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Skin Microbiome Profiles in RA, AS, BS and FMF: A Cross-Sectional Study

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Abstract

Introduction: Microbiota refers to all microorganisms colonising the body, whereas microbiome is a broader term covering the genetic material and ecosystem of this population. The skin is the largest organ of the body with a skin microbiota characterised by a bacterial density of >1×10⁶ bacteria per cm². The dominant phyla most frequently isolated are *Actinobacteria*, *Firmicutes*, *Proteobacteria* and *Bacteroidetes*, with *Staphylococcus epidermidis* (*Firmicutes*) and *Malassezia spp.* (fungal) species. **Objective:** This study aims to investigate the role of microbial dysbiosis in pathogenic mechanisms by comparing the compositional differences of skin flora in RA, AS, BS and FMF patients. **Method:** In this study, patients diagnosed with RA, AS, BS and FMF admitted to the Rheumatology outpatient clinic of Gaziantep City Hospital and a control group including healthy individuals were analysed. Swab samples were obtained from the axillary and scapula regions of patients and healthy individuals. The genus and species identification of the bacteria were performed using MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionisation-Time of Flight Mass Spectrometry) technology. **Result:** A statistically significant correlation was found between the diagnoses of the patients and the isolated microorganism combinations ($p < 0.001$). There was no statistically significant correlation between gender and isolated microorganism species ($p = 0.729$). **Conclusion:** The structure and composition of the human microbiome has a significant impact on health and disease status. This study revealed that the skin microbiota shows specific changes in chronic inflammatory diseases such as AS, RA, FMF and BS. The present findings may serve as a guide for further studies in this field.

Keywords: skin flora; rheumatologic disease; human microbiome

1. Introduction

Microbiota refers to all microorganisms colonising the body, whereas microbiome is a broader term covering the genetic material and ecosystem of this population (1). Microbiota composition exhibits a dynamic profile starting from the intrauterine period and is modulated by parameters including mode of delivery, genetic structure, dietary habits, environmental factors and immunoregulation (2,3). This ecosystem, which contains approximately 1.3 times more microbial cells than human cells, exhibits a heterogeneous distribution according to anatomical regions (4).

The skin is the largest organ of the body with a skin microbiota characterised by a bacterial density of >1×10⁶ bacteria per cm². The dominant phyla most frequently isolated are Actinobacteria,

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Firmicutes, Proteobacteria and Bacteroidetes, with Staphylococcus epidermidis (Firmicutes) and Malassezia spp. (fungal) species (5). These microorganisms inhibit pathogen colonisation by interacting with epidermal pH, hydration and immune homeostasis. In the presence of dysbiosis, pathological processes associated with dermatological and systemic diseases can be triggered.

Gut microbiota has been frequently been investigated in the literature. The gut microbiota has been reported to contribute to host defence through interleukin-10 (IL-10)-mediated immunomodulation. Dysbiosis activates Th1/Th17-mediated autoimmune responses and has been associated with diseases including rheumatoid arthritis (RA), ankylosing spondylitis (AS), Behçet syndrome (BS) and familial Mediterranean fever (FMF) (6). In this respect, it has been reported that Porphyromonas gingivalis is involved in the pathogenesis of RA, and there is a correlation between pathergy test positivity and streptococcal species in BS (7). However, skin microbiota dynamics in autoimmune diseases have not been researched sufficiently.

There is limited research on the interaction between diseases and skin microbiota in the current literature. This study aims to investigate the role of microbial dysbiosis in pathogenic mechanisms by comparing the compositional differences of skin flora in RA, AS, BS and FMF patients. This analysis may shed light on the interactions of the mucocutaneous-immune axis in the pathogenesis of autoimmunity.

2. Materıals And Methods

In this study, patients diagnosed with RA, AS, BS and FMF admitted to the Rheumatology outpatient clinic of Gaziantep City Hospital and a control group including healthy individuals were analysed. RA was defined according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria, AS was defined according to the 2009 Assessment of SpondyloArthritis International Society (ASAS) criteria, BS was defined according to the 2014 International Criteria for Behçet's Disease (ICBD) criteria and FMF was defined according to the 2009 Livneh criteria and 1997 Tel-Hashomer criteria.

The control group consisted of healthy subjects with an absence of history of systemic inflammatory disease, systemic antibiotic or immunosuppressive therapy in the last 1 month and skin lesions. Exclusion criteria for all patient and control groups: Topical or systemic antibiotic use in the last 1 month, presence of active skin infection, pregnancy and lactation, history of malignancy, diabetes mellitus and immunosuppressive conditions. The following procedures were applied in the study:

2.1. Sample Collection

-Swab samples were obtained from the axillary and scapula regions of patients and healthy individuals using cotton swabs moistened with saline.

-The samples were transferred to tubes containing 2 ml of saline and vortexed for approximately 30 seconds to obtain a homogeneous mixture.

2.2. Microbiological Analysis

- 100 µl samples were inoculated into each of the chocolate blood and EMB (Eosin Methylene Blue) media from the homogeneous mixture.

-The inoculated plates were incubated at 37°C for 72 hours.

