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REVIEW ARTICLE

Targeting the Gut Microbiome for Atopic Dermatitis: A Comprehensive Review of Mechanisms and Therapeutic Approaches

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ABSTRACT

Millions worldwide, particularly children, suffer from the prevalent inflammatory skin condition known as Atopic Dermatitis (AD), with its prevalence on a constant rise.It's impact extends beyond affecting merely the skin, contributing towards more complex health problems. The exact cause of this condition is multifactorial: genetic, environmental and immunologic factors all play significant roles; however, attention has recently focused on the role gut microbiota may have in relation to 'gut-skin' axis disturbances. Gut microbiota imbalances may be influenced by diet, antibiotic use as well as changes in environmental conditions that may contribute to Atopic Dermatits pathogenesis. New research concentrates on therapies including probiotics, prebiotics and faecal microbiota transplantation. Multi-strain probiotic formulas in particular, are promising; such products have shown to potentially help manage Atopic Dermatitis symptoms by altering the immune response and adjusting the composition of gut microbes. The available evidence also suggests that exclusion diets can be tailored to serve as a form of dietary management. Fecal microbiota transplantation represents an innovative approach that requires additional scrutiny regarding its efficacy and safety in treating Atopic Dermatitis. The complex relationship between skin barrier function, immune responses and gut microbial composition offers possibilities for developing novel therapies targeting the microbiome in Atopic Dermatitis management.

Key words: Gut microbiome, Atopic dermatitis, Probiotics, Dysbiosis, Short chain fatty acids

Introduction

Atopic dermatitis is a chronic, pruritic inflammatory skin disease affecting millions globally, notably children; its prevalence appears to rise.[1,2] Researchers estimate that 15-20% of children and 1-3% of adults worldwide grapple with this condition.[3]Some children may outgrow AD, but a significant proportion could advance to conditions such as allergic asthma and rhinitis.[4] This progression is known as the "atopic march." [3] It leads to compromised sleep quality, psychological challenges, and economic strain for those affected and their families.[3] We do not have a complete understanding of what leads to AD but there is enough evidence hinting at genetic factors such as filaggrin gene mutations and environmental factors among others.[5] Immunologic responses—specifically through Th2 and Th17 pathways—as well as epithelial barrier abnormalities also play crucial roles.[3,6] In industrialized countries, the prevalence of atopic dermatitis has more than doubled or tripled over the last thirty years.[7] Genetic factors alone do not fully account for these increases; instead, involvement from environmental elements like reduced microbial exposure and altered diets could be the contributing factors.[8] The role of gut microbiota and its connection to the "gut-skin" axis features prominently in studies on AD pathophysiology among these contributing factors.[1,4] Trillions of microorganisms that inhabit our gastrointestinal tract - constituting the gut microbiota, have garnered increasing recognition for their profound impact on both overall health and immune function: they play a crucial role in diet metabolism; and stimulate the intestinal immune response, thus offering protection against pathogenic microorganisms.[9,10] Several recent reports hint at an intriguing aspect of the potential influence of these gut flora populations over allergic disorders such as atopic dermatitis, food allergy and even asthma.[11, 12] Current research therefore focuses on the potential therapeutic targeting of gut microbiota; specifically probiotics, prebiotics, and faecal microbiota transplantation for atopic dermatitis.[9,10] This article critically reviews current literature exploring the link between gut flora diversity and atopic dermatitis; it scrutinizes potential mechanisms contributing to pathogenesis through alterations in microbial composition within the gastrointestinal tract.

