin.

3.2. Gut microbial mechanism

3.2.1. Immunologic pathway

The potential correlations of gut microbiosis and AD are summarized in Fig. 1 which include immunologic, metabolite and neuroendocrine pathways. The gut microbiome can modulate the immunologic pathway of AD through probiotics. Oral probiotics interact with gastrointestinal mucosa and gut-associated lymphoid tissue (GALT), where more than 70% of immune cells reside [48]. Specifically, probiotics can interact with macrophages, mucosal dendritic cells (DCs), and epithelial cells through various ways. Depending on the probiotic strain, they can either activate immune signaling by producing IL-12, IL-18 and TNF-α, or trigger immune tolerance by producing anti-inflammatory cytokines, such as IL-10 and TGF-β [49]. When DCs and macrophages are in the circumstance with enriched cytokine IL-10 or TGF-β, they can promote the generation of the induced regulatory T (Treg) cells. The balanced ratio of effector T cells and Treg cells is crucial to maintain peripheral immune tolerance. A recent birth cohort study has shown that intestinal colonization of *S. aureus* strains carrying a certain combination of SAgs and adhesion genes is negatively correlated with the subsequent development of AD in infancy [50]. That's probably because such a strain promotes the development of infant immune system though *S. aureus* often aggravates established AD. Also, the presence of specific gut microbiome, such as *Akkermansia muciniphila* (*A. muciniphila*), was associated with alterations in functional genes, which affected the development of the host immune system [51]. Another study suggested that feedback interactions between dysbiosis in *Faecalibacterium prausnitzii* (*F. prausnitzii*) and dysregulation of gut epithelial inflammation might underlie the chronic progression of AD by resulting in impairment of the gut epithelial barrier, which ultimately leads to aberrant Th2-type immune responses to allergens in the skin [52].

3.2.2. Metabolite pathway

Short-chain fatty acids (SCFAs) produced by the gut microbiome such as *A. muciniphila* [51], play important roles in inflammatory diseases including AD, which may account for the links among dietary feeding, microbiome and the skin immune system [53]. SCFAs, including butyrate, propionate and acetate, can interact with the gut epithelium barrier and execute anti-inflammatory and immune-modulatory effects [54]. *Clostridia* and *E. coli* in the intestine might be associated with AD *via* eosinophilic inflammation [24]. Oral administration of metabolites can help treat skin diseases by modulating their anti-allergic and anti-inflammatory effects. Linoleic acid and 10-hydroxy-cis-12-octadecenoic acid can relieve AD symptoms and modulate the gut microbiome in a mouse model [55]. In another study, administration of probiotic *Bifidobacterium animalis* subspecies *lactis* (*B. lactis*) can increase the levels of the metabolite kynurenic acid, which reduces scratching behavior in AD mice [56].

3.2.3. Neuroendocrine pathway

A new line of evidence supports the notion that a gut-skin axis is mediated by neuroendocrine molecules produced by the gut microbiome. The data suggests that differences in compositions and proportions of microbiome are associated with the productions of multiple beneficial neurotransmitters and neuromodulators that are correlated to the extent of AD symptoms [57,58]. They can lead to skin barrier impairment and immune system dysfunction, which are the crucial pathophysiological phenotypes of AD. Through direct and indirect pathways, the gut microbiome can regulate the gut-skin axis [59]. Tryptophan produced by the gut microbiome causes an itching sensation in the skin [57], whereas *Lactobacillus* and *Bifidobacterium* species can produce γ-aminobutyric acid (GABA), which inhibits skin itch [57,60]. *Escherichia* and *Enterococcus* species can produce serotonin, involving skin pigmentation [58,61]. Gut microbiota can indirectly regulate the levels of cytokines in the blood, thereby affecting brain function such as stress and anxiety [59]. Cortisol is usually released under stress and can alter the permeability and barrier function of the intestinal epithelium by changing the compositions of the microbiome [58]. It also alters the levels of circulating neuroendocrine molecules, such as tryptamine, trimethylamine and serotonin, thus modulating the skin barrier and skin inflammation [57,62].

