MARIAM ZATIASHVILI, TAMAR TABATADZE, MAIA MATOSHVILI, NINO ADAMIA, LAVRITA PACHUASHVILI, TAMAR ARAKHAMIA, MANANA KOBAKHIDZE, ANKA KOBAKHIDZE

ATOPIC DERMATITIS IN THE ERA OF INNOVATIONS

(Reviewing and exploring modern research and literature on treatment of atopic dermatitis with microbial transplantation)

M.Iashvili Childrens Central Hospital, TSMU

Doi: https://doi.org/10.52340/jecm.2025.03.02

მარიამ ზათიაშვილი, თამარ ტაბატაძე, მაია მათოშვილი, ნინო ადამია, ლავრიტა ფაჩუაშვილი, თამარ არახამია, მანანა კობახიძე, ანკა კობახიძე

ატოპიური დერმატიტი ინოვაციების ეპოქაში

(ატოპიური დერმატიტის მკურნალობის თანამედროვე კვლევებისა და ლიტერატურის განხილვა მიკრობული ტრანსპლანტაციის გამოყენებით)

მ.იაშვილის სახ. ბავშვთა ცენტრალური საავადმყოფო, თსსუ

რეზიუმე

ატოპიური დერმატიტი არის ქრონიკული ანთებითი კანის დაავადება, რომლის გავრცელებაც გლობალურად მუდმივად იზრდება და რომელიც გავლენას ახდენს როგორც ბავშვებზე, ასევე მოზრდილებზე. იგი ხასიათდება იმუნური სისტემის დისრეგულაციით, კანის ბარიერის დისფუნქციითა და გენეტიკური და გარემოს ფაქტორების რთული ურთიერთქმედებით.

ტრადიციული მკურნალობის მეთოდები, როგორიცაა ტოპიკური კორტიკოსტეროიდები, კალცინევრინის ინჰიბიტორები და ბიოლოგიური პრეპარატები, ფოკუსირებულია სიმპტომების მართვაზე, მაგრამ ისინი არ მოქმედებენ დაავადების ძირეულ მიზეზებზე. ამიტომ, სულ უფრო მეტ ინტერესს იწვევს მკურნალობის ალტერნატიული მიდგომები, მათ შორის მიკრობიომის თერაპიაზე დაფუძნებული მეთოდები.

ფეკალური მიკრობიოტის ტრანსპლანტაცია (FMT) ბოლო დროს გამოჩნდა, როგორც ახალი თერაპიული სტრატეგია ატოპიური დერმატიტის სამკურნალოდ. იგი ხელს უწყობს ნაწლავების მიკრობიომის მრავალფეროვნების აღდგენასა და იმუნური პასუხის მოდულირებას “მუცლისა და კანის ღერძის” მეშვეობით. უახლესი კვლევები მიუთითებს, რომ დისბიოზს (ნაწლავის მიკროფლორის დარღვევას) ატოპიური დერმატიტის პათოგენეზში მნიშვნელოვანი როლი აქვს, რაც ხელს უწყობს სისტემურ ანთებასა და დაავადების სიმძიმეს.

FMT-მა გამოაჩნა მისი პოტენციალი ატოპიური დერმატიტის სიმპტომების გაუმჯობესებაში, ნაწლავის მიკრობიომის ბალანსის აღდგენის, იმუნური რეგულატორული მექანიზმების გაძლიერებისა და ანთებითი ციტოკინების წარმოების შემცირების გზით. კლინიკური კვლევები ადასტურებს ამ მეთოდის ეფექტიანობას, თუმცა, სტანდარტიზაციის, დონორის შერჩევისა და გრძელვადიანი უსაფრთხოების კუთხით ჯერ კიდევ არსებობს გამოწვევები.