Gut microbiota

A complex, ever-changing community of microorganisms that resides in the gastrointestinal tract is known as gut microbiota, which plays an important role in various physiological functions such as immune modulation and nutrient metabolism. [11,13] The health of an individual can be affected by the composition of its gut flora which is highly influenced by diet patterns, lifestyles and stress levels. Several inflammatory conditions have been linked to dysbiosis or any form of imbalance within this intricate system.[14,11] Gut microbial composition and diversity can change to affect both immune response and skin barrier function leading to development of atopic dermatitis in those who are susceptible. [4]Maintaining the structural diversity of gut microbiota provides resistance to the invasion of pathogen bacteria by diminishing nutritional competition between potentially harmful bacteria and commensal varieties. Moreover, by participating in short-chain fatty acid (SCFA), amino acid, vitamin, and bile acid metabolisms; these microbial populations trigger the maturation of the innate and adaptive immune system.[15] The development of sequencing technology has unveiled in numerous studies the potential for regulating immune responses within the host by targeting its gut microbiota.[8] Indeed, this correlation between gut microbiota and human diseases such as allergic asthma and atopic dermatitis is well established. We now recognize the 'gut-skin' axis as a promising novel target in preventing and treating AD.[10] Several similar characteristics exist between the gut and skin, both being integral parts of our immune and endocrine systems.

Factors Influencing Gut Microbiota

DIET

Individuals who consume diets rich in plant polysaccharides, low fat and protein show an increased ratio of *Bacteroidetes* (beneficial bacteria) to *Firmicutes* within their microbial communities. On the other hand, in cases where one consumes animal-based diets or those high in refined carbohydrates and sugar, a shift towards a higher count of *Firmicutes* over *Bacteroidetes* emerges.[16] The *Firmicutes* phylum is often associated with metabolic disorders such as obesity and type 2 diabetes. A high-fat, low-fiber "Western diet" increases the risk of inflammation and autoimmune diseases due to the reduced microbial diversity.[17] On the contrary, a diet rich in fibrous and low-fat plant-based foods actively boosts short-chain fatty acids (SCFA) levels like Butyrate which maintain colonic homeostasis and prevent inflammation within the gastrointestinal tract.[15,18] Consuming prebiotics like inulin and oligosaccharides stimulates the growth of beneficial bacteria like Bifidobacterium and Lactobacillus. Fruits, vegetables and tea contain polyphenols that inhibit the growth of harmful bacteria while facilitating beneficial species due to their antimicrobial properties.[18] Similarly, omega-3 fatty acids have anti-inflammatory effects on the gut and promote

modulation of gut microbiota composition.[17] Furthermore, the makeup of our gut microbiome influences the metabolism of the various dietary components. Certain bacteria, for instance, metabolize dietary polyphenols into bioactive compounds which yield beneficial effects on human health.[10] Gut bacteria also influence the metabolism of vitamins and minerals.[18] Therefore, specific dietary components lead to complex and multifaceted effects on gut microbial communities. Some dietary components promote the growth of beneficial bacteria and contribute to gut health, while others can induce dysbiosis and escalate inflammation.

ANTIBIOTIC USE

The use of antibiotics significantly influences gut microbiota. Constant intake of these drugs over an extended period can inflict devastating effects on the gut microbiota. Many commensal bacteria, sensitive to such medications, rapidly decline in number. Surviving species capitalize on the released nutrient resources through changes in gut microbial community structure.[19] Even traditionally pathogenic species, resistant to gut colonies, may exploit this opportunity to establish themselves in the mucosal lining. This overgrowth of pathogenic bacteria can provoke inflammatory responses and cellular damage within the human gut; it might also heighten susceptibility and incidence rates of antibiotic-associated diseases.[5] Considering both these significant impacts on microbiota as well as potential health risks from extensive antibiotic use necessitates careful deliberation regarding its necessity for treatment purposes, clinicians need to balance possible harms of antibiotics against predicted benefits when making clinical decisions involving their prescription or administration. Monitoring and managing antibiotic use in livestock and poultry is essential. The emergence of public health concerns revolves around two key issues, that is, residues of these antibiotics in animal products, and their impact on human gut microbiota through dietary consumption.[16] A study focusing on the recovery of gut microbiota after antibiotics in children shows that although the diversity of the gut microbiota recovered to the initial level three to four months after antibiotic exposure, the relative abundance of some bacterial species remained significantly different from the pre-antibiotic state in individuals using antibiotics in the past year, suggesting that even transient antibiotic-induced disturbances of the gut microbiota may have long-term effects.[20] Apart from diminishing bacterial diversity, the use of antibiotics may prompt a transitory imbalance in gut microbial conditions. Some bacterial species indeed possess varying tolerances to antibiotics; moreover, opportunistic pathogens could leverage the reduced competition from commensal bacteria. This would allow them not only to proliferate during and post-antibiotic treatment but also expand their population significantly.[21]