4. Therapeutic interventions against microbiome

4.1. Topical steroids

Despite the recent development of targeted therapies, topical steroids are still the first option of AD treatment. However, a thorough assessment of their effects on microbiome remains absent. Steroids have immunosuppressive effects and have been considered potential predisposing factors for skin infections. The effect of cortical steroid alone on microbiome has not been well established. Giovanni Widmer found that the diversity and composition of cutaneous microbiota was not impacted after treatment with ciclosporin for one month followed by prednisone for another month, in a study with 6 atopic, asymptomatic Maltese-beagle dogs [63]. A study conducted by Gonzalez ME found that topical corticosteroid (TCS) was sufficient to induce clinical improvement and reduce surface bacterial load [64]. Brunner et al. investigated the effect of a mild topical steroid (triamcinolone acetonide)

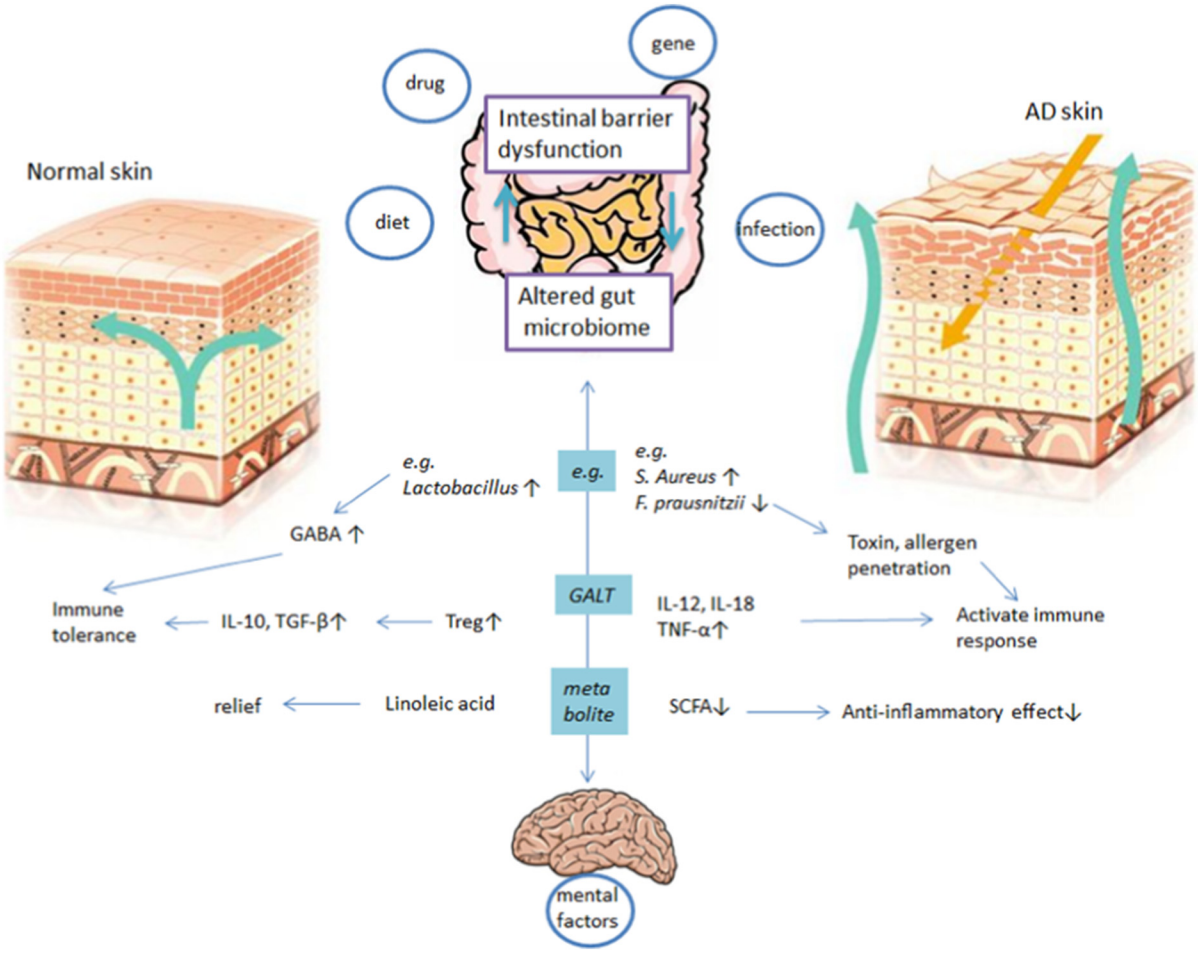

Fig. 1. Proposed correlations of gut microbiosis and AD. Various factors including diet and drug can affect gut microbiosis and intestinal barrier function. These factors are usually dependent on and crosstalk from each other. Gut microbiosis play important roles in dermatisis relief or severity through different pathways including immunological, metabolite and neuroendocrine pathways.

