Review Article

Skin microbiome dysbiosis in leprosy cases

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Received: 19 July 2021
Accepted: 16 August 2021

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ABSTRACT

The human skin possesses a microenvironment conducive to the growth of the skin microbiome, which plays in many physiological functions in cutaneous immunity homeostasis and maturation. The microbiome composition depends on many variables, such as endogenous (host condition) or exogenous (environmental) factors and topographic location. Host-skin microbes' interaction can be mutualism or pathogenicity. Dysbiosis or alteration in skin microbiota is associated with various dermatological diseases, including leprosy. Dysbiosis is driven by the alteration of the microbial communities themselves or due to the intrinsic features of the host. Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* targeting the nerves and skin, leading to loss of sensation on the skin, with or without dermatologic lesions, and correlated with long term consequences, such as deformities or disability. Microvascular dysfunction and significant alterations in capillary structure due to invasion of *M. leprae* lead to altered hydration levels of the skin caused by disruption of blood flow; which changes the resident microbial community structure. The skin microbiome composition differences in leprosy patient's skin lesions were observed; skin microbial diversity in the leprosy patients was lower than in healthy individuals. The diversity reduction was observed in freshly diagnosis leprosy patients, those at various stages of MDT, and post-MDT; indicated that both the interaction between skin microbial community and *M. leprae* or the ongoing therapeutic regimen impacted the skin microbiome variation.

Keywords: Leprosy, Skin microbiome, Dysbiosis, Microbial variation

INTRODUCTION

Skin is one of the largest organs in the human body that acts as physical, immunological, chemical, radiation, and free radical protection. The skin provides a conducive microenvironment for a large number of microorganisms' growth. One square centimeter of the skin contains one billion microorganisms. As the outer layer of the human body, the skin is continuously exposed to many different endogenous and exogenous factors which impact the skin homeostasis and potentially leading to inflammation. Microbial diversity and colonization alteration caused by specific microorganisms can contribute to pathologic conditions.[1] Associations between changes in the skin microbiota with different types of skin disorders, including leprosy, have been observed in many recent studies. Skin inflammatory reaction in leprosy induced by the *M. leprae* presence on the skin impacts the dysbiosis process of skin microbial. Further understanding is needed to assess the causality correlation between skin microbiome with the incidence of leprosy or use of MDT.

LEPROSY

Leprosy/Morbus Hansen (MH) is a chronic granulomatous disease caused by *Mycobacterium leprae* targeting the nerves and skin, leading to loss of sensation on the skin, with or without dermatologic lesions, and correlated with long term consequences, such as

deformities or disability. Leprosy transmission is poorly unknown. Although the inhaled droplets containing the causative agent is thought to be the main transmission pathway, skin contact transmission or other transmissions can still not be excluded. The incubation period of leprosy ranging from 2-20 years. Up to ninety-nine percent of patients exposed to *M. leprae* did not develop leprosy; host immunity plays an essential role in the disease development.[2,3]

Diagnosis of leprosy can be made by finding one (at least) of the cardinal signs, including: (1) Hipo-or anesthetic hypopigmented or reddish skin patch; (2) Enlarged or thickened peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve; (3) Acid-fast bacilli presence in a slit-skin smear. Histopathologically, skin lesions of leprosy patients are characterized by a preponderance of high CD8+ T cells and bacterial load, a flattened epidermis, and without granuloma formation.[4]

Based on WHO classification, leprosy is classified as paucibacillary (PB) or multibacillary (MB). Paucibacillary is a leprosy case with 1-5 skin lesions, without the presence of bacilli in a skin smear. Multibacillary have >5 skin lesions; or with nerve involvement; or with the demonstrated bacilli presence in a slit-skin smear, regardless of the number of lesions.[3]

Based on its clinical spectrum, leprosy is classified as tuberculoid, lepromatous leprosy, and a borderline group between these two polar forms. Tuberculoid leprosy (TT) presents erythematous or hypopigmented lesions with large size, raised margins, clear demarcation, and scaly presentation. Borderline tuberculoid (BT) presents as target appearance macules; with more lesions than TT and usually on one side. Mid-borderline (BB) is most closely emulating BT leprosy or border-lepromatous with its appearance of "punched out" macules with the central anesthetic area. Borderline lepromatous leprosy (BL)

appears as erythematous macules/nodules/papules with no distinct delineation of the lesions on the body, but there are still normal patches found. Lepromatous leprosy (LL) is progressed with body hair loss, enlargement of earlobes nodular, and mucosal invasion. The indeterminate type appears as erythematous/hypopigmented macule with hipo-or total anesthetic without bacilli finding in slit-skin smear.[5]

Nerve involvement in the early leprosy progression presents as a general hipo-or loss sensation in lesions. The neurologic manifestation can be found as: (1) Loss of sensation defined by hypo- or total anesthesia on the territory of the nerve; (2) Motor dysfunction, as in the case of interosseous muscle hypotrophy; or (3) autonomic alteration, as with skin sweating deficit.[2] Schwann cells in the peripheral nerves are primarily infected by *M. leprae*, leading to the disabilities development and progression.