ENVIRONMENTAL FACTORS

External environmental factors, including climate, hygiene, psychological stress and geography can exert influence on human microbiota. There is a reduction in microbial richness and diversity within industrialized countries.[10] Comparing the gut microbiota of European children to that of rural African children revealed lower diversity among Europeans along with a less beneficial *Bacteroidetes/Firmicutes* ratio; meanwhile, in Africa, there was a high diversity with a predominance towards *Bacteroidetes* species. Embracing a Westernized lifestyle, characterized by heightened fat and sugar intake, coupled with reduced physical activity levels--may produce notable effects on the gut microbiota.[10] This alteration in our microbial populations could subsequently influence atopic dermatitis development. The mode of childbirth also serves as an early environmental factor; it significantly impacts the colonization process of gut microbiota and is directly linked to potential risks for later onset of atopy-related diseases.[22] Infants delivered vaginally often exhibit gut microbiota enriched with beneficial bacteria such as Lactobacillus or Bifidobacterium, whereas those born via cesarean section typically harbour a microbial population within their guts that more closely resembles maternal skin flora, featuring higher instances of pathogenic species like Staphylococcus implicated specifically in elevating chances for developing atopic dermatitis.[17] Breast-fed infants and formula-fed infants indeed exhibit differing gut microbiota. The different composition is due to the inclusion of prebiotic oligosaccharides in breast milk which help to grow certain Bifidobacterium species and Lactobacillus. These particular bacteria may modulate immune response; thus, offering protection against atopic dermatitis development.[4]

Relationship between Gut Microbiota and Atopic Dermatitis

Mounting evidence recently suggests the gut microbiota's critical role in atopic dermatitis pathogenesis.[20] There is a significant variation in gut microbiota composition between AD patients and healthy individuals. [10,23] The risk and severity of atopic dermatitis correlate directly with certain bacteria's diversity and abundance; thus highlighting their significant association.[9] The changes in the microbiota of atopic patients were

supported by the fact that the harmful bacteria were found to be present in higher quantities and outnumbered the beneficial bacteria, which would normally not be the case.[24] Fascinatingly, researchers have also found that gut microbiota dysbiosis developed in early life in atopic dermatitis patients and could be detected even before any obvious sign of atopic dermatitis can be observed.[25] This means that lack of normal development and colonization of the gut microbiota in early life may be associated with the future development of atopic dermatitis. This is important because it suggests that restoring balanced gut flora through therapies in early life could potentially prevent or alter the course of this disease.[20] Furthermore, gut microbiota can also influence amounts and types of cytokines released. A diverse gut microbiome improves immunity by inducing regulatory T cells and generating short chain fatty acids that favor immune tolerance.[26] On the other hand, impaired gut microbial composition might lead to impairment of host immunity system and increased susceptibility to atopic dermatitis. Besides, some metabolites and microbial products from the gut can exert an influence on skin barrier integrity as well as general skin health too.[26]

DYSBIOSIS

Atopic Dermatitis often shows decreased taxonomic diversity in the genera of its gut microbiota.[17] Levels of beneficial bacteria such as Bifidobacterium, Faecalibacterium prausnitzii and Lactobacillus paracasei decrease while harmful strains like Staphylococcus and Clostridia increase.[6,17,27] Specific genera also act as unique gut bacterial signatures to distinguish those with AD from healthy individuals and indicate an association with disease severity. Atopic Dermatitis patients enriched genera such as Blautia and Butyricicoccus correlate positively with the severity of AD. Conversely, Romboutsia and Clostridium sensu stricto 1 exhibit higher abundance in the normal group.[26] These specific genera produce short-chain fatty acids (SCFAs), which play a significant role in gut-skin axis function by influencing immune responses, and inflammation levels, as well as maintaining skin homeostasis.[21,6] Essential for maintaining colonic T-regulatory cells and promoting gut barrier integrity, they play a crucial role. A deficiency in these elements would indeed impair the function of the gut barrier; this impairment could then allow allergens or toxins to translocate from the lumen of your intestine into underlying tissues, thus affecting systemic immune responses.[28] Modulating diversity and composition within our early-life gut microbiota might therefore offer us an effective strategy that could potentially reduce the onset as well as progression of AD. More experimental and longitudinal clinical studies must confirm the causal relationship between gut microbiota dysbiosis and atopic dermatitis's occurrence or severity.

