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Correlation Between Insulin Resistance and Psoriatic Arthritis Disease Activity: A Cross-Sectional Study

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Abstract

Objectives: Most psoriatic arthritis (PsA) research and studies focus solely on the skin and joint manifestations, but there is also an increased risk of metabolic disorders, including insulin resistance (IR). This study aims to discover the relationship between IR and disease activity (DA) in PsA and its phenotype. Materials and methods: Patients with PsA classified using the CASPAR criteria with the disease activity was measured using the DAPSA score, and IR was identified as an elevated HOMA-IR of >2.5. The disease phenotype was determined with Moll and Wright's classification of the PsA subtype. The Pearson correlation test examined the relationship between DA and IR. The descriptive analysis was conducted to determine the relationship between the DAPSA score and HOMA-IR value in each PsA phenotype. All tests were two-tailed, analysed with GraphPad Prism 9, and a *P*-value of less than .05 was considered statistically significant. Results: From thirty-one patients, there was a strong and positive relationship between DA and IR (r = .768, *P* = .000). We also observed variations in DAPSA score and HOMA-IR value across different phenotypes, with symmetrical polyarthritis exhibiting the highest DAPSA score (21.55 ± 3.50) and HOMA-IR value (2.913 ± .5392) despite asymmetrical oligoarthritis that being the most frequent phenotype. Conclusion: Our study revealed a significant association between disease activity and insulin resistance in PsA patients, with the symmetrical polyarthritis phenotype demonstrating the highest levels of DAPSA score and IR value. This finding allowed rheumatologists to behold this manifestation and could improve PsA patients' long-term outlook.

Keywords

chronic disease, disease activity in psoriatic arthritis (DAPSA) score, homeostatic model assessment of insulin resistance (HOMA-IR), insulin resistance, psoriatic arthritis

Introduction

Psoriatic arthritis (PsA) is a chronic autoimmune musculoskeletal condition that affects the joints, skin, nails, and other body structures and is often connected to cutaneous psoriasis. This disease is most frequently both in men and women between the ages of 40 and 50.[1] Inflammation played a role in interactions between metabolic changes and immune system disruptions in chronic disease,[2] incuding PsA, and leads to elevated risk of metabolic disorders such as diabetes and cardiovascular disease.[3]

Insulin resistance, a hallmark of metabolic syndrome, has been shown to play a role in the pathogenesis of various inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus.[4-6] However, the relationship between insulin resistance and PsA remains unclear. A mortality study shows an increase in mortality in rheumatoid arthritis patients, and the evidence shows the same potential increase in patients with PsA.[7] In addition, insulin resistance has garnered increasing attention, with potential effects on various disease spectrums.[7-9]

Several studies have suggested a link between PsA and higher prevalence of type 2 diabetes.[10,11] But there has been a lack of

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studies on the correlation between PsA and its phenotype with insulin resistance, particularly from Southeast Asia or Indonesia. It is important to note that genetic factors play a significant role in the development of autoimmune conditions, and may result in varying manifestations across different races, ethnicities, and populations within the region.[12]

Insufficient research on the correlation between disease activity and insulin resistance in PsA, compounded by the majority of PsA studies focusing solely on skin and joint manifestations, underscores the potential significance of this study in improving the management of PsA patients. Our study aims to investigate the relationship between insulin resistance and psoriatic arthritis, including its phenotype, and may provide valuable insights for the management of PsA, potentially improving patients' long-term outcomes.

Materials and Methods

Patients, Study Design, and Ethical Approval

This cross-sectional study included 31 patients from Dr Soetomo General Hospital's Department of Rheumatology over the age of eighteen with psoriatic arthritis classified using the Classification for Psoriatic Arthritis (CASPAR) criteria. This study has been conducted in accordance with The Code of Ethics of the World The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. Prior to participation, informed consent was obtained from all patients, and their confidentiality was ensured. This study was approved by the Research Ethics Committee of Dr Soetomo Hospital (Number: 0117/KEPK/XII/2020).