on gene expression in moderate-to-severe AD lesions [65]. After 16 weeks of treatment, the AD genomic signatures, including key cytokines/chemokines (IL-13, IL-22 and CCL17) and epidermal disease hallmarks (keratin 16 and loricrin), were significantly normalized, suggesting that even low-potency steroids could broadly affect immune and barrier responses in patients with AD.

4.2. Antibiotics

Since the colonization of *S. aureus* lead to AD aggravation, multiple therapeutic strategies have attempted to target *S. aureus* colonization specifically. However, until recently, not much clinical trials have shown satisfactions on the efficacy of antibiotics in treating AD. The most common topical/systemic antibiotics for *S. aureus* on AD lesions include flucloxacillin and mopirocin [66,67] After treatment of 4 to 8 weeks with antibiotics, there was not much improvement in AD patients and *S. aureus* colonization is easy to relapse [68]. In a randomized clinical trial, topical fusidic acid did show a better efficacy than corticosteroids and emollients [69]. Corticosteriods have also been used in combination with antibiotics to improve AD severity [70]. Though anti-inflammatory reagents are necessary, removal of *S. aureus* alone seems insufficient for AD treatment. One consideration is that antibiotic therapy for AD is relatively non-specific which also affects some beneficial bacteria such as *S. epidermidis* on the skin.

4.3. Ozonated oil/water topical therapy

Triatomic allotrope of oxygen, formed by recombination of oxygen atoms (O3), naturally releases ozone [71]. Ozone was initially used to sterilize microorganisms in drinking water [72]. Until now, ozone has been used for treatment of open wounds, herpes zoster and herpes simplex [73], because of its anti-microorganism effectiveness [74]. Lu et al. have conducted several studies using ozone oil/water topical therapy for AD. They have found that 7-day ozonated water bath along with ozonated oil treatment can relieve the severity of patients with modest to severe AD with decreases in SCORAD scores and *S. aureus* load [75]. The initial concentration of ozone in water produced by the ozone generator (HZ-2601B) decreases with the increase in temperature. Ozonated water of 20–30 degrees Celsius has good sterilization effect on common pathogens. The killing rate of *E. coli*, *S. aureus*, drug-resistant *S. aureus*, *Pseudomonas aeruginosa* and *Candida albicans* was 100%, 100%, 100%, 95% and 92%, respectively, with a treatment of 0.3 mg/L ozonated water for 1 min [76]. A study by Song et al. has demonstrated that ozonated oil and ozonated water have strong antibacterial effects against *S. aureus* and methicillin-resistant *S. aureus* (MRSA) *in vitro* [77]. Dr. Lu's group has shown that ozonated oil suppressed allergic skin inflammation by a significant decreased expression level of an AD severity marker, nerve growth factor (NGF), in a murine AD model [78]. The study has also found that ozonated oil inhibits expressions of Th2 cytokines in the allergic skin and serum and increases the expression of immunosuppressive cytokine IL-10. However, further studies to unveil the detailed relationships among ozone,

microbiome and cytokine regulation are needed [78].

4.4. Petrolatum/emollient

Petrolatum is a common moisturizer that is often used to prevent skin infections after surgeries or as a basic therapy of AD. Moisturizers have been shown to improve AD disease severity [79], transepidermal water loss (TEWL) [80], as well as to reduce rates of *S. aureus* colonization [81]. A study on 49 CE patients showed that 84-day emollient treatment alleviated the clinical symptoms. Microbial communities in lesions restored with an increased overall diversity and a decreased *S. aureus* abundance [81]. *Stenotrophomonas* species also increased in the improved patients of the study [81]. Czarnowicki et al. performed a double-blind, randomized, comparative study with 60 patients with moderate AD. They showed that an emollient for 28-day can equalize the bacterial composition of an affected area to a state similar to that of an adjacent unaffected area [82]. Recent studies have shown that emollients are effective in preventing the onset of AD in high-risk newborns [83]. A study carried on by Tali Czarnowicki, involving 36 healthy subjects and 13 patients of moderate AD, detected more significant up-regulation of key AMPs and innate immune genes in petrolatum- occluded skins than those with occlusion alone or control skins [82]. The same results were obtained after a 4-week treatment period with a topical corticosteroid. Worsening AD and dysbiosis on the skin are strongly associated. Application of certain emollients can increase microbiome diversity in AD [84].