-The colonies after incubation were first classified according to their macroscopic characteristics, followed by gram staining and descriptive tests.

-The genus and species identification of the bacteria were performed using MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionisation-Time of Flight Mass Spectrometry) technology.

2.3. Statistical Analysis

-Mean, standard deviation, median, minimum and maximum values were determined for quantitative variables.

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-Number and percentage values were determined for qualitative variables.
-The relationship between qualitative variables was analyzed by chi-square analysis.
-All analyses were performed using IBM SPSS Statistics 25.0 software and aSPSS Statistics 25.0 software and a significance level of $p<0.05$ was accepted.

2.4. Ethics

All studies were conducted the Declaration of Helsinki. Ethics committee approval was received on 15/05/2024 as 18/2024 registration number. Study-related documents were reviewed and approved by independent ethics committees and institutional review boards. All patients provided written informed consent before participation in the study.

3. Results

3.1. Relationship Between Microorganism Combinations and Diagnosis

As shown in Table 1, the combination of S. epidermidis, Corynebacterium spp. and Propionibacterium spp. was the most frequently isolated microorganism in all patient groups and in the control group. This combination was 22.2% in patients diagnosed with AS, 16.5% in patients diagnosed with RA, 18.9% in FMF patients, 25.0% in Behçet's disease patients and 25.5% in the control group. A statistically significant correlation was found between the diagnoses of the patients and the isolated microorganism combinations ($p<0.001$).

Table 1. The relationship between diagnosis and microorganism combination.

	AS n (%)	RA n (%)	FMF n (%)	BS n (%)	Control group n (%)	Total
S. epidermidis ,Corynebacterium spp ,Propionibacterium spp	20 (22.2)	15 (16.5)	7 (18.9)	6 (25.0)	13 (25.5)	61 (20.8)
Miccrococcus spp , S. haemolyticus ,S. epidermidis ,Corynebacterium spp	6 (6.7)	11 (12.1)	3 (8.1)	0 (0.0)	6 (11.8)	26 (8.9)
S. haemolyticus ,S. epidermidis ,Corynebacterium spp	8 (8.9)	7 (7.7)	3 (8.1)	0 (0.0)	0 (0.0)	18 (6.1)
S. haemolyticus , Corynebacterium spp ,Propinibacterium spp	9 (10.0)	2 (2.2)	0 (0.0)	0 (0.0)	4 (7.8)	15 (5.1)
S. haemolyticus , Corynebacterium spp	6 (6.7)	12 (13.2)	7 (18.9)	6 (25.0)	5 (9.8)	36 (12.3)
Corynebacterium spp , S. epidermidis	3 (3.3)	8 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	11 (3.8)
S. epidermidis , Propionibacterium spp	10 (11.1)	13 (14.3)	8 (21.6)	3 (12.5)	0 (0.0)	34 (11.6)
Miccrococcus spp , S. epidermidis ,Corynebacterium spp	5 (5.6)	0 (0.0)	0 (0.0)	3 (12.5)	11 (21.6)	19 (6.5)
S. epidermidis ,Corynebacterium spp , Fusobacterium spp	6 (6.7)	8 (8.8)	7 (18.9)	0 (0.0)	2 (3.9)	23 (7.8)

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S. haemolyticus ,S. epidermidis , Propionibacterium spp	0 (0.0)	5 (5.5)	2 (5.4)	3 (12.5)	0 (0.0)	10 (3.4)
Diğer	17 (17.7)	10 (11.0)	0 (0.0)	3 (12.5)	10 (19.6)	40 (13.6)
Total	90	91	37	24	51	293

*P value<0.001 **Fisher's Exact Test.

3.2. The Relationship Between Diagnosis and Microorganisms

The distribution of microorganisms found in diagnosed patients and healthy individuals showed that the prevalence of Corynebacterium spp., Micrococcus spp., S. epidermidis, S. haemolyticus and Propionibacterium spp. varied between groups. In addition, 1.6% Actinobacteria spp. and 1.6% Malassezia furfur were isolated in patients with AS, 0.8% Malassezia furfur in patients with RA and 5.0% Candida spp. in patients with Behçet's disease. A statistically significant correlation was found between the diagnoses of the patients and microbiota composition (p<0.001).

The distribution of microorganisms was as follows: 27.2% S. epidermidis, 26.7% Corynebacterium spp. and 19.8% Propionibacterium spp. in AS patients; 30.9% S. epidermidis, 26.7% Corynebacterium spp. and 14.4% Propionibacterium spp. in RA patients; 31.3% S. epidermidis, 27.3% Corynebacterium spp. and 17.2% Propionibacterium spp. in FMF patients ; 26.7% S. epidermidis, 25.0% Corynebacterium spp. and 25.0% Propionibacterium spp in BS patients; 31.5% Corynebacterium spp, 25.3% S. epidermidis and 18.5% Micrococcus spp. in control group respectively (Table 2).

Table 2. The relationship between diagnosis and microorganisms.

