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Evaluation of the effects of Lake Hévíz sulfur thermal water on skin microbiome in plaque psoriasis: An open label, pilot study

Ágota Kulisch[1] · Zsuzsanna Mándó[1] · Enikő Sándor[1] · Zsuzsanna Lengyel[2] · Anett Illés[3] · János Kósa[3,4,5] · Kristóf Árvai[5] · Péter Lakatos[3,4,5] · Bálint Tóbiás[4,5] · Márton Papp[6] · Tamás Bender[7]

Abstract

Psoriasis is a chronic inflammatory skin disease. It is associated with changes in skin microbiome. The aim of this study was to evaluate how Lake Hévíz sulfur thermal water influences the composition of microbial communities that colonizes skin in patients with psoriasis. Our secondary objective was to investigate the effects of balneotherapy on disease activity. In this open label study, participants with plaque psoriasis underwent 30-min therapy sessions in Lake Hévíz, at a temperature of 36 °C, five times a week for 3 weeks. The skin microbiome samples were collected by swabbing method from two different areas (lesional skin-psoriatic plaque and non-lesional skin). From 16 patients, 64 samples were processed for a 16S rRNA sequence-based microbiome analysis. Outcome measures were alpha-diversity (Shannon, Simpson, and Chao1 indexes), beta-diversity (Bray–Curtis metric), differences in genus level abundances, and Psoriasis Area and Severity Index (PASI). Skin microbiome samples were collected at baseline, and immediately after treatment. Based on the visual examination of the employed alpha- and beta-diversity measures, no systematic difference based on sampling timepoint or sample location could be revealed in these regards. Balneotherapy in the unaffected area significantly increased the level of *Leptolyngbya* genus, and significantly decreased the level of *Flavobacterium* genus. A similar trend was revealed by the results of the psoriasis samples, but the differences were not statistically significant. In patients with mild psoriasis, a significant improvement was observed in PASI scores.

Keywords Lake Hévíz · Plaque psoriasis · Balneotherapy · Microbiome · Sequencing

✉ Tamás Bender
bender.tamas@irgalmas.hu

1 St. Andrew Hospital for Rheumatic Diseases, Schulhof Vilmos sétány 1., Hévíz 8380, Hungary

2 Department of Dermatology, Venerology and Oncodermatology, Medical School, Clinical Center, University of Pécs, Akác utca 1., Pécs 7632, Hungary

3 Department of Medicine and Oncology, Faculty of Medicine, Semmelweis University, Korányi Sándor utca 2/a, Budapest 1083, Hungary

4 Endocrine Molecular Pathology Research Group, Eötvös Lóránd Research Network, Korányi Sándor utca 2/a, Budapest 1083, Hungary

5 Vascular Diagnostics Kft., Lechner Ödön fasor 3. C. Lház. 3. Em. 1., Budapest 1095, Hungary

6 Centre for Bioinformatics, University of Veterinary Medicine Budapest, István utca 2., Budapest 1078, Hungary

7 Polyclinic of the Hospitaller Brothers of St John of God, Árpád fejedelem útja 7., Budapest 1023, Hungary

Introduction

The microbiome is an ecological system made up of commensal, symbiotic, and pathogenic microorganisms living in the human body. The microbial flora normally occurring in different regions of the human skin has been investigated under the Human Microbiome Project (HMP) since 2008 (Grice et al. 2008). Different body parts have distinct flora; however, it is fairly consistent within the human population, although individual differences exist. Compared to culture-based techniques, genomic studies confirmed the presence of many more bacteria. Bacteria found on the skin can be classified into four major phylums: *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*; the differences lie in their distribution. While in the intestines, the dominant phylums are *Firmicutes* and *Bacteroidetes*, the dominant phylum of the skin is *Actinobacteria* (Whittle et al. 2019).

Sequencing-based metagenomics is suitable for determining the exact composition of complex microbial

communities without having to isolate and culture individual members of the community. Tests are based on the fast and high throughput determination of DNA extracted from communities using next-generation sequencing (NGS), which can be used to examine the genome of the entire community, including non-culturable microbes. Sequencing enables comprehensive examination of all genes of all microorganisms present, even in complex samples (Rogers and Bruce 2010).

Balneotherapy has been used for a long time in the treatment of dermatological diseases (Huang et al. 2018; Cacciapuoti et al. 2020). Available literature mainly discusses balneotherapy for psoriasis and atopic dermatitis (Péter et al. 2017; Darlenski et al. 2021). The keratolytic effect of sulfur water is well known, that is why it is used for the treatment of psoriasis. Hydrogen sulfide (H_2S) has a specific molecular effect on normal human keratinocytes (Gross-Amat et al. 2020). In addition to balneotherapy, balneophototherapy is also a well-established treatment procedure for patients with dermatological conditions, but data are already available even on the combined beneficial effects of concomitant biological therapy and balneotherapy (Peinemann et al. 2021; Cozzi et al. 2015; Halevy et al. 2001).

According to a recently published study, diversity of skin microbiota correlates with PASI score (Assarsson et al. 2018). Moderate to severe psoriasis and mild psoriasis differ in their microbiota composition (Hu et al. 2022). When comparing skin microbiome of healthy controls and patients with psoriasis, increased amounts of *Firmicutes* and decreased amounts of *Actinobacteria* were found in patients with psoriasis, which mostly appeared on the lesional skin and was at least partially reversed with systemic treatment (Yerushalmi et al. 2019). Presence of *Prevotella* and *Staphylococcus* showed significant association with lesional skin while the presence of *Anaerococcus* and *Propionibacterium* was associated with non-lesional skin. There was no significant difference in the amounts of bacteria cultured from the skin of healthy controls and patients with psoriasis (Langan et al. 2019). In the literature, only one human balneotherapy study was found assessing the effects of thermal water on skin microbiome in psoriasis patients (Martin et al. 2015).

The objectives of the study

The primary objective of the study is to assess and compare the microbiome composition of psoriasis-affected and unaffected skin and to investigate the effects of sulfur thermal-mineral water of Lake Hévíz on the microbiome of psoriatic plaques and unaffected skin areas.

The secondary objective of the study is to assess the effects of balneotherapy on the activity of psoriasis.

Patients and methods

The study protocol followed the principles of the Helsinki Declaration. This study was approved by the relevant Scientific and Research Ethics Committee (i.e., ETT TUKEB; its approval Number: 31262–6/2019/EKU), Clinical trial registration ID: NCT05431959. The study was also approved by the Institutional Research Ethics Committee.

Inclusion criteria

This study enrolled male and female patients between 18 and 70 years of age with plaque psoriasis diagnosed at least 6 months before the pre-treatment visit by a dermatologist.

