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Microbiome in Aesthetic and Dermatology. The role of prebiotics, probiotics, and synbiotics.

Vasiliki Kefala[1], Foteini Biskanaki[2]

[1]Aesthetician Cosmetologist, Pharmacist Professor, Laboratory of Dermatology-Aesthetics-laser applications (lablad), Sector of Aesthetics and Cosmetology, Department of Biomedical Sciences, Faculty of Health Sciences and Welfare, University of West Attica, Campus 1, Athens .Greece

[2]Aesthetician Cosmetologist MSc, PhDc, Academic Scholar, Laboratory of Dermatology-Aesthetics-laser applications (lablad), Sector of Aesthetics and Cosmetology, Department of Biomedical Sciences, Faculty of Health Sciences and Welfare, University of West Attica, Campus 1. Athens, Greece

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Summary. The skin supports a delicate ecosystem of microbial elements. Although the skin acts as a barrier these microbes interact with the internal environment of the body, disturbing the balance resulting in the appearance of several dermatologic diseases. Understanding the changes in the microbial flora of our skin is enabled to heal the problem and restore balance. There is a recent increase in the popularity of holistic and natural such as prebiotics, probiotics, symbiotic. Studies are being made to find alternative treatments to treat skin disorders through manipulation or supplementation of the microbiome.

INTRODUCTION

The skin, as human body's largest barrier, has natural and chemical defenses to protect the body from pathogens. Surprisingly, the skin lives in harmony with a huge ecosystem of bacteria, viruses, fungi, mites, and the archaea - the skin microbiome. A skin microbiota is defined as the sum of the microbial cells of a region, while a microbiome includes cells and their genetic. The term microbiome began to be used in 2001, and its study began in 1680. However, many questions are raised about its relationship with the human body: What is their purpose? How do they colonize? How do they affect the disease course?

The advent of next-generation DNA sequencing allows the isolation and identification of the constituents of the microbiome to the extent that has so far been impossible with existing culture techniques. (1-5)In the bacterial kingdom, 850 taxonomic units of 36 phyla were identified by sampling at different parts in the skin. (1) In the fungal kingdom, only 80 genera were found in the plantar heel (2). The microorganisms thatfound in different areas of the body, categorized as dry, moist, or sebaceous moist, or sebaceous.

Diversity in the skin microbiota have also been associated with differences in host factors such as age, diet, gender, geographic region, and climate (3-5). Competition between microbial species offers beneficial effects to the human host. For example, Staphylococcus epidermidis - the most common germ that is isolated on the skin not only coexists with the skin but also helps the immune system and, in response to

Corresponding author: Foteini Biskanaki, PhDc University of West Attica, Peloponnisou 14, Ag. Anargyroi GR-13562, Athens, Greece.
E-mail: fani.biskanaki@gmail.com

Send reprint requests to: Dr Helen S. Plessa, 9A Kanari Str., GR-15239, N. Penteli, Athens, Hellas, E-mail: pharmakonpress@pharmakonpress.gr, Tel. + 30210-9756332

upregulating protective virulence factor proteases against endogenous antimicrobial peptides. In addition, bacteria produce peptide toxins and free fatty acids that prevent the growth of other pathogenic organisms, such as Staphylococcus aureus and A Streptococcus (S pyogenes).(6-8)

Another common innocuous bacterium, Corynebacterium jeikeium, produces bacteriocin-like antimicrobial compounds and scavenges for nutrients, thus preventing colonization by other competing species. Corynebacterium jeikeium also produces superoxide dismutase, which protects bacteria from superoxide radicals while protecting the skin of the area from oxidative damage (4). Other bacterial effects may alter the function of the immune system by activating signaling pathways within cells. For example, some staphylococcal species produce Lipoteichoic acids. Lipoteichoic acid (LTA) is a major constituent of the cell wall of gram-positive bacteria. Lipoteichoic acids have been found to reduce inflammation by activating the Toll-like receptor (TLR) pathway in keratinocytes which then inhibits the TLR3 pathway which is an initiator of the inflammatory response in the skin. (9-11) Due to the complex relationship of the organism and its habiting microflora, changes resulting from endogenous or exogenous factors, such as modern diet and hygiene practices, and their role in dermatologic disorders are studied (5).

