DOI: https://doi.org/10.47391/JPMA.1415

Gut microbiome skin axis in the development of atopic dermatitis

Abstract

Atopic dermatitis mostly starts with children in early life. Besides the aetiological factors, like environmental, dietary or medical exposures, gut-skin axis microbiome studies have an impact to investigate and to understand the relation between the gut microbiome and changes to the skin microbiom as well as resulting skin diseases like atopic dermatitis. Infants start forming their microbiome in early life and some studies suggest that this phase has a crucial role in AD development. Balanced bacterial composition is important to maintain healthy skin as the gut microbiome dysbiosis may result in dramatic shifting in the skin microbiome that gives better chance for some bacteria, such as staphylococcus aureus, to prevail which has been reported to contribute to AD development. Among several factors, immunological activity has a strong relation to microbiome, changed composition and AD development. Supplements of prebiotic and probiotic could be a positive treatment approach. More studies regarding the gut-skin axis microbiome in general and diseases associated with microbiome, such as AD, are needed.

Key Words: Gut microbiome, Skin microbiome, Atopic dermatitis.

Introduction

Many studies have linked the gut microbiome dysbiosis with the development of atopic dermatitis (AD), especially among infants (1, 2). The human body is colonised by tons of microbial cells, especially in the gut, which outnumber the body's cells, and their genetic material is much more than the humane genomes(3). Metabolite activities in the bodies, for example, are considered to be limited without the aid of the huge amount of metabolic activity that gut

microbiome provide to the human body(4-6). Microbiome in the bodies are composed of different microorganisms, including viruses, archaea and bacteria, as well as other eukaryotic microorganisms, such as yeast and fungus. However, the main focus of most studies regarding microbiome is on bacteria(7, 8).

Infants' microbiome starts forming upon delivery through the mother's skin, vagina microbiome and nursing. However, the mother's microbiome itself tends to change over the course of pregnancy due to usage of, for example, antibiotics. Moreover, the delivery method, whether caesarean section (CS) or normal delivery, has a significant impact on the infant microbiome(9, 10). Some studies found that bacterial diversity is different in pregnant and non-pregnant women, with bacteria being less diverse in pregnant women, and also changing with the age factor(11). Microbiome has a role of protecting the foetus. One study shows that pregnant women's vagina would have increase prevalence of lactobacilli, which helps to keep potential of hydrogen (pH) level low and results in decreasing the diversity of bacteria and preventing them from reaching the uterus(12, 13). The new-borns obtain most of the microbiome from their mothers' vagina, faeces and skin(14-16). Breastfeeding in the first days of life promotes the growth of the babies' gut microbiome(17). Microbiome for the infant take evolutionary steps to reach a complex microbiome composition by the end of the first year of life and reaches an adult-like microbiome by the age of three years(18-21). In addition, infant immune and metabolic systems are developed by the microbiome interaction(22, 23). However, dysbiosis of infants' microbiome may result in metabolic and autoimmune diseases(24, 25).

Studies have shown that bacterial diversity within the gut is a sign for gut health and overall health status is associated with it as healthy individuals tend to have more diverse bacterial status in the gut than it is in those who are linked to immune-related and inflammatory disorders as well as obesity(26-30). There are some factors that may affect the stability and balance of gut microbiome and that is suggested to lead to some diseases(31, 32). Diet habit alteration or antibiotic

consumption, for example, cause a microbiome shifting, especially in the gut(33) and that would result in certain diseases, such as inflammatory bowel disease (IBD)(34), other autoimmune diseases, such as rheumatoid arthritis(35), or allergy diseases, like AD(36). The current narrative review was planned to focus on the link between the gut microbiome and AD devolvement in children.