Evaluation of Disease Activity and Insulin Resistance

The disease activity was measured with the DAPSA score. Using 66/68 joint counts, the DAPSA is calculated by summing the swollen joints, tender joints, patient pain, patients' global assessments, and CRP.[13] DAPSA score distributed as; >4 – ≤14 low disease activity (LDA), >14 – ≤28 for moderate disease activity (MoDA), and >28 for high disease activity (HDA).[14] The disease phenotype was determined with Moll and Wright's classification of the PsA subtype.[15] The homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using this formula: fasting insulin (μIU/L) × fasting glucose (mg/dL)/405. Based on the original HOMA research, insulin resistance was defined as an elevated HOMA-IR value of > 2.5.[16] Other risk factors, including sex, body mass index (BMI), and waist circumference also identified and measured in this study.

Statistical Analysis

The Shapiro-Wilk test was used to determine the normality of all data. Data on patients' basic characteristics were analyzed descriptively. The Pearson correlation test examined the relationship between disease activity and insulin resistance. The descriptive analysis was conducted to determine the relationship between disease activity and HOMA-IR value in each PsA phenotype. All tests were two-tailed, analyzed with GraphPad Prism 9 for windows, and a *P*-value of less than .05 was considered statistically significant.

Results

Table 1 shows the general characteristics of 31 PsA patients from Dr Soetomo General Hospital. The patients had an average age of 44.2 ± 13.4 years, with 87.1% of them being female and only 12.9% male. More than half of the patients (58.1%) had an overweight BMI, with the average male and female waist circumferences being 90.25 ± 9.18 and 85.37 ± 7.00, respectively. Asymmetrical oligoarthritis was the most frequent phenotype observed (41.9%), while none of the patients exhibited arthritis mutilans.

The DAPSA score was measured to evaluate disease activity. The average DAPSA score of all 31 patients was found to be 15.27 ± 5.54, with 16 patients categorized as having LDA and 15 patients categorized as having MoDA. None of the patients were in remission or HDA. The mean HOMA-IR value for all patients was 2.21 ± .89, where a value greater than 2.5 indicates insulin resistance. Out of the 31 patients, 10 had HOMA-IR values greater than 2.5, while 21 had values less than 2.5.

Each PsA phenotype exhibited different disease activity and insulin resistance in patients, as shown in Figure 1. Although asymmetrical oligoarthritis was the most common phenotype among patients, symmetrical polyarthritis had the highest disease activity (mean: 21.55 ± 3.50) and HOMA-IR value (mean: 2.913 ± .5392) compared to the overall phenotype. Conversely, the phenotype with the lowest disease activity and HOMA-IR value was the predominant axial, with mean DAPSA and HOMA-IR values of 9.58 ± 2.47 and 1.73 ± 1.02, respectively. The average DAPSA score of asymmetrical oligoarthritis and predominant DIP joint were 14.21 ± 3.478 and 13.80 ± 6.53, respectively. The mean HOMA-IR value of patients with asymmetrical oligoarthritis was 1.93 ± .76, while for the predominant DIP joint was 2.50 ± .91.

The Pearson correlation test was used to analyze the relationship between disease activity (DAPSA) and insulin resistance (HOMA-IR) variables. The of correlation coefficient (r) was .768 with a *P*-value of less than .001, suggesting a strong and positive association between disease activity and insulin resistance.

Discussion

This study aims to investigate the relationship between insulin resistance and psoriatic arthritis, including its phenotype. The general characteristics of patients with PsA in this study were consistent with the epidemiological data, which shows that it is more prevalent in females and the average age of onset is in

Table 1. Patients' Characteristics.

Characteristics	Value
Sex (male: Female) [n (%)]	4 (12.9%): 27 (87.1%)
Age (years) *(mean±SD)*	44.2±13.4
Onset (years) *(mean±SD)*	40.6±12.5
Duration of illness (years) *[median (95% CI)]*	2 (2-4)
BMI (kg/m^2) *[n (%)]*	
Underweight (<18.5 kg/m^2)	0
Normal (18.5-24.9 kg/m^2)	13 (41.9%)
Overweight (25-29.9 kg/m^2)	18 (58.1%)
Waist circumference (cm) *(mean±SD)*	
Male	90.25±9.18
Female	85.37±7.00
Disease phenotype *[n (%)]*	
Asymmetrical oligoarthritis	13 (41.9%)
Symmetrical polyarthritis	9 (29%)
Predominant axial	7 (22.6%)
Predominant DIP joint	2 (6.5%)
Arthritis mutilans	0
CRP (mg/dL) *[median (95% CI)]*	.43 (.27-.74)
Fasting insulin level (μIU/mL) *(mean±SD)*	10.42±3.81
Fasting glucose level (mg/dL) *(mean±SD)*	85.06±11.25