ამ მიმოხილვაში განხილულია ატოპიური დერმატიტის ეპიდემიოლოგია, FMT-ის იმუნოლოგიური მექანიზმები და მისი პოტენციალი, როგორც ხარჯეფექტური თერაპიის ალტერნატივა. მისი ხელმისაწვდომობისა და შესაძლო გრძელვადიანი სარგებლიანობის გათვალისწინებით, FMT-მა შესაძლოა უფრო ხელმისაწვდომი ალტერნატივა შექმნას ძვირადღირებულ ბიოლოგიურ თერაპიებთან შედარებით. დამატებითი კვლევებისა და რეგულაციების განვითარებასთან ერთად, FMT-ის ინტეგრაცია დერმატოლოგიურ პრაქტიკაში შეიძლება გარდამტეხი აღმოჩნდეს ატოპიური დერმატიტის მართვისთვის, რაც გააუმჯობესებს პაციენტების შედეგებს და შეამცირებს ჯანდაცვის სისტემაზე ზეწოლას.

Atopic dermatitis is remitting, relapsing, chronic eczematous pruritic disease. Atopic dermatitis is the leading contributor to skin-related disability and ranks 15th among all non-fatal disease globally. Nearly 5-9 million work days usually are lost due to atopic dermatitis.

According to the National eczema association atopic dermatitis affects approximately 10% to 20% of children and 2% to 10% of adults worldwide [1,2]. People of all skin color, races and ethnicities can be affected by atopic dermatitis [4,5]. 80% of individuals affected by atopic dermatitis experience disease onset prior to 6 years of age [48]. But atopic dermatitis is not solely a disease of childhood onset, 1 in 4 adults report adult-onset symptoms, and nearly 40% are affected with moderate to severe disease [3,6,7].

There are several factors that increase the risk of developing atopic dermatitis, one of the most prominent is genetic factor, individuals with a family history of eczema, asthma or allergies, have a higher risk of developing atopic dermatitis [8,9]. Pollution, climate and exposure to irritants can increase the likelihood of developing atopic dermatitis [10]. Children who live in urban environment have a higher risk for prolonged disease [11,12].

Itch is the most burdensome symptom of atopic dermatitis, followed by skin redness and sleep loss [13]. 60.5% of adults with moderate to severe atopic dermatitis have reported severe or unbearable itch in the past two weeks, 86% reported daily itch and 63% reported itching at least 12 hours per day [14]. During an atopic dermatitis flare, itch and redness are increased. Flare frequency, duration and average severity increases with disease severity [15]. Skin pain is another symptom of atopic dermatitis, with 61% of affected adults experiencing pain. Most often pain is reported as a burning sensation, it can also feel like tingling or stinging [16,17,46,47]. Between 20% to 40% of school-aged children and teens with atopic dermatitis experience bullying because of their disease [20].

More than 55% of adults with moderate to severe atopic dermatitis report inadequate disease control [13,18,19]. Despite the fact that treatments are available, over 50% of adults with atopic dermatitis still face concerns about long-term use, and over 50% have found a treatment to be ineffective [13]. Compared to the time of symptom onset, nearly half (48%) of atopic dermatitis patients report that at the present time, symptom severity even has worsened. Nearly two thirds (64%) report that more areas or different areas are affected; 49% indicate that frequency of flares is worse than at onset [13]. In modern times, many studies have been done about new treatment methods of this disease, and the microbiome of the skin has recently been shown to play an important role in the etiology of atopic dermatitis, as the microbiome functions as a regulator of innate and acquire immunity [21,22]. Studies have shown that the skin of atopic dermatitis patients is characterized by a high colony-formation rate of staph. aureus and reduced indigenous bacteria (Staphylococcus, Corynebacterium, Cutibacterium, and Proteobacteria) [21,22]. It has also been suggested that the diversity of the microbiome may correlate with the severity of atopic dermatitis [23].

Therefore, strategies to treat atopic dermatitis by regulating the skin microbiome (correcting dysbiosis) and replacing specific microorganisms are being investigated. Several studies suggest that gut microbiota may influence atopic dermatitis by immune system regulation, and many of them have very promising and positive results.

In humans, the intestinal microbiota is necessity for stimulating, educating and sustaining the immune system's equilibrium [41]. It is estimated that there are more than 1000 species-level phylotypes in human intestinal environments [42], of which Bacteroidetes and Firmicutes account for 90 percent [43]. As researchers study the links between gut microbiota composition and susceptibility

to disease, as well as how commensal microbiota and their metabolites affect human health, they are being spurred on to investigate targeted microbiota-based therapies [44].