Dysbiosis (also called dysbacteriosis) is a term for a microbial imbalance or maladaptation on / or inside the body. In the skin, dysbiosis has been studied for its effects on psoriasis, atopic dermatitis, acne, and rosacea. There are also a small number of studies focused on seborrheic dermatitis, body odor, and wound healing.

The relevance of the skin microbiome to alternative and complementary medicine in the poorly defined regulatory categorization of products and therapeutics aimed at altering, destroying, and / or restoring these commensurate organisms. Categories of therapeutic modalities targeting the microbiome:
1. Prebiotics
2. Probiotics
3. Bacteriophages
4. Transplantation

Prebiotics, Probiotics, Bacteriophages, Transplantation are usually included in functional foods or natural and complementary medicinal treatment groups because they are "naturally derived." Due to the wide range of action in prevention and treatment, their regulatory categorization remains unclear. (8,9) As global demand for these products continues to grow, the need for standardized regulatory categorization will be a necessary step towards the development of this industry. For example, Canadian probiotics are considered natural health products while in the USA they may fall into several categories such as dietary supplements, drugs, medical food, live biotherapeutic agents and biologic agents, depending on the product claim and use. (9) As these products continue to grow worldwide, standardized regulatory categorization is needed.

THE MICROBIOME AND HEALTY SKIN

Cultivation of the microbiome begins at birth and changes over time. Vaginal microorganisms, such as Lactobacillus, Prevotella and Sneathia, predominate in normal-born neonatal skin. In contrast to the skin flora of infants born by cesarean section, Staphylococcus, Corynebacterium and Propionibacterium are identified which resemble the composition of adult skin. (10) The relationship between host and commensal bacteria is established early in the postnatal period through the education of regulatory T cells. T cells are important for immune homeostasis in peripheral tissue. From the first week of life, a large number of regulatory T cells reach the epithelial barriers and develop tolerance to the microbes that reside there. The long-term effects of the mix of microbes acquired at birth have long been studied in relation to the gut microbiome, where the cesarean process is associated with a higher risk of developing autoimmune or inflammatory disorders such as celiac disease, type I diabetes, and asthma.

Four dominant phyla of bacteria are conserved among adult individuals:
1. Actinobacteria
2. Proteobacteria
3. Firmicutes
4. Bacteroidetes

The variability of the microbiome comes from less representative bacterial species. The skin is a determining factor in the diversity of bacterial communities. The skin contains three major ecologic environments: dry (eg, forearm), moist (eg, axilla), and sebaceous (eg, scalp).
Each microorganism thrives in this different environment: Staphylococcus and Corynebacterium colonize in moist areas that are occluded, because they prefer high humidity habitats. Propionibacterium, lipophilic bacteria

tend to colonize sebaceous areas. (8,11) In a 4 to 6 month study, dry environments were found to have a greater change in composition, while moist environments were typically stable (4,11) Composition can also vary greatly during different; for example, during there is an increased level of lipophilic bacteria due to an increase compared with the adult state described earlier. The composition may also vary significantly during different life stages eg puberty has an increase in lipophilic bacteria due to increased sebum production. (6)Secondary influencing factors are environmental factors, occupation, diet or hygiene habits (6,12)

The percentage of bacteria is an important factor in determining the skin as healthy. However, because the microbiome is a living ecosystem that interacts with the cutaneous immune system, interactions between host and bacteria determine a person's health.

PSORIASIS

Psoriasis (a disease of unknown etiology) affects 1% -3% of the population. Possible causes are genetics, age, comorbidities, trauma, and environmental factors. It is characterized by epidermal hyperproliferation, hyperkeratosis, dermal inflammation, and thickened angiogenesis, scaly plaques. (13,14) Studies of the relationship between the skin microbiome and psoriasis show imbalance in the distribution of microbacteria. (7, 14) In psoriatic lesions Propionibacterium and Actinobacteria species had a lower representation while Firmicutes, Proteobacteria, Acidobacteria, Schlegelella, Streptococcaeae, Rhodobacteraceae, Campylobacteraceae and Moraxellaceae species were overrepresented. (4,15) The differences - in the composition of cutaneous flora - are associated with secretion of antimicrobial peptides - cathelicidins and human β defensins - secreted by keratinocytes in psoriasis. Psoriasis has a reduced risk of skin infection (14,15)