Exclusion criteria

Exclusion criteria included subjects that are on systemic therapy for psoriasis, balneotherapy within 3 months prior to enrollment, and local or systemic steroid therapy within 1 month prior to enrollment. General contraindications to balneotherapy include decompensated cardiovascular status, uncontrolled endocrine and metabolic disorders, severe diseases affecting the internal organs, acute febrile infections, pregnancy, and decompensated mental illnesses.

Recruitment of the patients

After verbal agreement, the rheumatologists of the St. Andrew Hospital for Rheumatic Diseases invited the patients with plaque psoriasis to participate the study, bearing in mind the inclusion and exclusion criteria. Before enrollment, participants were informed verbally and writing about the purpose, procedures of the study. Prior to enrollment, subjects read the Patient Information Sheet and signed the Informed Consent Form. The rheumatologist cross-checked the inclusion and exclusion criteria before the study.

Intervention

The study took place at Spa Hévíz and St. Andrew Hospital for Rheumatic Diseases (H-8380 Hévíz, Dr. Schulhof Vilmos sétány 1, Hungary).

Participants underwent 30-min balneotherapy sessions in Lake Hévíz, at a temperature of 36 °C, five times a week for 3 weeks. The enrolled patients received the treatment as outpatients. They were able to continue their daily activities and work. Participants did not receive any other physiotherapy. During the study, further systemic or local therapy was not allowed. Patients were assessed two times, just before treatment (pre-treatment) and after

three weeks (post-treatment). The members of the Lake Hévíz Emergency Medicine Team were available during of balneotherapy sessions in case of emergency. The rheumatologists were on call to deal with side effects or other treatment-related problems. After consulting a dermatologist, the examining rheumatologist prepared a standardized photo documentation, which formed the basis of evaluating the Psoriasis Area and Severity Index (PASI). The samples were collected in the Laboratory Department of St. Andrew Hospital by clinical laboratory specialist. Before the study, the study personnel and the laboratory performing the analysis of the samples standardized and practiced the methodology of the sample collection.

Thermal water composition

The spring of Lake Hévíz is located at the bottom of the vertical sand wall, at 38.5 m depth. Water output of the lake is 420 L/s, and the water transposes in 3–3.5 days. The temperature of the lake reaches 37–38° in the summer, and is never lower than 22–23 °C during winter. The thick layer of mud covers the bed of the lake, which contains both organic and inorganic substances. The thermal mineral water of Lake Hévíz containing carbonate, sulfur, calcium, magnesium, hydrogen carbonate, and very low radon. During the study, the temperature of the lake was 36 °C. The total mineral content of the water was 754 mg/L, the sulfide content was 3.2 mg/L. The mineral composition of Lake Hévíz water is shown in Table 1.

Table 1 The mineral composition of Lake Hévíz water

Sodium	Na^+	27 mg/L
Potassium	K^+	6.8 mg/L
Ammonium	NH_4^+	0.32 mg/L
Calcium	Ca^{2+}	81 mg/L
Magnesium	Mg^{2+}	36 mg/L
Iron	Fe^{2+}	0.04 mg/L
Chlorine	Cl^-	23 mg/L
Bromine	Br^-	0.11 mg/L
Iodine	I^-	0.021 mg/L
Fluorine	F^-	1.4 mg/L
Sulfate	SO_4^{2-}	64 mg/L
Hydrogen carbonate	HCO_3^-	378 mg/L
Sulfide	S^{2-}	3.2 mg/L
Total hardness of water	CaO	198 mg/L

Others: mud, radon, metaboric acid, meta silica acid, organic acid, CO_2, soluble O_2

pH: 7.14

Total mineral substance: 754 mg/L

Materials

Samples were collected from 2 different areas of the patient's body (1. lesional skin, psoriatic plaque—elbow, 2. control non-lesional skin—right antecubital fossa), pre- and post-treatment with a Swab Collection and DNA Preservation System (Norgen, ON, Canada). Microbial DNA was isolated using the Microbiome DNA Isolation Kit (Norgen, ON, Canada). The purification is based on spin column chromatography. First, the swab collection tube was incubated at 65 °C with the presence of Lysis Additive in order to efficiently and rapidly homogenize the sample. The sample was then centrifuged, and the supernatant was transferred to a DNase-free microcentrifuge tube. Binding buffer was added, and the lysate was incubated for 10 min on ice. The lysate was then spun for 2 min to pellet any cell debris, the supernatant was collected, an equal volume of 70% ethanol was added to the lysate and the solution was loaded onto a spin-column. The bound DNA was then washed using the provided binding buffer and wash solution, and the purified DNA was eluted using the elution buffer. The concentration of the isolated DNA was determined using the Qubit dsDNA HS Assay Kit (Life Technologies, Carlsbad, CA, USA).

DNA amplicon library was prepared using the Ion 16S Metagenomics Kit (Life Technologies, CA, USA). The kit includes 2 sets of primers that can be used to amplify the corresponding hypervariable regions of the 16S rDNA gene in bacteria: primer set V2-4–8 and primer set V3-6,7–9. The primer sets are paired with Environmental Master Mix v2.0 that is optimized to tolerate high levels of PCR inhibitors and amplify targets from complex samples. After pooling and purification of the amplicons with Agencourt AMPure XP reagent (Beckmann Coulter, CA, USA), end repair was carried out. In the next step, sequencing adapters and sample-specific barcodes were ligated to each amplified DNA sample. After final purification, the concentration of the final library was determined by qPCR method run on QuantStudio instrument (Life Technologies, CA, USA).

Template preparation was performed with Ion OneTouch kit (Life Technologies, CA, USA) on semiautomated Ion One-Touch instrument using an emPCR method. After adding the sequencing primer and polymerase, the Ion Sphere Particle (ISP) beads were loaded into an Ion 520 sequencing chip, and the sequencing runs were performed using the Ion S5 Sequencing kit (Life Technologies, CA, USA) with 850 flows.

Outcome parameters, bioinformatics, and statistical methods

Quality evaluation of raw reads was performed with FastQC 0.11.9 (Andrews 2018). Reads were quality trimmed with Trimmomatic v0.39 (Bolger et al. 2014), using the following parameters: LEADING:3, TRAILING:20,

SLIDINGWINDOW:4:20, MINLEN:50. After quality control, fastq files were dereplicated and chimera filtered with vsearch v2.21.1 (Rognes et al. 2016). Taxon classification of the reads was performed with Kraken2 v2.1.2 (Wood et al. 2019) to the GreenGenes database (DeSantis et al 2006). Analysis of the sample bacteriome compositions was conducted in R environment with the aid of phyloseq (McMurdie and Holmes 2013) and microbiome (Lahti et al. 2019) R Bioconductor packages. Both Bacteria and Archea kingdoms were used for downstream analysis, with reads agglomerated at the genus level. Community compositions were evaluated in each sample with the Shannon (Shannon 1948), Simpson (Simpson 1949), and Chao1 (Chao 1984) alpha-diversity measures. Beta-diversity was measured with Bray–Curtis (Bray and Curtis 1957) dissimilarities and visualized through NMDS ordination (Kruskal 1964).