SD: standart deviation, CI: confidence interval, BMI: body mass index, CRP: C-reactive protein.

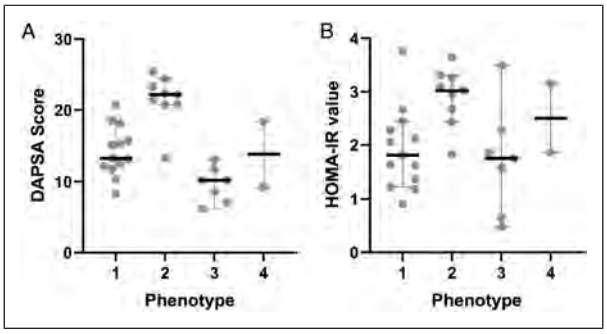

Figure 1. The disease activity and HOMA-IR value in each PsA phenotype. A. Disease Activity determined by DAPSA Score. B. HOMA-IR value. 1: Asymmetrical oligoarthritis (n: 13), 2: Symmetrical polyarthritis (n: 9), 3: Predominant axial (n: 7), 4: Predominant DIP joint (n: 2).

the fourth or fifth decade of life.[17] In addition, the high prevalence of overweight BMI in this study is consistent with previous studies that suggest a relationship between obesity and the development and progression of PsA.[18-20] These findings suggest that the characteristics of PsA patients in this study are representative of the broader population of PsA patients.

The results of the DAPSA score and HOMA-IR value of the PsA patients showed that none of the patients were in remission or HAD with insulin resistance present in 10 patients who had HOMA-IR values greater than 2.5. Patients with PsA commonly have mild to moderate disease activity, with a significant proportion of patients experiencing insulin resistance. There was also significant positive correlation between disease activity and insulin resistance in patients with PsA. These findings are in line with previous studies that have demonstrated a similar association between insulin resistance and various rheumatic diseases.[21-23] Clinicians may should consider this comorbidity in PsA patients to provide early interventions and prevent the development of complications strongly associated with insulin resistance, such as type 2 diabetes mellitus (DM) and cardiovascular diseases.

Insulin resistance is one of the characteristics of type 2 DM,[24] but the underlying pathways that link PsA to insulin resistance and DM are complex and not completely understood. One possible explanation for this correlation is that chronic inflammation in PsA leads to an increase in insulin resistance and promotes further inflammation. This vicious cycle can contribute to the development of various comorbidities commonly seen in PsA patients, such as cardiovascular disease and type 2 DM. In a large population-based cohort study, diabetes was found to be more common in PsA patients than in people of the sex and age match but without the disease (72%, HR 1.72). Interestingly, when BMI, alcohol consumption, smoking, initial glucocorticoid use, and comorbidities were controlled, the relationship was significantly reduced but remained significant (33%, HR 1.33) in PsA patients.[25]

Differences in the appearance of phenotypes in patients are also often associated with disease activity. Arthritis mutilans is the most severe and uncommon form of psoriatic arthritis,[26] as

our results, none of the patients have this phenotype in this study. On the other hand, despite asymmetric oligoarthritis being the most common phenotype in PsA patients in this study, symmetrical polyarthritis has the highest disease activity and insulin resistance indicated by the HOMA-IR value. However, no research has been conducted into the correlations between insulin resistance in each PsA phenotype. But numerous studies have found the sensitivity of HLA-related genes found in people with PsA. The *HLA-B**27 allele has been linked to more severe PsA phenotypes, while other HLA-related genes are found in people with PsA, including *HLA-B**07, *HLA-B**27, *HLA-B**38, and *HLA-B**39 alleles, have been identified as PsA risk factors.[27,28] Inter-phenotypic studies in PsA present challenges because patients may display a distinct combination and severity of disease domains, resulting in individual incidence and prevalence.[29] Moreover, PsA patients are susceptible to various comorbidities, contributing to disease variability and exacerbating disease management and research.[30]