Although leprosy is a chronic disease, there can be acute episodes of clinical inflammation, known as leprosy reaction. This condition poses a serious problem due to high morbidity even after the completion of treatment. This leprosy reaction is classified as type I (reversal reaction/RR) and type II (erythema nodosum leprosum/ENL) reactions. Type I reaction occurs in borderline patients (BT, mid borderline, and BL) caused by delayed-type hypersensitivity response to *M. leprae*. Whereas ENL occurs in BL and LL forms; related to the immune complexes deposition and elevation of TNF-α, IL-1β, IFN-γ, and other cytokines levels.[4]

Leprosy is treated with multi-drug therapies (MDT) of rifampicin, dapsone, and clofazimine. The MDT regimen is adjusted according to the type of disease (PB and MB). MDT is packaged in blister packs for four weeks' treatment. The effectiveness of MDT has been proved by its role in the elimination/ reduction of leprosy and the acceptability of the patients.[6]

Tabel 1: Clinical features of leprosy.[4]

Variables	Tuberculoid	Borderline tuberculoid	Mid-borderline	Borderline lepromatous	Lepromatous leprosy
Number of lesions	1-3	≤10	10–30	>30, asymmetrical	Innumerable, symmetrical
Size	Variable, usually large	Variable, some are large	Variable	Small, some can be large	Small
Surface changes	Hypopigmented	Dry, scaly, look bright, and infiltrated	Dull or slightly shiny	Shiny	Shiny
Sensations	Absent	Markedly diminished	Moderately diminished	Slightly diminished	Minimally diminished
Hair growth	Nil	Markedly diminished	Moderately diminished	Slightly diminished	Not affected initially
Skin smear	Negative	Negative or 1+	1–3+	3–5+	Plenty, including globi (6+)
Lepromin test	Strongly positive	Weakly positive	Negative	Negative	Negative

Table 2: Multi-drug therapy for paucibacillary (PB) type.[6]

Drugs	<10 years	10-15 years	>15 years	Note
Rifampicin (mg/month)	300	450	600	Taken in front of an officer
Dapsone (mg/month)	25	50	100	Taken in front of an officer
	25 mg/day	50 mg/day	100 mg/day	Taken at home

Duration of therapy: treatment is given in 6 doses during 6-9 months.

Table 3: Multi-drug therapy for multibacillary (MB) type.[6]

Drugs	<10 years	10-15 years	>15 years	Note
Rifampicin (mg/month)	300	450	600	Taken in front of an officer
Dapsone (mg/month)	25	50	100	Taken in front of an officer
	25 mg/day	50 mg/day	100 mg/day	Taken at home
Clofazimine (Lamprene) (mg/month)	100	150	300	Taken in front of an officer
	50 mg twice a week	50 mg once every 2 days	50 mg/day	Taken at home

Duration of therapy: treatment is given in 12 doses in 12-18 months

SKIN MICROBIOME

Human skin consists of millions of bacteria, fungi, and viruses that compose the skin microbial, which plays in many physiological functions in cutaneous immunity homeostasis and maturation. Microbiome is the collective genome of the microorganisms; moreover, the skin microbiome is defined as the genome of the microorganisms present on the skin. The skin microbiome plays an essential role in the cutaneous innate and adaptive immune system modulation. Meisel et al identified that the expression and modulation of 2820 mice's genes in response to microbial colonization showed roles in cytokine/complement cascade and the T cells signaling.[7] Interaction between the acidic metabolites produced by skin-resident bacteria, sweat's lactic acid, and from the free fatty acids derived from lipase-mediated of hydrolysis phospholipids during cornification contribute to surface's acidic pH; pathogens cannot tolerate this low pH condition.[8]