Differences in genus abundances were evaluated for the most dominant genera, determined with the core function of the microbiome R package (Lahti et al. 2019), with detection 100 and prevalence 0.1. Statistical analysis of differential abundance of these dominant genera was performed with paired DESeq2 (Love et al. 2014) analysis. Three comparisons were made: normal samples compared pre-treatment and post-treatment, psoriasis samples compared pre-treatment and post-treatment, and the comparison of normal and psoriasis samples pre-treatment.

Psoriasis Area and Severity Index (Fredriksson and Pettersson 1978) data were entered into and analyzed with MS Excel software. Statistical comparisons were made using single-sample (paired) t tests. The level of significance was set at $p < 0.05$.

Results

Recruitment of patients began in July 2021 and the study was launched at the end of August 2021. Of the 16 patients included in the study, 16 completed more than 80% of the therapy course. Demographic and baseline clinical characteristics of patients are shown in Table 2.

The balneotherapy was well tolerated and no adverse reactions were observed.

Psoriasis area and severity index

Within-group comparison to baseline showed significant improvement of Psoriasis Area and Severity Index (95% CI − 3.3 to − 0.8) $p = 0.006011$. Five patients had disease activity above Psoriasis Area and Severity Index (PASI) score of 10; in response to balneotherapy, disease activity decreased in two patients in this group, while in patients with PASI score < 10, all patients improved with one exception.

Alpha- and beta-diversity

Genus level alpha-diversity of samples were evaluated with Shannon-, Simpson and Chao1 indexes (Figs. 1, 2, and 3). Based on these metrics, neither sampling timepoint (pre- or

Table 2 Demographic data and Psoriasis Area Severity Index (PASI) pre-treatment, post-treatment, changes compared to pre-treatment, and statistical data of group at various time points of the study

Patient number sex male/female	PASI I pre-treatment	PASI II post-treatment	Changes compared to pre-treatment, %	
1. Female	2	1	− 1	50%
2. Male	15	15	0	0%
3. Female	13	13	0	0%
4. Female	1.8	0.9	− 0.9	50%
5. Female	6	2.4	− 3.6	60%
6. Female	5.4	2.7	− 2.7	50%
7. Male	2	1.2	− 0.8	40%
8. Female	4	1.2	− 2.8	70%
9. Female	4	3	− 1	25%
10. Female	20	20	0	0%
11. Male	14	8	− 6	43%
12. Male	3	1.4	− 0.6	54%
13. Female	18.6	9.3	− 9.3	50%
14. Female	3	3	0	0%
15. Male	3	1	− 2	67%
16. Female	2.4	1.8	− 0.6	25%
Age, years Mean (SD): 48.8 (10.2)	Mean (SD): 7.3 (6.4)	Mean (SD): 5.2 (6)	Mean (SD): − 2 (2.5) 95% CI: − 3.3 to − 0.8 p value < 0.01	

Fig. 1 Shannon diversity of samples calculated at the genus level. Patients (*x*-axis) and Shannon index (*y*-axis) values are plotted for different sampling timepoints (columns) and sample locations (rows)
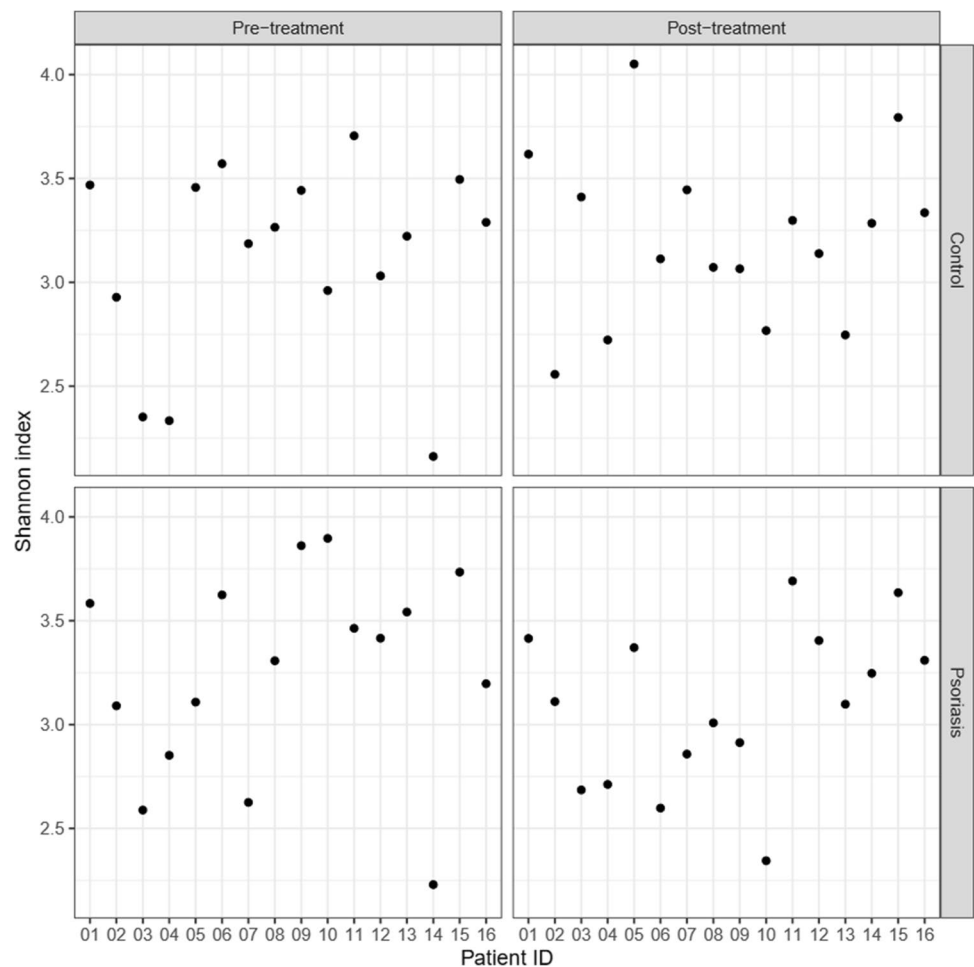
post-treatment), nor sample location (lesional skin or non-lesional skin) had shown systematic differences in sample genus composition complexities.