Mikroorganizma adı	AS n (%)	RA n (%)	FMF n (%)	BEHÇET n (%)	Kontrol n (%)	Toplam
Actinobacteria spp	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4
Candida spp	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	0 (0.0)	3
Corynebacterium spp	65 (26.7)	65 (26.7)	27 (27.3)	15 (25.0)	46 (31.5)	218
Fusobacterium	6 (2.5)	10 (4.1)	7 (7.1)	0 (0.0)	2 (1.4)	25
Malessesia furfur	4 (1.6)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	6
Miccrococcus spp	16 (6.6)	13 (5.3)	3 (3.0)	3 (5.0)	27 (18.5)	62
S. epidermidis	66 (27.2)	75 (30.9)	31 (31.3)	16 (26.7)	37 (25.3)	225
S. haemolyticus	34 (14.0)	43 (17.7)	14 (14.1)	8 (13.3)	17 (11.6)	116
Propionibacterium spp	48 (19.8)	35 (14.4)	17 (17.2)	15 (25.0)	17 (11.6)	132

*P value<0.001 **Fisher's Exact Test.

3.3. The Relationship Between Gender and Microorganisms

There was no statistically significant correlation between gender and isolated microorganism species (p=0.729) (Table 3).

Table 3. The relationship between gender and microorganisms.

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	Actinobacteria spp n (%)	Candida spp n (%)	Corynebacterium spp n (%)	Fusobacteriu m n (%)	Malessesia furfur n (%)	Micrococcus spp n (%)	S. epidermidis n (%)	S. haemolyticus n (%)	Propionibacterium spp n (%)
Male	2 (0.6)	2 (0.6)	98 (27.8)	8 (2.3)	4 (1.1)	28 (8.0)	95 (27.0)	50 (14.2)	65 (18.5)
Female	2 (0.5)	1 (0.2)	120 (27.3)	17 (3.9)	2 (0.5)	34 (7.7)	130 (29.6)	66 (15.0)	67 (15.3)

*p-value 0.729 **Fisher's Exact Test.

4. Discussion

Microbiomes are communities of microorganisms that are present in various parts of the human body, especially in areas such as the oral cavity, skin surface, gastrointestinal tract, oesophagus and lungs. These ecosystems involve a variety of microorganisms such as bacteria, archaea, viruses, phages and fungi. Bacteria are the predominant microbiota component in terms of species diversity (9).

Microbiomes play a critical role in human health and disease in interaction with genetic and environmental factors. In this study, the relationship between the bacterial components of microbiomes and immune-mediated disease pathologies in the human host was evaluated. Among human microbiomes, the most detailed studies have primarily focused on the gut microbiota (10). Microbiota alterations have also been documented in lung diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD) and pneumonia. However, the composition of the healthy lung microbiota has not yet been fully elucidated.

Skin is the largest organ of the human body and provides protection against external factors with its physical and chemical barrier function (11). Skin microbiota may exhibit 'fingerprint'-like specificity among individuals (12). Disruption of the microbiota balance is defined as dysbiosis, and this can result from host or environmental factors. Dysbiosis has been associated with many diseases such as inflammatory bowel diseases, autism spectrum disorders, autoimmune diseases, obesity, cancer and metabolic syndrome. However, the etiological mechanisms of this association have not yet been fully characterised.

Dysbiosis in skin microbiota is also related with dermatological diseases such as seborrheic dermatitis, acne, psoriasis, atopic dermatitis and wound infections (13). Therefore, in this study, the analysis of skin microbiota in chronic inflammatory diseases such as AS, FMF, RA and BS was investigated.

In patients with AS, changes in skin barrier function and differences in microbiota composition were detected. In particular, changes in the ratios of Propionibacterium and Staphylococcus species were especially observed. In subjects with psoriasis, it was reported that Proteobacteria species increased and Staphylococcus and Propionibacterium species were presented at high levels in the area with lesions (14). Since a similar cytokine pathway plays a role in the pathogenesis of psoriasis and AS, changes in microbial pathogens in the skin flora of AS patients may lead to differences in the clinical presentation of the disease.

Microbiota compositions also varies according to age groups. It has been reported that the diversity of intestinal microbiota decreases and a dysbiotic profile develops in elderly individuals (15,16). This may lead to increased intestinal permeability, impaired nutritional absorption and dysregulation of the immune system. In addition, it has been suggested that there is a reciprocal interaction between sex hormones and microbiota. It has been reported that microbiota differences between the genders become apparent during puberty (17,18). In the present study, a statistically significant relationship was not revealed between gender and microorganism composition.

There are some limitations in this study;

-Inadequate number of patients diagnosed with RA, AS, FMF and BS

- Sampling from different skin areas (armpit and scapula areas)

- The colony numbers of the isolated microorganisms were not documented.

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5. Conclusıon

The structure and composition of the human microbiome has a significant impact on health and disease status. This study revealed that the skin microbiota shows specific changes in chronic inflammatory diseases such as AS, RA, FMF and BS. The present findings may serve as a guide for further studies in this field. However, more comprehensive, high-resolution microbiome analyses and functional research are needed to fully elucidate the mechanistic basis and potential therapeutic implications of the relationship between skin microbiota and chronic immune-mediated diseases.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval was received on 15/05/2024 as 18/2024 registration number.

Informed Consent: Informed consent was obtained from all participants included in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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