This study became the initials to investigating insulin resistance in patients with PsA and each phenotype, particularly from Southeast Asian populations. The study's findings provide valuable information for rheumatologists in this region, where PsA is known to be prevalent but has been relatively understudied. Furthermore, this study could lead to future research on the role of insulin resistance in PsA pathogenesis and management. But this study has several limitations; the HOMA-IR which may not fully reflect insulin resistance in PsA patients, future studies could consider other measures of insulin resistance to provide a more accurate evaluation; the cross-sectional design limits the ability to establish a causal relationship between insulin resistance and PsA disease activity, further longitudinal studies are needed to determine whether insulin resistance is a predictor of disease activity in PsA patients.

Conclusions

According to the findings of this study, there is a significant positive relationship between PsA disease activity and insulin resistance ($r = 0.768$, $P = .000$). Furthermore, we discovered differences in disease activity and HOMA-IR values between PsA phenotypes, with symmetrical polyarthritis being the most severe and having the highest HOMA-IR values. Larger-scale research is required to understand better the relationship and mechanism of insulin resistance in PsA severity, which could be useful for reliable PsA diagnosis and treatment in the future.

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Declaration Of Conflicting Interests

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Consent

Participants provided written informed consent.

Ethics

Ethics approval was not necessary for the literature review.

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Original Research

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Paradoxical Effects of Depression on Psoriatic Arthritis Outcomes in a Combined Psoriasis-Psoriatic Arthritis Center

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Abstract

Backgroud: Psoriatic arthritis (PsA) is a chronic, inflammatory arthritis that, when left untreated, can lead to erosions, deformities and decrease in quality of life. PsA is known to be associated with multiple comorbidities, including cardiovascular, metabolic and mental health syndromes, all of which can increase its overall morbidity and mortality. **Objective:** To characterize a cohort of patients with PsA and understand the impact of depression on PsA outcome measures. **Methods:** 527 consecutive patients with PsA were enrolled in an observational, longitudinal registry that followed them prospectively at standard of care visits. Demographics, medical history, medication use, and clinical exam were all recorded. **Results:** Depression was reported in 22.8% of the population, anxiety in 18%, and attention deficit hyperactivity disorder in 4%. Depression was more common in female participants ($P < .001$). At baseline, individuals with PsA and concomitant depression had similar tender and swollen joint counts and RAPID3 compared to those without depression, and had lower body surface area affected by psoriasis ($P = .04$). At year one, all patients had improvement in clinical outcomes. However, patients with depression had a significantly higher tender joint count compared to those without depression ($P = .001$), despite similar swollen joint count and body surface area. **Conclusion:** In patients with depression, there is a discrepancy between improvement in physician assessed measures and patient reported outcomes. These observations underscore the importance of addressing depression and psychological distress as part of PsA treatment outcomes and points towards the need to address residual pain through co-adjuvant approaches.

Keywords
psoriasis, psoriatic arthritis, depression < comorbidity < psoriasis, treatment outcomes < treatment < psoriasis, patient-reported outcome < psoriasis

Keywords
psoriatic arthritis, depression, pain

Introduction

Psoriatic arthritis (PsA) is a common immune mediated inflammatory arthritis with a prevalence on the rise in both the United States[1] and across the world.[2] PsA has a complex and diverse phenotype, and affects up to 30% of patients with psoriasis. It involves multiple domains, including skin, nails, peripheral arthritis, axial disease, dactylitis, and enthesitis. The spectrum of inflammatory changes has a significant interindividual variability and can become evident either as isolated clinical manifestations or as part of a multi-domain syndrome. This phenotypic diversity also contributes to the

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significant underdiagnosis and undertreatment of PsA,[3] which are known to negatively impact disease outcomes.[4]