Inter-sample genus composition differences were assessed by the Bray–Curtis beta-diversity metric. Bray–Curtis dissimilarities were visualized in the 2-dimensional space by NMDS ordination (Fig. 4). Similarly to alpha-diversity, treatment and sample location have not affected genus composition differences. Samples from the same patient have clustered relatively close to each other in some cases (e.g., patient 02), or only the samples before treatment can be found close together (e.g., in the case of patient 03 or 04). In most cases, however, samples from the same patient can be located far from each other in the 2-dimensional space.

## Differential abundance of the dominant bacterial genera

Differences in genus abundances of samples were evaluated on the most dominant genera (determined at detection 100 and prevalence 0.1 of the core function in the microbiome

R Bioconductor package). Differences in genus abundances were compared between control samples pre-treatment and post-treatment, psoriasis samples pre-treatment and post-treatment, and control and psoriasis samples pre-treatment. Significant differences at the FDR level were found in *Leptolyngbya* ($\log_2$FC = 4.5804, *p* value (FDR corrected) < 0.0001) and *Flavobacterium* ($\log_2$FC = − 1.7835, *p* value (FDR corrected) = 0.0496) genus in control, non-lesional skin regions between treatments (positive $\log_2$ Fold Change indicates higher relative abundance post-treatment). Considering the rest of the dominant genera found in our analysis, we could not reveal any significant differences. More details in abundance differences can be found in Tables 3, 4, and 5.

Discussion

Climatotherapy and balneotherapy have already been proven as effective means of achieving clinical improvement in psoriasis. Severe adverse events following this type of therapy are rare (Timis et al. 2021). The results of our study confirm

Fig. 2 Simpson diversity of samples calculated at the genus level. Patients (*x*-axis) and Simpson index (*y*-axis) values are plotted for different treatments (columns) and sample locations (rows)
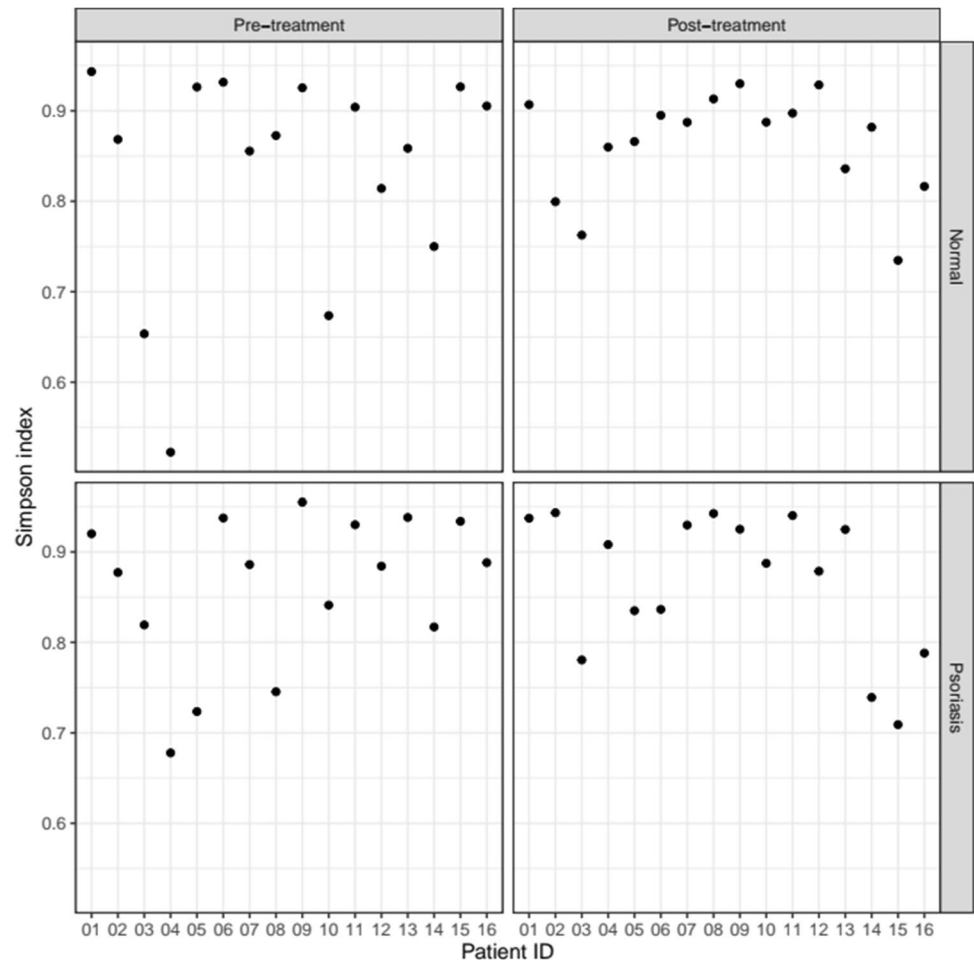

the beneficial effects of balneotherapy in plaque psoriasis. In healthy skin areas, the amounts of *Leptolyngbya* genus dramatically increase, whereas the amounts of *Flavobacterium* genus decrease as a result of bathing. The same tendency is observed in lesional psoriatic areas; however, significance has disappeared after correcting the p-values for multiple comparisons.

Leptolyngbya is a genus of *Cyanobacteria* phylum. *Flavobacterium* is a genus of *Bacteroidota phylum.* Only very few human studies were published on *Leptolyngbya* and *Flavobacterium* genera. *Leptolyngbya* is mainly found in aquatic environments, including marine, in ground and river water, and its antioxidant and anticancer effects have been shown in in vitro studies (Senousy et al. 2020). Examination of a Tunisian thermal spring showed that the *Leptolyngbya* species have abundant natural antioxidant properties which may have prophylactic and therapeutic effects on many diseases and toxicities (Trabelsi et al. 2016). Studying the microbiome composition of the thermal mud from Balaruc spa revealed that *Cyanobacteria* extracts may have anti-inflammatory therapeutic potential, including inhibition of the

secretion of proinflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8 (Demay et al. 2020). Five types of *Cyanobacteria* strains were isolated and demonstrated antioxidant, anti-inflammatory, and anti-proliferative effects, which seems promising in the local treatment of psoriasis (Lopes et al. 2020). In a recently published paper, it was suggested that *Cyanobacteria* may clinically cause a so-called thermal crisis or balneointoxication, but our work has proven the opposite (Cobo et al. 2022).

Even fewer human studies were published on *Flavobacteria* genus than on *Leptolyngbya* genus. Their pathological role is unclear, but by being Gram-negative, they can be the source of several infections (Beathard et al. 2021; Mosayebi et al. 2011). It is also interesting to note that the *Flavobacterium* genus content in the intestine of rheumatoid arthritis patients is higher than that of healthy controls (Yu et al. 2022). It is known that *Flavobacterium* species are regularly found together with *Cyanobacteria*. They can inhibit or enhance the growth of *Cyanobacteria* and degrade compounds synthesized by *Cyanobacteria.* The ecological implications of these close interactions remain largely unknown (Péquin et al. 2022).