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disorder. It appears in childhood with asthma, allergic rhinitis and conjunctivitis. (17) AD has a complex pathophysiology and clinical phenotype accompanied by changes in barrier function and strong Th2 response to environmental antigens. People with genetic origin of AD exhibit abnormalities to skin barrier function, such as loss of the role of (18) the skin microbiome. Abuse of hygiene products modifies immune tolerance. Skin microbiome in child's skin has an important role immune system development. (19) Differences in skin microbiome are associated with predisposition to AD in the antecubital and popliteal folds. (20). Barrier permeability alteration may play a role (10). The role of the intestinal microbiota in the pathogenesis of AD has been recently investigated but remains unclear. (21)In AD, modification of the skin microbiome increases susceptibility to S.aureus colonization and increases S epidermidis colonization. (19,22) In AD, an altered skin microbiome may increase susceptibility to S aureus. (23,24)If properly treated, the healthy skin microbiome is regenerated. (19)Recent studies indicate that AD worsens when there is lower skin bacterial (25)Traditional AD treatment with anti-inflammatory and antimicrobial medications has been associated with greater microbial diversity, specifically increasing in populations of Streptococcus, Corynebacterium and Propionibacterium. (10) Among traditional therapies, the effect of narrowband UV therapy indicates an increase in microbial diversity. (30)

ROSACEA

Rosacea is a chronic inflammatory condition of the blood vessels and pilosebaceous facial units that commonly presents with flushing, blushing, and sensitive skin. The role of the microbiome in the pathogenesis of rosacea is related to Helicobacter pylori, S epidermidis, Chlamydia pneumonia, Bacillus olenorium and Demodex mites (17). However, it cannot be considered a causative agent. Patients with Rosacea develop TLR2 abnormalities in the skin. This leads to abnormal production of cathelicidin antimicrobial peptides and increased expression and activity of serine protease kallikrein. (27,28) Demodexfolliculorum is a commensal mite that is found in almost all people. The mites colonize throughout the body, but they prefer areas with sebaceous glands because they can use sebum as a food source. Demodexfolliculorum is found in Subtype II rosacea in patients up to five times the amount of healthy patient skin. Demodex mites are implicated in other skin lesions. Specific to rosacea, Demodex mite acts as a vector for Bacillus olenorium bacteria. It is hypothesized that the mites cause the distention of the follicles to allow the bacteria to enter the innate immune system through the pilosebaceous unit, and a subsequent mononuclear cell proliferation and induction of neutrophils follows. (26-29)

ACNE

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units and occurs in sebaceous areas of the face, neck, chest, and back. Acne usually occurs in adolescence and is associated with increased androgens. Androgens affect cellular differentiation, proliferation, lipogenesis, and comedogenesis in sebocytes and keratinocytes resulting from acne development. (30,31) Propionibacterium hydrolyzes triglycerides in sebum to produce free fatty acids which acidify and weaken the skin. Although the connection between P. acnes and acne vulgaris has long been acknowledged, further knowledge of the skin and follicular microbiome may challenge the importance of this relationship. Propionibacterium is a commensal organism in healthy patients and its presence alone cannot fully explain the pathogenesis of acne. In addition to P acnes, colonies of S epidermidis, Propionibacterium humerusii and Propionibacterium granulosum are also found in healthy and acne-prone individuals. Two strains classified as ribotype 004 and ribotype 005 were unique only to acne patients and may play a role in the pathogenesis of acne. (32) Sebum with the influence of endogenous and exogenous factors - such as diet and exposure to UVR - can change composition. Patients with acne show increased sebum production but its composition is modified resulting in a high amount of squalene peroxide and a small amount of vitamin E.

OTHER CONDITIONS

The role of the microbiome in body odor, and in particular in regard to axillary odor was studied in 1981.They were identified in the Staphylococcus arm (S aureus, S epidermis and S saprophyticus), Propionibacterium species, and Corynebacterium species. Of the above, only the possible Corynebacterium is thought to cause axillary malignancy as studies have elucidated the interaction between microbiota and the axillary microbiota.(33-35)Recent review determines the relationship between the axillary microbiota and biotransformation of secretions in the production of medium chain volatile fatty acids and thioalcohols responsible for axillary odor. (34) Studies on the effects of deodorants and antiperspirants on axillary bacterial communities indicate that their use alters the axillary microbiome. However, the consequences of these changes are unclear. (36-38)

PREBIOTICS, PROBIOTICS AND SYNBIOTICS

Ilya IlyichMechnikov (1845-1916) Russian zoologist and Nobel Prize winner in the early 1900s attributed the longevity of Bulgarian peasants to the consumption of lactic acid-producing bacteria found in yogurt lactic acid. This observation will serve as a basis for probiotics in health and medicine.