Gut Microbiome

In childhood, microbiome may have an important role protecting children from various diseases and boost their health status by contributing to the development of the immune system through the cross-talk process with the host cells(37-39). Therefore, it is substantial to know what constitutes the normal health status of children gut microbiome in order to better understand and spot any defects that may lead to certain diseases. It has been reported that a healthy child's gut microbiome, on average, is composed mostly of two phyla among other bacteria; bacteroidetes and firmicutes (40, 41). Although microbiome are more diverse in adult, children gut microbiome are found to be richer in genes that are essential to their development(42, 43). Thus metabolite production by some types of bacteria in cases of gut microbiome dysbiosis throughout infancy to adulthood results in some kind of defects of immune system that contributes in some ways to disease development, like AD(44, 45). Among environmental factors, such as stress and pollutants, direct factors, like antibiotic consumption and diet, have a substantial role in forming the composition of the gut microbiome, especially in early life of the host, and some studies have even found the connection between the patient age, severity and even the AD phenotype along with other factors and the gut microbiome which substantially affect AD development(44, 46-48). The relation between the gut microbiome and specific microbes to AD is still not clear and more studies in this area are needed(2).

A huge number of antibiotics are prescribed for children and up to one-third of these prescriptions are avoidable(49). Antibiotics are responsible for low

diversity in gut microbiome. One study followed some children for the first three years of their lives where some of them were exposed to antibiotics and some were not, and the results showed less diverse composition of bacterial species and strains in the gut of those exposed to antibiotics(50). Antibiotic over-prescriptions have contributed greatly not only in microbiome dysbiosis, but also to many cases of adverse effects related to antimicrobial drug use and promoting a superbug development, according to the World Health Organisation (WHO)(51). For infants' gut microbiome, antimicrobial resistance gene prevalence increases with age, and infants delivered by CS mode tend to obtain great quantity of antimicrobial resistance genes which are reported to have a role in the increasing events of mortality and morbidity(49, 52).

Another factor having a clear effect on the gut microbiome and playing a huge role in dysbiosis and rebalance is diet. Milk is the first form of nutrition that infants consume for a few months until other source of food start to be included in their diet. Thus, one of the major observations was between the infants who were breastfed and the infants who had non-human source of "formula" milk. The breastfed infants harboured different microbiome in abundance, like bifidobacteria and lactobacilli, than the formula-fed infants who had enterococci and enterobacteria (49, 53). Also, there were differences in microbiome profiles between the two groups in terms of total count(54). Human milk has probiotic (milk microbiome), prebiotic (bacterial growth factors) and antimicrobial properties, such as secretory immunoglobulin A (SIgA), from the mother's immune system memory(49, 55).

Skin Microbiome

Skin is the largest organ, as the modern science would describe it, and has a diverse microbiome that contributes to some health conditions of the skin(56). While knowledge regarding gut microbiome is more broadened now, skin

microbiome is less comprehended and needs more studies. Microbiome colonisation of a newborn starts with the exposure to the close surrounding environment as well as the mother's microbiome(57). Following the acquisition of a complex variation of microbiome phyla, maintaining a balanced microbiome harmony is affected by number of factors, such as change in pH, water content, transepidermal water loss (TEWL)(58), and lipid content is strongly associated with some disease development. AD in particular has been shown to have elevated levels of long-chain unsaturated fatty acids and ceramide AS (α-Hydroxy fatty acid/sphingosine base) which are linked with higher abundance of propionibacteria and corynebacteria, which, in turn, are responsible for requiring outer free fatty acids (FFAs) because they do not produce fatty acids synthase, and staphylococcus (S.) aureus, respectively(59). Another sensitive risk factor regarding AD development is the filaggrin gene (FLG) encoding mutation which plays a critical role in the skin barrier function, like maintaining good level of pH regulation and epidermal hydration(60). In an effort to find the relation between skin microbiome composition and FLG and the link to AD, one study found a higher abundance of S. caprae in AD nonlesional skin patients compared to the healthy controls(61).

Balanced abundance and richness of the skin microbiome is a key to healthy skin. One study tested the skin microbiome diversity of 339 AD patients; 169 of them being children aged 2–12 years(62). Microbiome diversity reduced significantly in case of methicillin-sensitive S. aureus (MSSA), and more reduction was encountered with methicillin-resistant S. aureus (MRSA) colonisation. Streptococcus and propionibacterium, for example, had a dramatic decrease in samples with MSSA and MRSA high abundance compared with AD samples with no S. aureus detection. Moreover, skin is the first line of defence against external agents, including skin microbiome, which helps in the development of the immune system. Cytokine production by the skin T cells responded weakly to inflammation in germ-free mice compared to normal mice(57, 63, 64).