IMMUNE SYSTEM DYNAMICS

Gut microbes' diversity vitally shapes the immune system and diminishes immune-mediated disorders, such as allergies. Recent studies illuminate the vital role of gut microbes' diversity in shaping the immune system and reducing immune-mediated disorders, notably allergies. Furthermore, the immune system vigilantly scrutinizes the gut microbiota, promptly identifying any disruptions or imbalances and then responding accordingly.[19] Maintaining a healthy gut environment hinges on this crucial communication between the immune system and microorganisms. In instances where gut integrity suffers compromise, such as with leaky gut syndrome or intestinal inflammation, the immune system springs into action, activating an immune response to neutralize harmful pathogens and reestablish balance.[24] The release of cytokines constitutes one key mechanism through which the immune system communicates with microorganisms. These signalling molecules aid in the regulation of immune responses. Certain cytokines like IL-10 and IL-17A perform the crucial task of maintaining immune homeostasis within the gut. Research demonstrates that an imbalance in the IL-10:IL-17A ratio can contribute to immune-mediated disorders, including allergies and inflammatory bowel diseases. [35] Exposing children to a diverse array of natural environments, from parks and green spaces or even nature-centric daycare centres demonstrated increased skin and gut microbial diversity correlating with a healthier immune system.[19] The plasma samples of these children show a higher IL-10:IL-17A ratio. Moreover, Toll-like receptors (TLRs) are very important as they help in communication between the immune system and gut microbiota.[15,19] They are recognized by TLRs since they have specific microbial components that cause immune responses. The interaction between the immune system and microorganisms can be affected due to variations in TLR genes, like the TLR4 SNP rs10759932. For example, TLR4 recognizes certain strains of E. coli, and its variation can influence the development of allergic sensitization in early childhood.[19,29] Moreover, the composition of the gut microbiota itself plays a significant role in immune-mediated diseases. Infants with atopic eczema, exhibit lower levels of Ruminococcaceae; this correlates negatively with TLR2-induced cytokines. Conversely, TLR4-induced cytokines have demonstrated negative associations with Enterobacteriaceae.[19] To develop strategies for alleviating immune-mediated diseases effectively, it is important to

understand the intricate communication between the immune system and microorganisms in the gut.

SKIN BARRIER FUNCTION

The concept of the gut-skin axis suggests that changes in the gut microbiome can impact the skin.[3] This influence could result from two potential mechanisms- a direct activation of the immune system through gut bacteria and their components' release or signals travelling via the bloodstream from these same microbes affecting diverse organs including, but not limited to, the skin.[30] If dysbiosis triggers far-reaching effects of this kind, including the activation of skin immune responses, this could help to explain how atopic dermatitis develops as a more general skin condition, with chronic inflammation a key feature in most cases. Furthermore, gut dysbiosis disrupts lipid and ceramide production and weakens tight junctions compromising the overall barrier function of our epidermis.[31] This breakdown allows allergens or pathogens to trigger inflammation in remote areas such as the gastrointestinal tract or respiratory system via a breach in this protective barrier. Bacteria such as Staphylococcus epidermidis, produces antimicrobial peptides that shield our skin against harmful pathogens.[22] These peptides are natural antibiotics and prevent the growth of harmful bacteria on the surface of our skin, thus preventing infection. Other gut bacteria, such as Bifidobacterium and Lactobacillus enhance ceramides production; essential components of the skin barrier. By retaining moisture in the skin, preventing water loss and maintaining elasticity, ceramides play a vital role.[32] An imbalance in the gut microbiota potentially diminishes the production of beneficial compounds, thus compromising the skin's barrier function and heightening susceptibility to dryness, irritation or infection.[33] Emerging research proposes a bidirectional communication system known as the gut-skin axis where interactions between gut microbiota and skin mutually influence health conditions.[1] The mechanisms underlying this connection are complex and multifactorial. One possible explanation is that the gut microbiota is involved in modifying systemic inflammation, which can affect skin inflammation as well as immune responses.[32]

In addition, the gut microbiota generates metabolites such as short-chain fatty acids which are anti-inflammatory and promote the barrier function of the skin.[30] Furthermore, it also takes part in metabolism and absorption of essential nutrients, vitamins and minerals for healthy skin.[30] There is a need to further explore the complex mechanisms behind gut-skin axis and develop specific treatments to enhance the general condition of skin.