Probiotics are defined by the Food and Agriculture Organization of the United Nations and the World Health Organization as "living micro-organisms which, when administered in sufficient quantities, provide a health benefit to the person receiving them" (39). Therefore most studied probiotic strains are Lactobacillus and Bifidobacteria. There are many types of products available: fermented milk products from pills to powders to topical preparations.

Prebiotics began to be studied in the 1980s with references to the bifidogenic properties of inulin, oligofructose, fructooligosaccharides, and galactose and xylose-containing oligosaccharides. The term prebiotic was officially introduced in 1995. A prebiotic is defined as "a nondigestible food ingredient that benefits the host by selectively stimulating the growth and / or activity of one or a limited number of bacteria in the colon and thus improves health". (40) The most common prebiotic compounds are inulin-type fructans and galactooligosaccharides [inulin-type fructans and galactoligosaccharides]. Prebiotics are safe and economical, making them an alternative option to probiotics which is a combination of both pre- and probiotics has been found to provide a synergistic effect of synergistic effect on the gut microbiota. (41)

Data on the benefits to the body of oral prebiotics and probiotics come from gastroenterology literature Oral pre- and probiotics help restore the intestinal microbial flora, and thus have a positive effect on the immune system. Clinical manifestations of acute gastroenteritis, irritable bowel syndrome, necrotizing enterocolitis, inflammatory bowel disease, and constipation are improved. (41-48) Studies indicate that probiotics may play a role in the prevention of colon cancer. (35-40)In dermatology, the use of pre-, pro-, and synbiotics in AD, acne, rosacea, and wound healing has been suggested. The management of the gut microbiome in psoriasis is important. Pre- and probiotics are promoted for cosmetic use and in skin maintenance and health, although scientific data on these uses are poor.

Atopic dermatitis

Most data on the use of pre-, pro-, and synbiotics in dermatology come from studies conducted in AD. Pre-, pro-, and synbiotics have been found to affect the immune system through modulation of the Th1 / Th2 axis and T-regulatory lymphocytes in the gut. They may have an effect on the gut barrier when exposed to allergens involved in allergic conditions such as AD. A search of the literature on the use of pre-, pro-, and synbiotics in the treatment and prevention of AD has yielded 13 English language meta-analyzes and countless other reviews (49-56) The most recent meta-analysis focused specifically on the use of synbiotics for the prevention and treatment of AD. Several evidence has been found to support the pre-, pro-, and synbiotics were less favorable and do not support the use of probiotics in the treatment of AD. A similar meta-analysis supports the early use of probiotics in the prevention of AD. The benefit of using pre-, pro- and synbiotics in the prevention and treatment of AD remains controversial. There is, however, evidence that pre-, pro-, and synbiotics may have a role in preventing AD when administered both prenatally and then after birth. Finally, similar treatment may exist in the treatment of pre-, pro-, and synbiotics in children and adults but not infants.

Acne

Although little is known about the clinical use of pre- and probiotics in the treatment of acne, their use in acne is a must. The main rationale for the use of pre- and probiotics in acne partly comes from the gutbrain-skin axis theory which shows a link among gut microflora, mental health, and inflammatory conditions of the skin. (57) The improvement of acne observed using probiotics is done through mechanisms:

a. Modulation of systemic insulin-like growth factor release

b. Selective reduction of P. acnes by specific bacterial species, such as Staphylococcus

c. Synergy of use with oral antimicrobials such as minocycline

d. Through modulation and optimization of skin barrier function and ceramide production. (58–63)

Rosacea

The causative pathogen of rosacea is multifactorial and recently included dysbiosis and small intestinal bacterial overgrowth. In a long-term follow-up study, 64.5% of patients with rosacea with small intestinal bacterial overgrowth were treated for 10 days of rifaximin and have reduced the symptoms of the disease for over 3 years. (64) The reduction of gut bacterial overgrowth in patients with rosacea is impressive use of synbiotics in children 1 year of age or older.