FMT was evaluated for the first time in humans at Tel Aviv Medical Center for adults with moderate to severe AD. The results showed a marked improvement from baseline in signs and symptoms of AD. Following each FMT, the average Scoring Atopic Dermatitis value decreased significantly at week 4. In the total of 9 participants, there were 7 and 6 patients achieved reduction of 50 % and 75 % at week 18 (after 8 weeks since the last FMT), respectively.

However, two of the patients experienced quick relapse after treatment. The clinical results were hampered by the limited sample size, the lack of double-blinded design, and other factors that had to be taken into account [40,45]. Oral microbiome regulators are under development, with several being tested in phase I trials. The following describes these topical formulations. Staphylococcus hominid A9 (ShA9) a bacterium isolated from healthy human skin, has been shown in animal studies to have two activities: killing staph. aureus and inhibiting the production of staph. aureus derived toxins [24]. In a phase I/II study, ShA9 was applied twice daily for seven days in patients with moderate to severe atopic dermatitis, who were tested positive for staph. Aureus colony formation. The result showed that Sh9A reduced staph. aureus colony formation and improved. Nitrosomonas eutropha (B244) is a bacterium that produces nitric oxide [26]. Nitric oxide is an important mediator with potential anti-inflammatory effects, and thus, has therapeutic potential for atopic dermatitis [25]. In a phase II study in adults with atopic dermatitis, B244 administered as a spray significantly improved pruritus. A phase II study on B244 is also currently underway.

Widya Mandala Catholic University's department of dermatology and venerology (Indonesia) has published an article about "Gut-skin axis modulation via fecal microbiome transplant: An ecological approach for atopic dermatitis treatment". They made the article by reviewing publications related to fecal microbiome transplantation and atopic dermatitis in order to further elaborate its potential use in the management of atopic dermatitis. Fecal microbiota transplantation is a recently developed gut microbiome reconstruction procedure, which allows long-lasting reintegration of certain microbiome in the gut [26,27]. There are several methods to administer the donor derived FMT microbial filtrate and oral capsule is a new preparation which offers non inferiority compared to other methods [51]. FMT has an immunomodulatory action and is an FDA approved treatment [52]. It has been vastly investigated for other conditions such as autoimmune disorder, metabolic disease, and neurologic conditions [53].

FMT effectively alters the gut microbiome profile and furthermore modulates the immune regulation. There is a growing body of evidence in the use of fecal microbiome from healthy persons thus restoring gut microbiome balance. The restoration of microbiome homeostasis leads to the restoration of the systemic and gut-skin-axis immunomodulation. FMT has demonstrated its efficacy in conditions such as recurrent clostridium difficile infection, autoimmune disorders, and Crohn's disease, which is strongly correlated to atopic dermatitis. This article was reviewing the potential use of FMT to regain the gut-skin-axis balance for treatment of atopic dermatitis. Results of a large cohort study revealed that the gut microbiome of infants suffering from atopic dermatitis, had a higher colonization of e. coli and clostridium difficile, than in infants without atopic dermatitis [54]. Both these microbiomes induce eosinophilic inflammation and are associated with atopic dermatitis [55]. Although the presence of staph. aureus strain on the skin induces atopic dermatitis exacerbation, its

presence in the gut early in life may promote the maturation of the immune system and is inversely correlated with the incidence of atopic dermatitis [56,57]. Skin barrier of atopic dermatitis patient is further compromised due to gut dysbiosis evoked itch [58] and increased reactivity toward oxidative stress [59].