Fig. 3 Chao1 diversity of samples calculated at the genus level. Patients (*x*-axis) and Chao1 index (*y*-axis) values are plotted for different treatments (columns) and sample locations (rows)
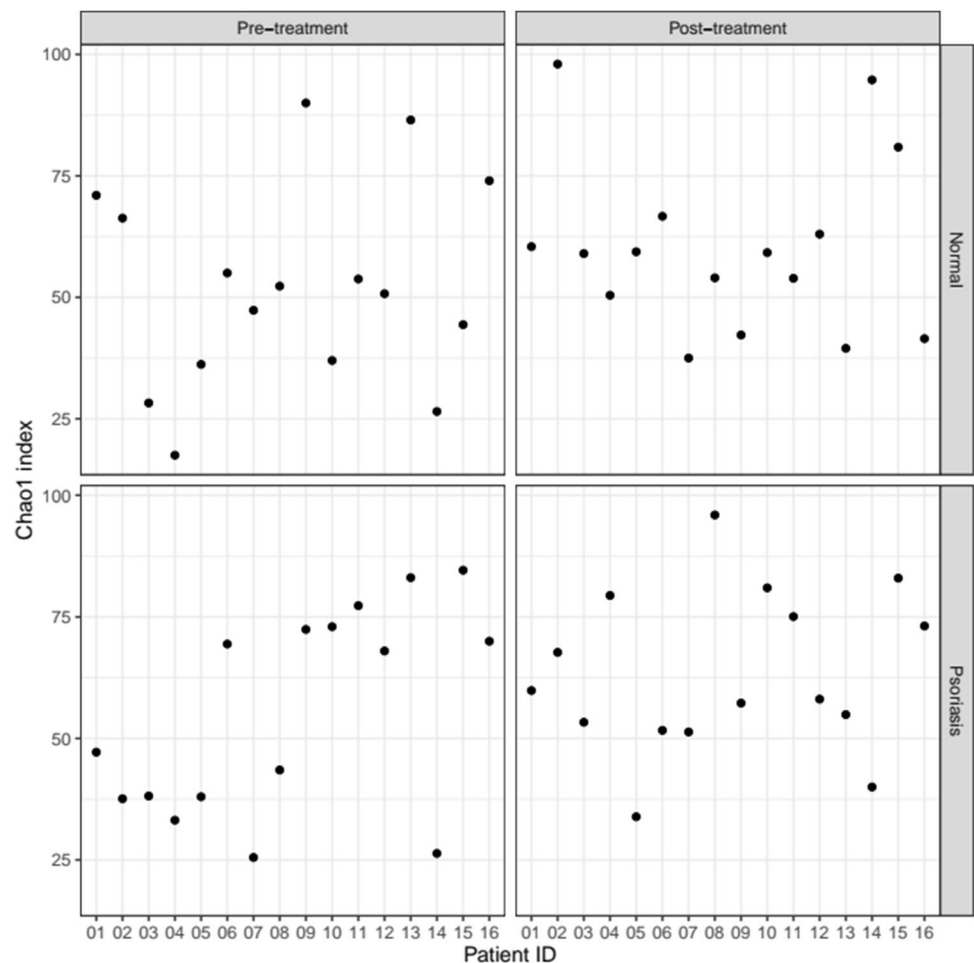

Our study was among the first to investigate the effects of balneotherapy on skin microbiome. In a previous study, the bacterial and fungal characteristics of the skin of healthy volunteers were examined during Dead Sea climatotherapy. After sun exposure and Dead Sea bathing for a 21-day period, diversity of the healthy human skin bacterial microbiome remained undisturbed, while fungal diversity significantly decreased (Brandwein et al. 2018). French authors investigated the effects of 3-week balneotherapy (high-pressure filiform shower, bath, facial, and body spray treatment) on skin microbiome in patients with psoriasis. Our results confirm what they observed, specifically that the bacterial communities were similar on psoriatic and non-lesional skin before treatment and at the end of the third week. They noticed that balneotherapy on both unaffected and adjacent affected skin significantly increased the level of *Xanthomonas* genus, and a lesser increase in the level of *Corynebacterium* genus. The *Xanthomonas* strain belongs to the *Xanthomonadaceae* family, which is part of the *Proteobacteria* phylum community known for its keratolytic effect. Disease activity of psoriasis improved after balneotherapy treatment (Martin et al. 2015). This study was conducted using medicinal water containing bicarbonate, calcium, silicate, and selenium, while our study was carried out with sulfur-containing water.

In the recent decades, the microbial diversity of thermal spring waters has been extensively investigated by a combination of traditional and new molecular biological approaches. Studies of microbial populations inhabiting mat communities of hot springs in Yellowstone National Park have been conducted, which showed the dominance of *Cyanobacteria* and *Chloroflexi* in the area (Ward et al. 1998, 2006). The major phylotypes, including P*roteobacteria*, *Bacteroidetes*, *Cyanobacteria*, and *Firmicutes* have also been reported in other thermal springs at various geographical locations (Hedlund et al. 2012; Kambura et al. 2016; Ghilamicael et al. 2017; Saghatelyan et al. 2021).

The development of molecular biological techniques has provided more information about the microbial communities of thermal springs and their taxonomic diversity, their adaptation mechanisms, and functional roles. Based on the literature biogeography and geological history, along with abiotic factors such as temperature, pH, and mineralization, these factors will collectively contribute to the dynamics and