Bacteria dominate the composition of skin microbial. At least 19 phyla are known; most of the identified genera are *Propionibacterium*, *Corynebacterium*, and *Staphylococcus*. Although the proportions are minor, fungi, viruses, and mites are also important parts of the skin microbiota. Fungi only comprised <1% of the body's microbiota (except for the region around the ears and forehead). The primary fungi were *Malassezia* spp., with most commonly, *M. restricta*, *M. sympodialis*, *M. globose*. Most of the skin viruses are uncultivable and there still no consensus sequences that can be targeted by high input molecular methods; this made the skin viral microbiota more rarely investigated. However, recent studies detected on high diversity of eukaryotic DNA viruses, such as *Papillomaviridae, Polyomaviridae,* and *Circoviridae* various. Foulongne et al identified that in the superficial layers of the skin in most individuals, cutaneous beta and gamma human papillomaviruses (β and γ-HPVs) were commonly present.[9,10]

Skin microbiome change and develop over time. Skin colonization begins during the birthing process. The newborn skin microbiome is less diverse and simpler than adults. Dominguez-Bello et al., identified that different delivery modes impact the skin microbiome composition; which vaginally delivered newborn acquired bacterial resembling their mother's vaginal microbiota (dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* spp.), whereas the skin microbiomes of the cesarean section delivered newborns resemble that of adult skin (includes various *Corynebacterium*, *Staphylococcus*,and *Propionibacterium* species).[1,11]

Early neonatal skin colonization is essential to establish immune tolerance responses to commensal microorganisms. Scharschmidt et al, observed an abrupt inflow of highly activated regulatory T cells (Treg) into neonatal skin within the first 13 days of life. Interaction between commensal microorganisms and T cells shaped the adaptive immune responses to commensals. Several studies assumed that alteration of neonatal's skin microbiome composition might affect the established tolerance to many microbial antigens, increase the possibility of chronic inflammation risk.[12] Skin and nares microbiomes shift during childhood to adulthood transition; *S. aureus* was overrepresented in the nares of younger subjects; therefore, colonization of *S. aureus* induced cutaneous disorder was highly found in children and resolved in the adolescence/adulthood periods. During adolescence, an increasing in acne vulgaris incidence was observed. These might happen due to over colonization of commensal bacteria *Cutibacterium* caused by sebum over production. In older subjects, skin microbiome composition has been found to remain stable, although the age-related physiologic, such as alteration in

sebum/sweat production and changes in the function of the immune system, may affect the skin microbiome structure and composition.[13]

The microbiome composition depends on many variables, such as endogenous (host condition) or exogenous (environmental) factors, and topographic location. The age, site, and gender contribute to the variability of the microbial flora of the skin. For example, male and female cutaneous environments differences such as sweat, sebum, and hormone production play roles in skin microbiota. Different skin topography results in a different type of compositional variation; associated with moist, dry, and sebaceous microenvironments. Sebaceous sites (Glabella, external auditory canal, alar crease, occiput, back, and manubrium) were dominated by lipophilic *Propionibacterium* species, whereas *Staphylococcus* and *Corynebacterium* species thrive in humid/moist environments (Nare, axillary vault, interdigital webspace, antecubital fossa, inguinal and gluteal crease, umbilicus, popliteal fossa, and plantar heel). Dry sites such as the volar forearm, palm, hypothenar, and buttock consist of multiple phyla, such as *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteriodetes*. In contrast, fungal community composition, dominated by genus *Malassezia,* was similar across the core body.[14,15]

Exogenous environmental factors such as occupation, skin products and antibiotic usage, environment temperature, humidity, and UV exposure may modulate the skin microbiome colonization. For example, Ying et al. identified skin microbiome composition changes between urban and rural populations; caused by microbial sources differences (soil, water, indoor versus outdoor occupations, etc.). Rural subjects have significantly greater microbial composition variation than urban subjects. These might explain the differences in the prevalence of cutaneous disease in rural and urban populations; for example, the risk and prevalence of atopic dermatitis were higher in urban than in rural subjects.[16,17]
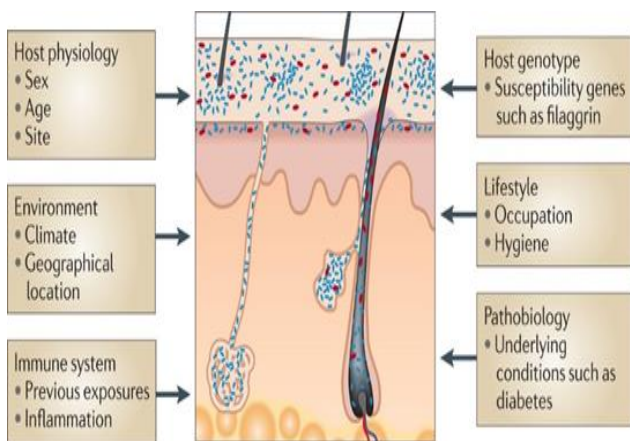
Figure 1: Factors contributing to variation in the skin microbiome.[14]