Possible microbial mechanisms of microbiosis in AD

There are three factors that contribute to skin microbiosis and AS development, which are skin barrier, immune system and pathogen(65). Disruption of the bacterial environment on the skin has been noticed to influence the change of the bacterial composition of an AD case. One of the factors that have a role in skin microbiome disruption is pH. S. aureus growth, for example, is promoted by the rising level of pH on the skin surface(66, 67). Another factor is that certain surface markers of keratinocytes basal cells in the skin, such as fibronectin and fibrinogen, are found expressed on the cell surface when exposed directly to microbes, and this expression promotes S. aureus because it binds to fibronectin-binding proteins (FnBPs)(68, 69).

Disrupting the harmony of the skin microbiome can be attributed to immunological factors. One of the most important defence lines in the skin is antimicrobial peptides (AMPs). It has cathelicidin and beta-defensins (DEFBs) types which have an essential role in fighting off pathogenic microbes, such as S. aureus(70, 71). The reduction of AMP expression has been associated with the development of AD lesions(72). AMP stimulation reduction is due to the activity of T helper cells$_2$ (Th$_2$) cytokines which may result from allergy effect(73). Thus, this insufficient expression of AMPs would promote the growth of S. aureus.

Studies have shown the relation between some alteration upon certain bacteria and AD development and severity. One important example is S. aureus. There are two factors that S. aureus uses in its contribution to AD development and severity level(74). One factor is superantigens (SAgs) (Table), which bind to major histocompatibility class II (MHCII) molecules on both antigen-presenting cells (APCs) and T cell receptor, making the cells more interactive without specific need for an antigen which results in T cell cytokine over-production, leading to cytotoxicity. Also, SAgs have a role in prompting immunoglobulin E (IgE) response as an allergen factor(74). The other factor that is suggested to increase the severity of AD is alpha (α)-Toxin that causes cell lysis as a result of

heterodimer complex formation on the cell membrane besides being very toxic to keratinocytes cell(75, 76). Similarly, corynebacterium (C.) bovis has been linked to acute AD feature due to intense Th_2 cell response. However, further investigation is needed to actually link it to AD development as abnormal colonisation of C. bovis has been noted with high IgE syndrome (HIES)(77). On the contrary, S. epidermidis is reported to have a protective role in the skin against S. aureus colonisation and other pathogens. Also, a study revealed support to immune system by boosting T cell efforts (IL-1)(63). On top of that it has other pro-immunity activities both in vivo and in vitro, such as the protective role of AMP expansion, preventing S. aureus biofilm formation in the nasal cavity, and in the skin it can inhibit some pro-inflammatory bacteria, such as propionibacterium acnes which has a role boosting the synthesis of IL-6 and tumour necrosis factor-alpha (TNF-α)(78-82).

Gut-Skin Axis

To better comprehend the relation between the gut and the skin in a manner of health and diseases, immunological, metabolic and neuroendocrine pathways have to be well understood. A brief overview about the pathways and how they are related to AD is essential(2).

Immunological pathway, besides the skin barrier physical factor, has been well associated with AD development(2). Especially with infants, gut microbiome alteration might have a great effect on the immune system development(83). About 70% of the immune systems are located in gastrointestinal (GI) mucosa and gut-associated lymphoid tissue (GALT) where most probiotic interaction takes place(84). Imbalance of Th1/Th2 result in Th2 cytokines production, such as IL-13, IL-5 and IL-4, which is the reason behind high IgE production which is also followed by S. aureus binding to AD skin(85).

Fibres from dietary food sources can only be digested and turned into short chain fatty acids (SCFAs) by some of the gut microbiome, like akkermansia

muciniphila, low-level prevalence of which is associated with inflammatory diseases, such as AD(86-88). Low level of SCFAs was associated with a group of children who had eczema compared to a non-allergic group of children where SCFAs were found to be anti-inflammatory by reducing and controlling some types of pro-inflammatory cytokine, metalloproteinases, nitric oxide expression as well as lymphocyte proliferation(89, 90). Another study showed the effect of some strains of faecalibacterium prausnitzii in reducing the prevalence of bacteria responsible for high production of SCFAs. Butyrate and propionate, in particular, are producers, including faecalibacterium prausnitzii strain A2-165(87). Metabolites can possibly have either good or bad influence over the body. One study had linoleic acid and 10-hydroxy-cis-12-octadecenoic acid given to a mouse which resulted in changing their gut microbiome composition and thus increasing AD development. Another example of feeding AD mice with bifidobacterium animalis subsp. lactis LKM512 probiotic had the opposite effect as the metabolite kynurenic acid level increased and resulted in lowering the side-effect of AD, such as scratching behaviour(91).