Fig. 4 NMDS ordination of the Bray–Curtis dissimilarity measures between samples. Circles represent samples collected from unaffected-control skin areas, while triangles denote samples from psoriasis lesions. Colors indicate sampling timepoints while patient IDs are represented as numbers
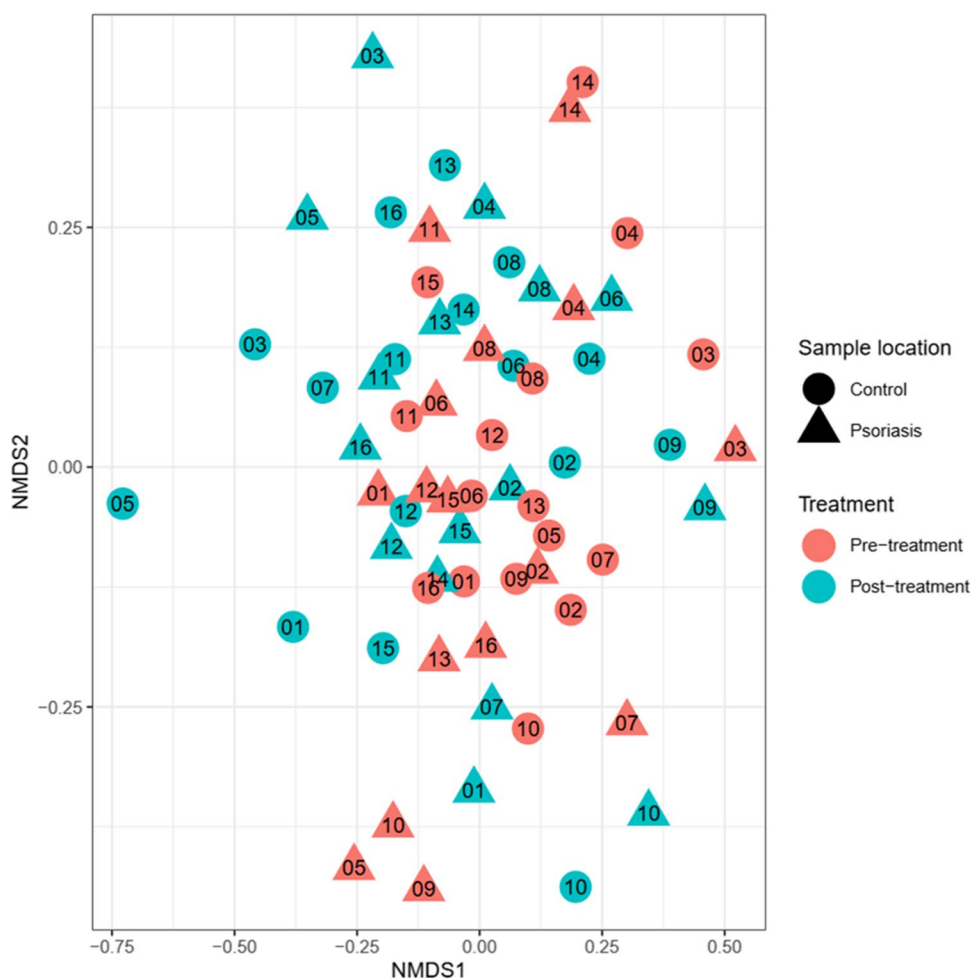
structure of microbial populations (Li et al. 2015; Saghatelyan et al. 2021; Pedron et al. 2022).

Cyanobacteria obtain their energy through photosynthesis and some cyanobacterial species are involved in the global nitrogen cycles by fixing atmospheric nitrogen. Environmental factors influence the dynamic, physiological characteristics, and metabolic profiles of *Cyanobacteria*. This results in their ability to adapt and survive in diverse ecosystems. *Cyanobacteria* produce many secondary metabolites, which are considered to be rich sources for drug discovery and development (Li et al. 2020). Thermal springs harbor potential thermotolerant *Cyanobacteria* strains for biotechnological applications and many new thermophilic bacterial strains have been isolated from these springs and evaluated for their biotechnological potential (Amarouche-Yala et al. 2014; Saghatelyan et al. 2021; Keshari et al. 2022).

Avène Thermal Spring Water from the Montagne Noire in France is used to treat inflammatory skin diseases. Over a 4-year sampling period, in-depth prospection of Avène thermal spring water reveals a stable microbial community, with a relatively constant richness of species. *Nitrospirae* and *Proteobacteria* phyla were the most prevalent (Bourrain et al. 2020). A biological concentrate, from culture

of an Avène aquatic microflora isolate namely *Aquaphilus dolomiae*, showed immunomodulatory, anti-inflammatory, antipruritic, and tolerogenic activities in atopic dermatitis pharmacology models (Nguyen et al. 2017).

The bacterial communities of Lake Hévíz were studied between 2009 and 2015, using various microbial methods such as denaturing gel electrophoresis, direct cell count determination, cultivation, molecular cloning, pyrosequencing. Significant seasonal differences were noticed regarding the total bacterial community composition. Due to the high output of the spring, no clear vertical stratification was observed in the bacterial communities. From the water of Lake Hévíz besides the aerobic or facultative anaerobic heterotrophic bacteria (e.g., *Aquiluna rubra*, *Rheinheimera aquatic*, *Polynucleobacter cosmopolitanus*, *Polynucleobacter acidiphobus*, *Gemmobacter lanyuensis*), dominant and permanent presence of chemolithotrophic (e.g., *Thiobacillus*) and photolithotrophic (e.g., *Cyanobacteria* and *Chloroflexi*) autotrophic bacteria were identified (Krett et al. 2016).

First published in the literature, Italian authors characterized the microbial community of sulfurous-bromine-iodine thermal water, flowing from springs to points of use, and of muds during the various maturation stages using next-generation

Table 3 Differences in abundances of the dominant genera in our analysis between control-non-lesional skin and lesional skin regions before treatment. Each genus was selected by the threshold detection 100 and prevalence 0.1 of the core function in the microbiome (Lahti et al. 2019) R Bioconductor package. Columns of the table represent the $\log_2$ Fold Change estimates (*log2FoldChange*), its standard error (*lfcSE*), *p* values (pvalue), and FDR corrected p-values (padj) as calculated by the paired DESeq2 analysis. Significant differences are indicated with asterisks (FDR corrected *p* value < 0.05). Positive $\log_2$ fold change indicates that the genus had higher abundance in psoriasis samples

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Burkholderia	−0.329	0.281	0.241	0.757	
Neisseria	0.408	0.323	0.206	0.757	
Paracoccus	0.376	0.248	0.130	0.757	
Rhodobacter	0.183	0.319	0.567	0.931	
Rubellimicrobium	0.553	0.434	0.202	0.757	
Methylobacterium	0.373	0.340	0.273	0.757	
Roseomonas	1.046	0.510	0.041	0.568	
Sphingomonas	0.367	0.321	0.253	0.757	
Kaistobacter	−0.064	0.359	0.859	0.948	
Acinetobacter	0.090	0.187	0.629	0.931	
Enhydrobacter	0.103	0.210	0.625	0.931	
Pseudomonas	0.061	0.238	0.798	0.948	
Haemophilus	0.178	0.303	0.557	0.931	
Stenotrophomonas	0.280	0.380	0.460	0.883	
Erwinia	0.070	0.377	0.852	0.948	
Campylobacter	−0.948	0.388	0.015	0.553	
Corynebacterium	−0.024	0.171	0.886	0.948	
Micrococcus	0.082	0.228	0.720	0.948	
Kocuria	0.277	0.196	0.156	0.757	
Rothia	0.202	0.269	0.451	0.883	
Propionibacterium	−0.159	0.172	0.354	0.831	
Actinomyces	0.053	0.194	0.785	0.948	
Brevibacterium	−0.392	0.197	0.047	0.568	
Microbacterium	−0.015	0.268	0.954	0.970	
Nocardioides	0.616	0.377	0.102	0.757	
Brachybacterium	0.045	0.278	0.871	0.948	
Janibacter	0.210	0.363	0.563	0.931	
Mycobacterium	0.166	0.355	0.641	0.931	
Rhodococcus	0.351	0.359	0.328	0.831	
Dietzia	0.520	0.397	0.190	0.757	
Pseudonocardia	0.477	0.424	0.260	0.757	
Streptomyces	0.189	0.234	0.420	0.883	
Gordonia	0.841	0.381	0.027	0.553	