Skin microbes-host interaction can be mutualism or pathogenicity. Transitioning from commensalism to pathogenicity is a complex process. Host factors such as immunosuppression induce microbiome towards pathogenic behavior, whereas homeostatic conditions induce them towards mutualistic behavior; for example, *S. epidermidis* is biased towards mutualistic behavior such as amplify host immune defense against pathogens and help to maintain host immunity, whereas *S. aureus* displays more pathogenic character. In a mutualistic relationship, nutrients were provided by the host, while the microbiome promoted immune and epithelial homeostasis. In the pathogenic relationship, the microbiome invades past the epithelium and induces inflammation.[18]
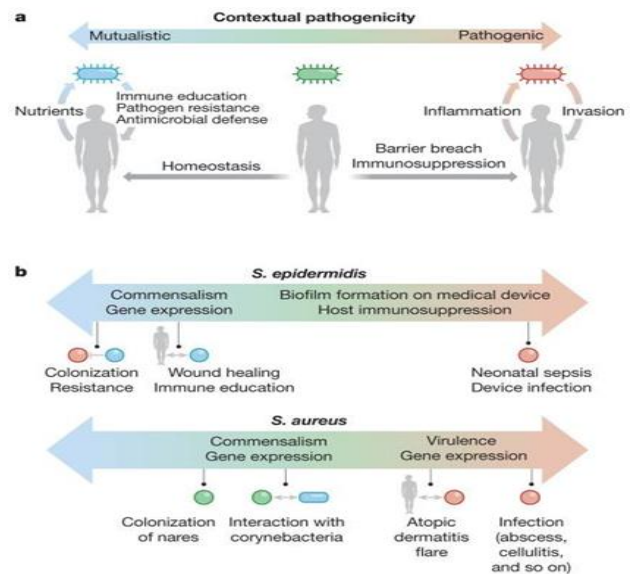

Figure 2: Contextual pathogenicity.[18]

SKIN MICROBIOME DYSBIOSIS IN LEPROSY PATIENTS

Increasing evidence supports the skin microbiome' importance in physiology, metabolism, immune responses, and how dysbiosis in the normal skin microbiome is associated with cutaneous disorder. Dysbiosis, or alterations of the skin microbiome, may lead to immune system activation dysfunction, resulting in abnormal regulation of immune responses to commensal microbes.[19] Several studies have identified that certain strains of microbes have been substantially linked with specific cutaneous disorders such as eczema, psoriasis, and acne vulgaris.[20-22]

Dysbiosis is driven by the alteration of the microbial communities themselves or due to the intrinsic features of the host. However, the causative relationship between the microbiome alterations and cutaneous disease remains unclear; which one happens first.[23] *M. leprae* invade and proliferate in Schwann cells, leading to the development of anesthetic skin patches and the thickening of

peripheral nerves. It also identified that *M. leprae* invasion could induce abnormal alteration in microvascular function and capillary structure. Abnormal blood flow changed the hydration levels of skin that impacted the resident microbial community structure.[24]
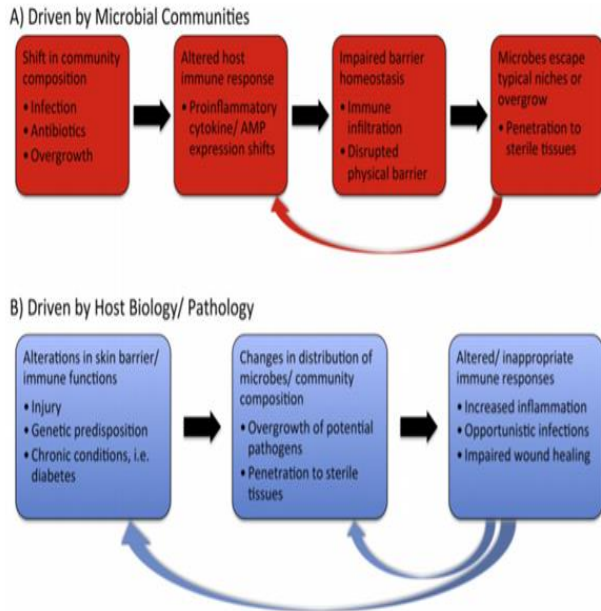
Figure 3: Models of dysbiosis of skin-resident microbes.[23]