Another study reviewing the effects of both pro- and synbiotics in AD found similar results. (50) A decrease was observed in mean differences in SCORAD values in children aged 1 to 18 years, with no decrease in infants less than one year old. Decreases in mean differences in SCORAD values were also observed using synbiotics versus probiotics alone, using mixtures of bacteria versus single species, and treatment duration was greater than 8 weeks when treating moderate to severe AD versus patients with mild atopy. Nine of the 25 studies reported gastrointestinal disorders while no serious adverse events were reported. Findings from other meta-analyzes of and may in the future be the use of pre-, pro-, and synbiotics as a new and effective alternative to antimicrobials. In one case a report of a rare form of scalp and ocular rosacea treated successfully with a combination of doxycycline and probiotic therapy (65)

Wound healing

Published studies on the use of probiotics in cutaneous wound healing are limited, but preclinical data are promising. Animal studies (five topical and one oral route) showed that the administration of probiotics was effective and accelerated the healing of skin wounds at an early stage. (66) In this review, sterile kefir extracts, containing filtered supernatants of kefir culture fermentation, proved to be more effective than bacteria and yeast.

Cosmetics

The antiaging benefits of probiotics have been emphasized since the time of ElieMétchnikoff (1845-1916). The demand for "natural" remedies has led the booming cosmetics market to develop microbiome-based cosmetic products. Cosmetic companies are promoting the benefits of their technologies, many of which promises to restore and maintain the "natural skin microbiome" in order to improve skin barrier integrity and promote healthier and better skin quality and texture.

However, there are insufficient studies to support these claims. However, probiotics have been found to have antioxidant properties that are capable of reducing the damage caused by ultraviolet radiation, promoting skin hydration and dermal thickening.

Recently, a team from Korea found that consumption of Bacillus licheniformis (a probiotic isolated from traditional Korean food products)

could enhance the longevity of the nematode Caenorhabditis elegans (67-69). This animal model is the first to determine the antiaging benefits of probiotics, but its effect on humans has not yet been demonstrated.

Phage therapy

Global concerns over increased antibiotic resistance have led to a revival of interest in in phage therapy. Bacteriophages (phages) are viruses that infect bacterial cells. Bacteriophages (phages) reproduce rapidly, carry DNA and cause cell lysis. (70) Because of these properties, they are considered to be a useful tool for altering or restoring the microbiome balance or enhancing the effectiveness of antimicrobials in the treatment of bacterial-based dermatologic diseases.

When the hosts reach the phages, they are directed to specific sites, unlike traditional antimicrobials, and replicate to the required amount based on the bacterial population. Phage therapy was introduced in Georgia, Russia, France and Poland in the early 1900s for the treatment of infectious diseases such as dysentery, shigellosis, and typhoid. However, it did not prevail as a cure for deficiency appropriate clinical trials of the success of antimicrobials. It is still considered an experimental procedure. (71-74) Phages, although not prophylactic, fall under the purview of a "live microorganism," which confers an advantage to the host. Studies of in vitro models in the context of acne promise much. (71) Phage therapy is also being investigated for the treatment of ulcers, burns and skin infections.

In vivo there are positive results. Specifically phage- and antibiotic-loaded creams and bandages and antibiotics were applied externally to the affected skin. Care of wounds against bacterial infection is currently practiced in Georgia. (70, 73) However, there are many limitations due to the lack of confirmatory studies. As with all treatments, there will inevitably be levels of resistance to treatment. One potential mechanism of resistance is “pseudolysogeny,” in which the phage genome does not integrate into the bacterial genome and does not cause lysis. (74)

CONCLUSION

As the technology that isolates microbes improves, it is easier to understand the pathogenicity of the dermatological disorders and the therapeutic potential of the microbiome. Understanding the mechanisms that change during a disease course will elucidate how the microbiome composition in problematic areas needs to be changed and what pre-, pro-, or synbiotic therapies can be used to achieve normal composition. Pre-, pro- or co-biotic treatments can be used to achieve normal composition. Also in wound healing, or in preventative use against oxidative damage and UV protection, the microbiome can be modified to use the advantageous aspects of certain microbes. Because the intestinal microbiome is also involved in certain disorders, in addition to the role of the skin microbiome, there are more modes of transmission of pre-, pro-, and synbiotics and bacteriophages possible to pro-, pro-, syn- and bacteriophages. The advancement of knowledge in this field opens up a wide range of complementary and alternative therapeutic options to the treatment of dermatologic disorders.

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