Beyond its deleterious effects in skin and joints of patients, PsA is associated with multiple comorbid conditions (ie, cardiovascular and metabolic disease), which contribute to increased rates of morbidity and mortality.[5] In addition to its physical toll, PsA can lead to decreased quality of life, high levels of psychosocial stress, and increased rates of unemployment and reduced productivity.[6,7]

Depression and anxiety also have a high prevalence amongst patients with psoriatic disease.[8] Previous studies have suggested that depression may impact the ability of patients to achieve remission in both rheumatoid arthritis and PsA.[9] However, the underlying effects of depression in psoriatic disease is neither well characterized nor commonly acknowledged in clinical practice. In fact, and despite significant progress in therapeutics over the last two decades, treatment of inflammation in PsA remains substandard and residual symptoms (most notably pain and fatigue) are not resolved in a significant proportion of patients, hampering their ability to achieve a state of remission or even low-disease activity.[10] We therefore hypothesized that the presence of depression significantly affects PsA outcomes and may be at least partially responsible for the endurance of these residual symptoms.

Here, we describe the prevalence and extent of psychiatric comorbidities in a longitudinal PsA cohort from an urban, tertiary care, combined clinical setting and further assessed the effects of depression on PsA outcomes.

Methods

Patients

Consecutive adult patients meeting CASPAR criteria for PsA[11] were prospectively enrolled from the established New York University (NYU) Psoriatic Arthritis Center (PAC) from January 7, 2015 (inception of standardized electronic health record template) to December 3, 2020 into an observational, prospective cohort registry. During this time period, 527 patients were evaluated. Participants with fibromyagia were not excluded. Demographic and outcome information was extracted from clinical visits utilizing a PsA-specific template in the electronic health record (EHR; Epic) and subsequently entered into a REDCap[12] database. Baseline visit was defined as the first clinical interaction regardless of timepoint in disease duration or treatment. Patients were followed for up to 2 years from their baseline visit, for an average of 14.2 months [range .23-23.97 months]. All participating physicians are trained rheumatologists with specialization in psoriatic disease and practicing in a combined, dermatology-rheumatology clinic setting. The study was approved by the NYU Institutional Review Board (s20-00084) and individual patient consent was waived as all collected information was deidentified.

Demographic data, comorbidities, and family history were recorded. Mental health conditions (ie, depression, anxiety, and attention deficit disorder (ADHD)) were defined by established diagnosis (patient report and/or ICD code) and/or use of psychiatric medication. Physical exam findings such as tender (TJC) and swollen joint counts (SJC), and body surface area affected by psoriasis (BSA) were recorded from clinical notes as assessed by their primary NYU PAC rheumatologist. Patient reported outcomes such as the Multidimensional Health Assessment Questionnaire (MDHAQ)[13] and the resultant RAPID3[14] were entered by the patients on iPads at each clinical visit as part of routine care and directly transmitted to the EHR.

Statistical Analysis

Baseline characteristics of study participants during the first visit were summarized using frequency and proportion for categorical variables and mean and standard deviation for continuous variables. Statistical comparisons between the depressed and non-depressed groups, the primary exposure of interest, were performed using ANOVA and Wilcoxon rank sum tests for continuous variables, and chi-square tests for categorical variables. The association of depression with longitudinal PsA outcomes were assessed using mixed-effects Poisson regression models for tender and swollen joint counts and mixed-effects linear regression models for RAPID3 and BSA, adjusting for age, sex, race, medication use, comorbidities, and time since baseline. The model also included random intercepts for the individual patients, and interaction between depression and time. Estimates of rate ratios (RR) for the count outcomes and differences for the continuous outcomes along with 95% confidence intervals (CI), comparing the two exposure groups, were reported at the baseline, 1- and 2-year follow-up. All analyses were performed using R v4.1.2 software (R Foundation for Statistical Computing).[15]

Results

At the time of analysis, the NYU PAC cohort consisted of 527 patients with diagnosed PsA as defined by meeting CASPAR criteria. Patients were 46.7% female with a mean age of 49 years. The population was mostly white (79.7%), but did have a significant number of patients who identified as other races or ethnicities (Table 1). PsA phenotype was heterogeneous in clinical presentation, with 93.2% of patients showing peripheral joint involvement at any timepoint in disease course, 31.9% with axial involvement, 99.2% with skin involvement, 62.2% nail involvement, 35.1% entheseal involvement, and 33.6% dactylitis. Type of psoriasis was mostly in plaque form (75.1%) with 55.2% having nail involvement. Other types of psoriasis included: inverse (18.2%), guttate (4.7%), palmoplantar (3.6%), pustular (4.6%), and erythrodermic (.4%). Patients had a diagnosis of PsA for an average of 7.1 years.