Growing evidence identified the lower diversity in the leprosy patient's skin microbiome than in the healthy subjects; assumed to be associated with the disease severity, colonization of pathogens, and the use of MDT. Significant shifts of the skin microbiota negatively impact the commensal microbial. Reduction in the diversity of skin microbiota was observed in freshly diagnosis leprosy patients, those at various stages of MDT, and post MDT; these indicated that both the interaction between *M. leprae*-skin microbial community and the ongoing therapeutic regimen impacted the skin microbial variation.[24-26]

Silva et al., studied how microbiota of leprous lesions had different bacterial skin composition than healthy subjects using Sanger and massively parallel small subunit rRNA (SSU) rRNA gene sequencing. Four main phyla were observed in the taxonomic analysis of leprous skin lesions: *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*. *Proteobacteria* was the most diverse phyla. The same phyla were found in the skin from atopic dermatitis and psoriasis patients; however, it has different distribution with leprous cases. *Proteobacteria* and *Bacteroidetes* enriched in leprosy patients, while *Firmicutes* and *Actinobacteria* markedly diminished compared with healthy skin. *Actinobacteria* were also underrepresented in psoriatic skin; it was suggested that the observed reduction might result from the pathologic ecological of the infected skin, turning it unconducive to

these bacteria.[27] This might explain the same phenomenon that was found in the leprous lesion.[28]

Bayal et al also assessed the affected and unaffected skin microbial diversity of leprosy patients in Indian using next-generation 16S rDNA sequencing. Samples were collected from two different geographical locations in India to identify the homo- or heterogeneity of skin microbial composition. Stark differences were identified between the taxonomic profiles in the healthy controls' skin microbiome samples compared to that from participants affected with leprosy; distinct depletion of *Staphylococcus* was found in leprosy subjects. A similar finding was also found by Silva et al, which were *Staphylococcus* and *Streptococcus* were the significantly decreased in leprosy patients.29 It also found that the uniformity of healthy control' skin microbiome in different geographical locations. In contrast, the leprosy' skin microbiome profiles appear to have significant differences.19

Another study by Gunawan et al compared the skin microbiome composition in the Indonesian leprosy population to healthy subjects. Taxonomic analysis of leprous skin lesions revealed five main phyla: *Staphylococcus*, *Corynebacterium*, *Acinetobacter*, *Micrococcus*, and *Propionibacterium*. *Staphylococcus*, *Micrococcus*, and *Acinetobacter* were enriched in leprosy patients, while *Corynebacterium* and *Propionibacterium*, which have a protective role in normal skin, were diminished in leprosy patients compared to healthy individuals. Leprosy reaction also impacts dysbiosis due to abnormal immune system alteration. In reversal reaction, Th1 activity upregulation caused changes in the microbiota' composition. Differences in the order of the microbiota phylum (*Actinobacteria*, *Firmicutes*) and genera (*Propionibacterium*, *Micrococcus*) composition in leprosy patients during treatment with/without reversal reaction was found in this study.[25]

Despite the disease itself, the use of multi-drug therapy/MDT (combination of rifampicin, clofazimine, and dapsone) also impacts the leprous skin microbiome' composition and dynamics. *Firmicutes* was the most MDT-impacted phylum, followed by *Actinobacteria*, *Proteobacteria*, and *Bacteroidetes*. This finding suggested that MDT exerts strong selective pressure on the indigenous skin microbiome. Patients treated for 12 months with MDT exhibited a shift in their microbiome that persisted for up to 5 months after last sampling without MDT.[26,29]

These studies showed that the microbial composition of the leprous lesion could be different based on the patient's geographical sites. The alteration of skin microbiota significantly depend upon age, skin site, environmental, stage of disease, and therapeutic phases.[24] Long term monitoring is recommended to assess the microbiome resilience. Other studies that observed the resilience in the human intestinal microbiome after

antibiotic cessation show that the *Bacteroides* population did not return to its original composition for up to 2 years after treatment stopped. Further studies are needed to estimate the duration of normalization of commensal microbial back to its original condition.[30]

Currently, there are no studies on the differences in the skin microbiome in various clinical types of leprosy and how the improvement of the skin microbiome can affect the condition of leprosy lesions.

CONCLUSION

The skin microbiome composition differences in leprosy patients were observed; skin microbial diversity in the leprosy patients was lower than in healthy individuals. This could result from a disturbance in the skin microbial community caused by *M. leprae* invasion and/or the use of multi-drug therapies. Investigations of the association between the human skin microbiome and cutaneous disease, especially in leprosy cases, need to be utilized and focused on to develop adequate treatment strategies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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