Therapeutic Approaches Targeting Gut Microbiota

PROBIOTICS AND PREBIOTICS

When administered in adequate amounts, probiotics (live microorganisms primarily used for disease prevention and treatment or immune system modulation) confer a health benefit upon the host.[11] Non-digestible food ingredients known as prebiotics selectively stimulate specific bacteria growth and activities within the colon when consumed.[34,35] Many different strains of probiotics exist, with the most commonly employed being Lactobacillus and Bifidobacterium species.[2] These probiotics fortify the gut barrier function and regulate immune systems by enhancing mucus production, releasing antimicrobial peptides, reducing pro-inflammatory cytokine production and promoting an increase in anti-inflammatory cytokines.[7] In a recent clinical trial, a probiotic formulation (Bifidobacterium animalis subsp. lactis CECT 8145, Bifidobacterium longum CECT 7347, and Lacticaseibacillus casei CECT 9104) significantly improved the SCORAD index and helped in reducing topical steroid use in children (4–17 years) with atopic dermatitis (AD). The probiotic group displayed escalated levels of Bacteroides, Ruminococcus and Bifidobacterium and decreased levels of Faecalibacterium in comparison to the placebo cohort.[17] *Faecalibacterium* was significantly found to be positively correlated with AD severity. For this reason, it may be crucial for those suffering from AD to consume probiotics as a way of reinstating favorable bacteria imbalance (Bifidobacterium and Lactobacillus). This contributes to a balanced gut microbiota and systemic immune responses.[7] Probiotic effectiveness is observed to be better in children over 1 year old, and particularly beneficial in those with moderate to severe AD.[28] Multi-strain preparations, particularly those that combine lactobacillus and bifidobacteria have superior therapeutic effects than their single-strain counterparts.[36] Oral administration of Lactobacillus acidophilus, Lactobacillus casei, and Lactobacillus salivarius, either alone or in combination with other probiotics, proves effective in improving clinical symptoms and reducing IgE levels in AD children.[13,26] Pregnant women's probiotic supplementation during prenatal and postpartum periods, as well as infant probiotic intake, demonstrates a reduced risk of AD in children.[28]

Probiotics affect the synthesis of nutrients, the production of short-chain fatty acids and competitive inhibition against pathogen growth.[3] In addition, they generate short chain fatty acids which are crucial in educating the immune system, promoting IgA production, balancing Th1/Th2 immune responses and reducing pro-inflammatory

cytokines.[7,36] Additionally, probiotic consumption is related to tryptophan metabolism, aryl hydrocarbon receptor (AHR) activation and regulation of skin inflammation. Also, it reduces itchiness, improves intestinal barrier function and increases levels of anti-inflammatory cytokine IL-10.[7,37] Probiotics also enhance anti-allergic effects; regulate immune factors; inhibit pathogen reproduction; and support the intestinal barrier function.[34,37] They present a promising strategy for AD management. Nevertheless, more research needs to be done using larger samples and precise experimental designs to get conclusive evidence. It's essential to ensure both efficacy and safety in probiotic interventions, considering strain-specific immunomodulation and potential health concerns associated with certain strains.[16]