Table 3 (continued)

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Streptococcus	0.056	0.212	0.792	0.948	
Lactococcus	0.525	0.406	0.196	0.757	
Alloiococcus	0.461	0.414	0.265	0.757	
Facklamia	−0.271	0.460	0.555	0.931	
Aerococcus	−0.086	0.286	0.763	0.948	
Lactobacillus	0.066	0.191	0.728	0.948	
Leuconostoc	−0.592	0.673	0.379	0.857	
Granulicatella	0.096	0.359	0.789	0.948	
Staphylococcus	0.150	0.290	0.604	0.931	
Jeotgalicoccus	0.257	0.425	0.545	0.931	
Exiguobacterium	0.106	0.330	0.748	0.948	
Bacillus	0.492	0.318	0.121	0.757	
Anaerococcus	−0.326	0.204	0.110	0.757	
Finegoldia	−0.037	0.192	0.846	0.948	
Peptoniphilus	0.480	0.353	0.174	0.757	
Veillonella	−0.008	0.296	0.979	0.979	
Leptolyngbya	1.461	0.653	0.025	0.553	
Prevotella	0.230	0.248	0.352	0.831	
Porphyromonas	−0.188	0.395	0.634	0.931	
[Prevotella]	0.115	0.631	0.856	0.948	
Bacteroides	0.029	0.326	0.929	0.970	
Capnocytophaga	0.118	0.402	0.769	0.948	
Flavobacterium	0.518	0.426	0.223	0.757	
Chryseobacterium	0.390	0.375	0.297	0.789	
Leptotrichia	0.275	0.375	0.463	0.883	
Fusobacterium	0.2614	0.341	0.443	0.883	
Deinococcus	0.866	0.527	0.101	0.757	
Photobacterium	−0.025	0.405	0.950	0.970	

sequencing technologies. Despite the slight fluctuations in genera variety and abundance caused by temperature variations along the pipelines, their data highlighted the presence of a typical microbial community, mainly composed of sulfur-cycling bacteria (*Desulfomonile*, *Thermodesulfovibrio*, *Geothermobacterium*, *Thermus*, *Thiofaba*, and *Syntrophomonas* genera). The three predominant genera in the microbial community of mud were *Pelobacter*, *Desulfomonile*, and *Thiobacillus*. The abundance of these genera varied during the maturation process. The results showed that the microbiome of mature mud was dominated by *Pelobacter* genus capable of lipid biosynthesis, suggesting that these bacteria may play a role in the anti-rheumatic properties of thermal mud (Paduano et al. 2018).

Table 4 Differences in abundances of the dominant genera in our analysis between control non-lesional skin areas before and after treatment. Each genus was selected by the threshold detection 100 and prevalence 0.1 of the core function in the microbiome (Lahti et al. 2019) R Bioconductor package. Columns of the table represent the $\log_2$ Fold Change estimates (*log2FoldChange*), its standard error (*lfcSE*), *p* values (pvalue), and FDR corrected *p* values (padj) as calculated by the paired DESeq2 analysis. Significant differences are indicated with asterisks (FDR corrected *p* value < 0.05). Positive $\log_2$ fold change indicates that the genus had higher abundance post-treatment

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Burkholderia	0.142	0.341	0.676	0.878	
Neisseria	0.957	0.413	0.021	0.234	
Paracoccus	0.198	0.248	0.425	0.722	
Rhodobacter	0.736	0.439	0.094	0.314	
Rubellimicrobium	−0.886	0.556	0.111	0.314	
Methylobacterium	−0.220	0.345	0.524	0.800	
Roseomonas	0.690	0.624	0.269	0.549	
Sphingomonas	−0.483	0.354	0.172	0.409	
Kaistobacter	−0.619	0.414	0.135	0.344	
Acinetobacter	−0.069	0.371	0.852	0.962	
Enhydrobacter	0.766	0.382	0.045	0.294	
Pseudomonas	−0.046	0.400	0.908	0.976	
Haemophilus	0.801	0.388	0.039	0.294	
Stenotrophomonas	−0.803	0.591	0.174	0.409	
Erwinia	−0.847	0.509	0.096	0.314	
Campylobacter	−0.001	0.491	0.999	0.999	
Corynebacterium	0.287	0.181	0.113	0.314	
Micrococcus	−0.125	0.294	0.671	0.878	
Kocuria	0.018	0.297	0.951	0.983	
Rothia	0.534	0.278	0.055	0.294	
Propionibacterium	−0.246	0.320	0.443	0.722	
Actinomyces	0.295	0.289	0.308	0.569	
Brevibacterium	−0.088	0.331	0.790	0.926	
Microbacterium	−0.584	0.302	0.053	0.294	
Nocardioides	−0.910	0.400	0.023	0.234	
Brachybacterium	−0.047	0.400	0.907	0.976	
Janibacter	0.214	0.372	0.565	0.821	
Mycobacterium	0.039	0.357	0.912	0.976	
Rhodococcus	−0.351	0.316	0.267	0.549	
Dietzia	0.197	0.432	0.649	0.878	
Pseudonocardia	0.039	0.453	0.932	0.980	
Streptomyces	−0.100	0.288	0.729	0.890	
Gordonia	−0.338	0.477	0.479	0.749	

Table 4 (continued)