4.5. Bleach bath

Sodium hypochlorite (NaClO) has been used as a disinfectant agent for a long time in daily life. When mixed with water, NaClO generates highly reactive HClO, which can effectively kill most of bacteria, spores, fungi and viruses depending on its concentration. Its mechanisms of action on AD are not well understood. Bleach bath improves clinical symptoms of AD and restores surface microbiome by eradicating bacteria, most notably *S. aureus*. Its antimicrobial effect can reduce the need for topical corticosteroids or topical antibiotics [85]. A study showed significant reductions in Eczema Area and Severity Index (EASI) scores and *S. aureus* density after a bleach bath treatment [86]. Gonzalez found both TCS with bleach bath or with water bath had significant improvements in total EASI score, investigator's global assessment (IGA) and reduction in *S. aureus* loads. However, the synergic effect of bleach bath and anti-inflammatory agents remains unknown [64].

4.6. Probiotic therapy

Recently, several meta-analyses and systematic reviews have summarized the effect of probiotic supplementation during early stage of lives and its incidence of AD [56,87]. Probiotics are live microorganisms that can diversify the intestinal microbiome especially during early, critical stages of development, to potentially influence the immune system and prevent AD. For example, results from the studies of Rosenfeldt et al. [88] and Kalliomäki et al. [89] suggested that *Lactobacillus rhamnosus* (*L. rhamnosus*) was effective in the prevention of pediatric AD at high risk. A recent meta-analysis, including 6 treatment studies and 2 prevention studies on AD, found that synbiotics (the simultaneous use of pre- and probiotics) was supported for use in children aged 1 year and older despite the significant heterogeneity [90]. Similar results have been found in another recent meta-analysis reviewing the treatment effects of both pro- and synbiotics in AD [91]. However, findings from an earlier meta-analysis of pre-, pro-, and synbiotics were less favorable, reporting little or no evidence to support the use of probiotics for the treatment of AD [92]. Probiotics could be preventive against AD at early age, but in some studies, the effect was not sustainable in infants at low risk [93]. The benefit of using probiotics and synbiotics in the prevention and treatment of AD remains inconclusive. Many limitations among various studies such as significant heterogeneity in study design (different strains, time, does) have been making it difficult to interpret those results conclusively. The mechanism of probiotic therapy is thought to modulate systemic immune functions in response to gut microbiome alterations. In general, current evidence seems to support that pre-, pro-, and synbiotics may have a role in the prevention of AD when it is administered both prenatally and then after birth. However, there are currently no general guidelines or recommendations for probiotic use in pregnancy and/or infancy to prevent AD.

Another two studies conducted by both SH Silva [94] and Lars Käre Dotterud [95] have confirmed that UVB, particularly narrowband UV-therapy, have shown that the skin microbiome can be regenerated after adequate therapy, presenting an increase in microbial diversity and a decrease in SCORAD of AD patients. An altered skin microbiome appears on patients with AD during flares. Staphylococcal cutaneous microbial population levels in AD patients are higher compared with the levels in the controls.

5. Conclusion

The cause of AD involves in genetics, immune system dysfunction, environmental exposures and damage with skin barrier function. Apparently, the balance of microecology in skin and gut in our bodies plays critical roles to lower disease severity and reduce the risk of recurrence. Recent studies have shown a strong association between worsening disease severity and lower skin bacterial diversity. The rich diversity of microbiome in the skin means the boosted immune response or normal barrier function of host. Gut microbiome come into play mainly by the way of colonization resistance, fermentation of residues and endogenous mucus and salvage of energy as short-chain fatty acids. From a future perspective, skin and gut microbiome examination can be a potential new diagnostic and therapeutic target for inflammatory skin diseases. While it is still a great challenge for us to completely understand the exact mechanism occurred in disease progression and more research programs and suitable clinical trials are required to further demonstrate the curative effect of therapeutic intervention against microbiome in AD.

Conflict of interests

The authors declare no conflict of interests.

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