FECAL MICROBIOTA TRANSPLANTATION

The procedure of faecal microbiota Transplantation (FMT) involves the introduction of healthy donor-derived faecal microbiota into a patient's gut. It can be done through a nasogastric tube, upper gastrointestinal endoscopy, colonoscopy, or enema.[10] The gut microbiota composition of the patient tends to change after FMT and reflects the donor's microbiota composition for a month before it starts to show similarity with the patient's original composition. When conventional antibiotic treatments have proven ineffective against recurrent Clostridium difficile infection (rCDI), FMT emerges as an effective and successful treatment.[33] The idea for the use of FMT in atopic dermatitis treatment has originated from studies suggesting the effectiveness of FMT in rCDI by restoring the gut microbiota to a state of eubiosis. Our current knowledge of the gut microbiota in atopic dermatitis does not provide any strong evidence in favor of FMT as a treatment.[18] There is also an urgent need for further investigations that can lead to the discovery of new and better treatments for atopic dermatitis such as fecal transplantation. Validating the effectiveness of FMT in atopic dermatitis through large-scale, randomized and well-controlled trials remains crucially important. Inherent risks of FMT include infection, bleeding and other types of complications from invasive procedures and minor gastrointestinal symptoms, allergic reactions due to the transplanted material in some patients. It is therefore important to address safety concerns comprehensively through research aimed at determining the short-term and long-term safety profile of FMT before it can be used as a standard therapy for atopic dermatitis.[35] Again, establishing how different procedural variations influence clinical outcomes is vital for its successful application. Ethical issues are also a major concern in FMT practice apart from the safety issues related to the technique.It is crucial to choose donors who are healthy and free from any infectious diseases that could be transmitted to the recipient.[30] Donors should also undergo thorough screening to ensure they have a diverse and stable gut microbiota composition. Moreover, it is important to find the required number of administrations and examine their impact on microbiota in the gastrointestinal tract of patients and its further clinical recovery.[30]

DIETARY AND ENVIRONMENTAL INTERVENTIONS

Researchers also explore dietary interventions as a therapeutic approach that targets gut microbiota; they demonstrate the significant impact of diet on gut microbiota's composition and activity.[18] Specifically, an association exists between high-fat diets and reduced diversity within the gut microbiota.[19] Conversely, research demonstrates that a diet abundant in fruits, vegetables and fibre; supplemented with fermented foods significantly enhances the diversity of gut microbiota.[19] By altering the composition and activity of gut microbiota through diet, we can enhance the integrity of the gut epithelial barrier; diminish systemic inflammation and even restore immune tolerance.[37] In addition, interventions that enhance exposure to a range of environmental factors like nature-oriented preschools have shown encouraging effects on both gut microbial diversity and the general health status of children's immune system.[22] From these insights, we can potentially formulate novel strategies for individuals with immune-mediated disorders. As such, further research is required to elucidate the best dietary regimen for atopic dermatitis improvement as well as determine how such dietary changes may affect the gut microbiota and the disease pathogenesis.

Conclusion

We need a healthy gut microbiome to maintain a balance between health and disease. Unfortunately, current lifestyles marked by high levels of stress, fewer social interactions, less outdoor exposure, a sterile environment, diets deficient in fibre, and excess antibiotic use can upset this equilibrium and contribute to the development of numerous disorders. "Let food be thy medicine, and medicine be thy food" dates back to Hippocrates, the father of medicine. This statement is still pretty relevant today and stresses the importance of a healthy diet to maintain good health. The food we consume can take up both preventive and therapeutic roles. The involvement of the gut microbiome in atopic dermatitis underscores an exciting possibility of its potential therapeutic significance. Probiotics appear beneficial, reshaping the gut flora, inhibiting pathogenic colonization, and restoring immune

balance, leading to decreased inflammation and clinical improvement in AD. However, despite these promising results we still don't fully comprehend how precisely probiotics alleviate symptoms of AD. A thorough understanding of the interactions between probiotics, gut microbes and skin remains crucial for manipulating targeted gut microbiota effectively. Ongoing trials of probiotics and FMTs may support a strategy for treating AD based on the microbiome. It is fully understood that the opportunity for microbiome targeted therapies is quite thrilling however, we should be careful because of the recent fallacies and misunderstandings in this regard as revealed in a Nature article. Employing both whole genome shotgun sequencing and metabolomics on AD patients' microbiomes will help to fortify our knowledge about gut-skin interactions and open up new avenues of therapeutic targets and methods. The gut microbiome surely stands at the forefront of future research and therapeutic interventions in Atopic dermatitis.

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