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Streptococcus	0.386	0.257	0.133	0.344	
Lactococcus	0.167	0.533	0.755	0.902	
Alloiococcus	0.432	0.572	0.450	0.722	
Facklamia	−0.656	0.537	0.222	0.501	
Aerococcus	−0.474	0.441	0.283	0.556	
Lactobacillus	−0.142	0.379	0.709	0.883	
Leuconostoc	−0.294	0.592	0.619	0.877	
Granulicatella	0.384	0.406	0.344	0.618	
Staphylococcus	0.129	0.270	0.633	0.877	
Jeotgalicoccus	1.148	0.449	0.011	0.162	
Exiguobacterium	−0.344	0.575	0.550	0.818	
Bacillus	0.007	0.374	0.985	0.999	
Anaerococcus	−0.400	0.240	0.096	0.314	
Finegoldia	−0.352	0.343	0.305	0.569	
Peptoniphilus	0.153	0.404	0.705	0.883	
Veillonella	0.564	0.297	0.058	0.294	
Leptolyngbya	4.580	0.673	0.000	0.000	*
Prevotella	0.574	0.319	0.072	0.314	
Porphyromonas	0.283	0.375	0.450	0.722	
[Prevotella]	0.981	0.480	0.041	0.294	
Bacteroides	−0.090	0.449	0.842	0.962	
Capnocytophaga	−0.690	0.626	0.270	0.549	
Flavobacterium	−1.784	0.566	0.002	0.050	*
Chryseobacterium	−0.816	0.496	0.100	0.314	
Leptotrichia	1.136	0.399	0.004	0.089	
Fusobacterium	0.748	0.468	0.110	0.314	
Deinococcus	1.059	0.617	0.086	0.314	
Photobacterium	−1.656	0.920	0.072	0.314	

Overall, our study highlights the importance of skin microbiome and the beneficial effects of balneotherapy in psoriasis patients. Further studies with larger number of patients are needed to clarify how waters with different mineral content, concentration, and bacterial communities affect the skin microbiome system.

Limitation of the study

Only 16 patients were enrolled into our study. This sample size is obviously not enough for a detailed statistical analysis, but the obtained trend clearly confirmed the effects of balneotherapy on skin microbiome.

Table 5 Differences in abundances of the dominant genera in our analysis between lesional skin before and after treatment. Each genus was selected by the threshold detection 100 and prevalence 0.1 of the core function in the microbiome (Lahti et al. 2019) R Bioconductor package. Columns of the table represent the $\log_2$ Fold Change estimates (*log2FoldChange*), its standard error (*lfcSE*), p values (pvalue) and FDR corrected p values (padj) as calculated by the paired DESeq2 analysis. Significant differences are indicated with asterisks (FDR corrected p value < 0.05). Positive $\log_2$ fold change indicates that the genus had higher abundance post-treatment

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Burkholderia	0.218	0.344	0.526	0.862	
Neisseria	0.178	0.322	0.582	0.862	
Paracoccus	−0.389	0.257	0.131	0.622	
Rhodobacter	0.224	0.413	0.587	0.862	
Rubellimicrobium	0.432	0.441	0.328	0.769	
Methylobacterium	0.167	0.415	0.687	0.888	
Roseomonas	−0.380	0.381	0.319	0.769	
Sphingomonas	−0.294	0.396	0.458	0.847	
Kaistobacter	0.028	0.420	0.947	0.993	
Acinetobacter	−0.088	0.372	0.814	0.967	
Enhydrobacter	0.594	0.371	0.109	0.622	
Pseudomonas	0.124	0.464	0.789	0.962	
Haemophilus	−0.003	0.335	0.993	0.993	
Stenotrophomonas	−0.833	0.534	0.119	0.622	
Erwinia	−0.403	0.369	0.274	0.696	
Campylobacter	0.755	0.396	0.056	0.622	
Corynebacterium	0.153	0.179	0.394	0.823	
Micrococcus	−0.410	0.288	0.155	0.631	
Kocuria	−0.058	0.273	0.832	0.967	
Rothia	0.260	0.294	0.378	0.823	
Propionibacterium	−0.500	0.341	0.143	0.623	
Actinomyces	0.218	0.340	0.521	0.862	
Brevibacterium	0.469	0.312	0.132	0.622	
Microbacterium	−0.047	0.330	0.888	0.982	
Nocardioides	−0.730	0.470	0.121	0.622	
Brachybacterium	−0.706	0.382	0.064	0.622	
Janibacter	−0.543	0.415	0.191	0.653	
Mycobacterium	−0.222	0.440	0.614	0.862	
Rhodococcus	−0.746	0.481	0.121	0.622	
Dietzia	−0.227	0.383	0.553	0.862	
Pseudonocardia	−0.532	0.477	0.265	0.696	
Streptomyces	−0.400	0.336	0.234	0.696	
Gordonia	−1.309	0.466	0.005	0.238	
Streptococcus	0.413	0.300	0.169	0.645	

Table 5 (continued)

Genus	log2Fold-Change	lfcSE	pvalue	padj	Significance
Lactococcus	−0.285	0.466	0.541	0.862	
Alloiococcus	0.100	0.495	0.841	0.967	
Facklamia	−0.442	0.386	0.252	0.696	
Aerococcus	−0.582	0.505	0.249	0.696	
Lactobacillus	0.037	0.362	0.918	0.982	
Leuconostoc	0.253	0.580	0.662	0.878	
Granulicatella	0.315	0.378	0.405	0.823	
Staphylococcus	−0.132	0.267	0.621	0.862	
Jeotgalicoccus	0.500	0.543	0.358	0.808	
Exiguobacterium	−0.060	0.505	0.906	0.982	
Bacillus	−0.520	0.340	0.126	0.622	
Anaerococcus	−0.012	0.281	0.966	0.993	
Finegoldia	−0.214	0.287	0.456	0.847	
Peptoniphilus	−0.706	0.363	0.052	0.622	
Veillonella	0.426	0.379	0.261	0.696	
Leptolyngbya	1.668	0.627	0.008	0.238	
Prevotella	0.144	0.318	0.651	0.878	
Porphyromonas	0.342	0.440	0.438	0.847	
[Prevotella]	0.224	0.578	0.698	0.888	
Bacteroides	−0.288	0.452	0.524	0.862	
Capnocytophaga	0.009	0.395	0.982	0.993	
Flavobacterium	−1.176	0.507	0.020	0.415	
Chryseobacterium	−0.314	0.460	0.494	0.862	
Leptotrichia	0.107	0.384	0.780	0.962	
Fusobacterium	0.234	0.455	0.607	0.862	
Deinococcus	0.635	0.487	0.193	0.653	
Photobacterium	−0.090	0.859	0.916	0.982	

Conclusion

In this study, we evaluated the effect of balneotherapy on skin microbiome in patients with plaque psoriasis. The composition of microbial communities were similar on psoriatic plaque and non-lesional skin at baseline and after balneotherapy. Balneotherapy in the unaffected area significantly increased the level of *Leptolyngbya* genus, and significantly decreased the level of *Flavobacterium* genus. A similar trend was revealed in the lesional skin. Balneotherapy with sulfur-containing water was proved to be an effective treatment modality for the management of mild plaque psoriasis. With the results of our study, we can get closer to clarifying the mechanism of action of balneotherapy, but further studies are needed with waters containing other minerals (radon, salt, iodine, etc.).

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