Oral capsule FMT allows alteration of microbiome profile to become similar to that of microbiome profile to become similar to that of the donor in adult patients with moderate to severe atopic dermatitis. Some subjects responded immediately after the first FMT while others improved after few weeks. With the administration of FMT, microbial engraftment occurs rapidly with recipient gut microbiome composition resembling that of the donor within 3 days post procedure. This composition was related until the 4-month, follow-up and was accompanied by amelioration of CDI symptoms [60]. Study done on animals also demonstrated the efficacy of oral capsule FMT in improving gut microbiome diversity, producing clinical improvement, and increasing skin barrier on dogs [61]. Not only does it exhibit clinical improvement, oral capsule FMT also reduces the risk of developing atopic dermatitis on dog [62].

The question is how gut microbiome restoration improves atopic dermatitis? Transplantation of the gut microbiome leads to greater alpha diversity with microbiome profile similar to that of the donor within the first week. The gut microbiome is essential in the differentiation of naive T cells into Th1, Th2, Th17, or Foxp3+ Tregs. Tregs terminates the proliferation of faulty T cells into Th cells and impede inflammatory activities of mast cells, eosinophils and basophils. Th cells also inhibit IgE production and induce IgG4 production [27]. FMT helps regain Th1/Th2 balance via Treg signaling. The concentrations of Th2 cytokines (IL-4, IL-5, and IL-13), which plays a role in the development of AD, were significantly decreased. On the other side, concentrations of Th1 cytokines, such as IL-12, IFN-γ, and TNF-α were significantly increased. Tregs secreted cytokines (i.e., IL-10 and IL-1β) were significantly lower. Serum levels of IgE and concentration of calprotectin were significantly decreased at the 8th week. This finding is concomitant with significantly lower dermatitis scores. This finding is also in line with a study done on off-spring of mouse models previously given gut microbiota which were then given oxazolone to induce AD. This study found a strong association between gut microbiome, clinical inflammation, and Treg cytokines production by the macrophage (IFN-γ, TNFα, IL-1 β, and IL-6). Off-spring of this mouse models demonstrated gut microbiome profile enriched with Firmicutes and Lactobacillus spp and had milder AD upon induction with oxazolone. Fecal gut bacteria donor specimen from a mouse exhibiting high AD response upon oxazolone induction showed a higher abundance of the genus Bacteroides, in which Bacteroides fragilis is proven to exert anti-inflammatory and contributes to development of host immunity [28,29].

Results of one study indicates the importance of microbial relative abundance and a higher ratio of donor to recipient relative species abundance in determining the success of microbial transplant in FMT. Microbial investigation in the first week post-transplant was characterized by abundance of both recipient's pre-existent microbiome and the donor transplanted microbiome. Over the subsequent 10-12 weeks, donor microbiome stably persisted while recipient pre- existent microbiome abundance continued to decrease. Data sets presented in this study suggested that gut microbiome genera such as Bacteroides, Blautia, Coprococcus and Eubacterium that are persistently identified in healthy individuals are frequently transplanted in rCDI patients in great relative abundance [32].

On the other hand, there is a study demonstrating correlation between strain persistence and engraftment in which microbiome strains that are persistently found in the gut of healthy persons and donors has a preeminent rate of engraftment in the recipient. Analysis of these microbiome strains showed high ecology competitiveness and fitness which is pivotal in order to compete against dysbiotic microbiome found in the gut [33]. The importance of strain fitness in gut colonization is also explained by a concept which described the tenacity of Bacteroides species as part of the host microbiome, in which the species was acquired by vertical transmission through birth and was persistently found as part of the host microbiome regardless of antibiotic use [34]. Owing to the great influence of the microbiome fitness in the success of transplant, each microbiome capacity to colonize against pathogens found in dysbiotic ecology [35] and endurance against ecological disturbance [36] must be taken into account, perhaps through an ecological identification of fitting microbiome [37].

A metagenomic gut microbial analysis suggests that microbiome fitness, which is estimated by their widespread presence over the gut, is a better predictor of colonization success compared to microbiome abundance from the donor. This finding demonstrated the potential role of adaptive rather than neutral ecological colonization processes in microbial transplant establishment. High fitness microbiome, which were able to globally colonize the gut, demonstrated a metabolic ability to biosynthesize seven of nine essential amino acids and a higher capacity to biosynthesize cobalamine, riboflavin, and tetrahydrofolate. Further analysis demonstrated that these microbiomes are [38] also capable of modulating the bioproduction of pantothenate, thiamine, biotin, and folate which are known to convey host microbiome interaction [39]. Low fitness microbiome also exerts these biosynthesis capacities, although in a rather low magnitude [38].