Neuroendocrine molecules are another factor added by studies related to the equation that link gut and skin microbiome to each other. Alteration of gut microbiome may influence the neurotransmitters and neuromodulators which are not only related to AD symptoms degree, but also affect the skin permeability and immune response defection which are key factors in AD development(92, 93). There are direct and indirect ways gut microbiome affects skins(94). An example of the direct way is when the gut microbiome produces tryptophan and cause an itchy feeling in the skin, while gamma (γ)-aminobutyric acid (GABA) produced by lactobacillus species and bifidobacterium species have repealing effect on the skin itching(92, 95). On the other hand, neuroendocrine molecule levels are subjected to change by the effect of cytokines produced and altered by the microbiome composition formed in the gut. Cytokines in the bloodstream have an influence upon the brain function, stress and anxiety which have a side-effect

of raising the level of cortisol that lead to gut microbiome alteration and therefore results in gut epithelium permeability and barrier function changes(92-94, 96). It is all connected with each other, so each organ is linked and affect another.

The role of pre and probiotics as a treatment (probiotic therapy)

In the United States, 31.6 million people (10.1%) have some form of AD; 9.6 million (13%) of them are children aged <18 years, according to the National Eczema Association (97). In Europe, especially the northern part of it, the percentage of infants and toddler affected by eczema is up to 23% based on the European Centre for Allergy Research Foundation (ECARF) (98). One of the options for AD treatment is to give a course of pre and probiotics supplements (99). The definition of the probiotics, as stated by the Food and Agriculture Organization (FAO) and WHO in 2001, is, "living bacteria that, when administered in adequate amounts, confer a health benefit on the host"(100). More studies are emerging as proof of the benefits of probiotics on preventing AD, especially in case of pregnant women and newborns or infants(101, 102). Two strains of probiotics, lactobacillus (L.) rhamnosus (LGG) in combination with bifidobacterium animalis subsp lactis (BB-12), were applied to children in their late infancy, aged 8-14 months, prior to attending day-care, and it was found that there was a preventive effect on AD development, but not on other allergic diseases, sensitisation or food allergy(102). Moreover, a study found that L. rhamnosus and L. reuteri microbiome introduced to AD children helped reduce the severity by 56%(103). The other part is prebiotic, which is defined as "non-digestible food components that can promote the growth of certain bacteria in the gut". Some example of a common prebiotics are galacto-oligosaccharide (GOS) and fructo-oligosaccharide (FOS)(104). Similar impact of prebiotic as probiotic in preventing AD was reported when GOS, inulin and pectin were incorporated into the diet of 1-year-old infants who had low AD risk. The preventive effect was not observed at the age of 5 years(105, 106). Prebiotic may have a health

effect on the skin, including enhancing skin hydration and decreasing the levels of urine and serum phenol that are produced by gut bacteria(107, 108). Unlike probiotics, prebiotics, although promising, are far less investigated and need further studies.

Conclusion

Prebiotic and probiotic supplements could be a positive treatment approach in AD cases. More studies regarding the gut-skin axis microbiome in general and diseases associated with microbiome, such as AD, are recommended.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

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Table: Bacterial effects on skin through certain factors.

Bacteria	Factor	Action/result
S. aureus	SAgs	-Binds to MHCII and result in T cells cytokines overproduction. -Induce IgE response.
	α-Toxin	increase AD severity
S. epidermidis	Colonization	Protective role against pathogens.
C. bovis	Increase colonization	Th_2 increased response

S: Staphylococcus; C: Corynebacterium; MHCII: Major histocompatibility class II; IgE: Immunoglobulin E; AD: Atopic dermatitis.