For patients suffering from AD, FMT might be a safe and efficacious therapeutic intervention. Further explorations are required to confirm the immune response, gut metabolites, and adverse effects in clinical studies. There is a disruption in the gut barrier among AD patients, which makes them more vulnerable to the risks of FMT. The development of alternative GM-targeted therapies by combining appropriate microorganisms or microbial metabolites may therefore be a rational approach for treating AD in the future. As more research solidifies its efficacy, FMT could become a game-changer, not only as an alternative but also as a complementary therapy to conventional treatments. Unlike immunosuppressants or biologics, which can be costly and come with potential side effects, FMT offers a more natural way to restore immune balance by addressing gut dysbiosis - one of the underlying contributors to atopic dermatitis. One of the key advantages of FMT is its cos-effectiveness compared to many biologic treatments currently available for atopic dermatitis. while biologics can be expensive and require long-term administration, FMT has the potential to offer lasting benefits with fewer application. This budget-friendly nature makes it an attractive option, especially in healthcare systems looking for sustainable and accessible treatment methods. However, before FMT can become widely available, certain priorities must be addressed. Standardization of procedures, rigorous safety protocols, and regulatory frameworks need to be established to ensure safe and effective use. Additionally, public awareness and education will be crucial in overcoming potential skepticism about the procedure. If these challenges are addressed, FMT could pave the way for a new era in dermatology, providing atopic dermatitis patients with a more holistic and long-lasting treatment option. Given its potential benefits, we hope to see FMT introduced in Georgia soon. As a budget-friendly and highly effective treatment, its integration into dermatological practice could

greatly improve patient outcomes while also reducing the financial burden on both individuals and the healthcare system. With continued research and support, FMT may soon become widely accepted and accessible therapy, offering hope to those struggling with chronic skin conditions.

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MARIAM ZATIASHVILI, TAMAR TABATADZE, MAIA MATOSHVILI, NINO ADAMIA, LAVRITA PACHUASHVILI, TAMAR ARAKHAMIA, MANANA KOBAKHIDZE, ANKA KOBAKHIDZE

ATOPIC DERMATITIS IN THE ERA OF INNOVATIONS

(Reviewing and exploring modern research and literature on treatment of atopic dermatitis with microbial transplantation)

M.Iashvili Childrens Central Hospital, TSMU

SUMMARY

Atopic dermatitis is a chronic inflammatory skin disease with growing global prevalence, affecting both children and adults. It is characterized by immune system dysregulation, skin barrier dysfunction, and a complex interplay between genetic and environmental factors. Conventional treatments, such as topical corticosteroids, calcineurin inhibitors, and biologics, focus on symptom management but do not agree the underlying causes. This has led to an increasing interest in alternative approaches, including microbiome-targeted therapies. Fecal microbiota transplantation (FMT) has emerged as a novel therapeutic strategy for atopic dermatitis by restoring gut microbiota diversity and modulating immune responses through the gut-skin-axis. Recent studies suggest that dysbiosis plays a crucial role in atopic dermatitis pathogenesis, contributing to systemic inflammation and disease severity. FMT has shown potential in improving atopic dermatitis symptoms by rebalancing gut microbiota, enhancing regulatory immune pathways, and reducing inflammatory cytokine production. Clinical trials have demonstrated promising efficacy, but challenges remain regarding standardization, donor selection, and long-term safety.

This review explores the epidemiology of atopic dermatitis, the immunological mechanisms of FMT, and its potential as a cost-effective treatment. Given its affordability and potential long-term benefits, FMT could provide an accessible alternative to expensive biologic therapies. With further research and regulatory advancements, integrating FMT into dermatological practice could offer a transformative solution for atopic dermatitis management, improving patient outcomes and reducing the burden on healthcare systems.

Keywords: atopic dermatitis, innovations, literature review