At the baseline visit, individuals had an average of 1.8 swollen joints (SD 3.1) and 3.1 tender joints (SD 4.6), with 31% of participants showing at least one area of active enthesitis. The average percent BSA was 2.6% (SD 5.3) with a mean RAPID3 score of 10.9 (SD 6.7). At baseline, 217 patients were previously

Table 1. Baseline Characteristics.

Characteristic	All (n = 527)	Depression (n = 120)	No Depression (n = 407)	*P*-value[#]
Age- mean (SD)	49.0 (14)	52.1 (15.2)	48.1 (13.6)	.01
Female- n (%)	244 (46.7)	74 (62.7)	170 (42.0)	<.001
Race- n (%)				.86
White	420 (79.7)	99 (82.5)	321 (78.9)	
Black	7 (1.3)	0 (.0)	7 (1.7)	
Asian	42 (8.0)	4 (3.3)	38 (9.3)	
Other	7 (1.3)	2 (1.7)	5 (1.2)	
Hispanic ethnicity- n (%)	51 (9.7)	15 (12.5)	36 (8.8)	.23
Body Mass index- mean (SD)	27.9 (5.9)	28.5 (6.2)	27.8 (5.7)	.24
Comorbidities- n (%)				
Anxiety	95 (18.0)	61 (50.8)	34 (8.4)	<.001
ADHD	21 (4.0)	7 (5.8)	14 (2.4)	.36
Cardiovascular disease[a]	171 (32.4)	50 (41.7)	121 (29.7)	.02
Metabolic disease[b]	68 (12.9)	12 (15.8)	49 (12.0)	.35
Medication use- n (%)[c]				
Any	386 (73.2)	93 (77.5)	293 (72.0)	.28
Methotrexate	100 (19.0)	28 (23.3)	72 (17.7)	.21
Apremilast	35 (6.6)	8 (6.7)	27 (6.6)	1.00
Biologic or JAK inhibitor	223 (45.1)	55 (47.8)	168 (44.2)	.56
TNF inhibitor	160 (30.4)	36 (30.0)	124 (30.5)	1.00
2+ medications	64 (12.1)	16 (13.3)	48 (11.8)	.77
PsA duration—mean (SD)	7.1 (9.3)	8.1 (11.0)	6.9 (8.8)	.33

[a]Cardiovascular disease includes hypertension, myocardial infarctions, hyperlipidemia, heart failure, angina, coronary artery disease, and stroke.
[b]Metabolic disease includes diabetes and obesity.
[c]Any medication includes oral DMARDs (sulfasalazine, leflunomide, methotrexate), oral small molecules (apremilast and JAK inhibitors) and biologics. Of those on biologics, 72% were on tumor necrosis factor inhibitors. The remaining classes included IL-(12/)23 antagonists and IL-17 antagonists.

seen at the PAC, 248 were new to the PAC but had previously been seen by other rheumatologists, and 62 were new to PAC and had never been seen by rheumatology. At the baseline visit, 73.2% of patients were already on a biologic or non-biologic DMARD, with 45.1% of them on anti-cytokine therapy or janus kinase inhibitors (JAKis) (Table 1). Patients had relatively high rates of comorbidities including hypertension, hyperlipidemia, diabetes, obesity, inflammatory bowel disease (IBD) and uveitis. Our cohort also displayed high rates of psychiatric disease including depression (22.8%), anxiety (18%), and ADHD (4%), with depression and anxiety co-existing in 11.6% of participants (Table 1). Of those patients with depression, 47.5% were on at least one medication classified as an antidepressant. Rates of depression were higher in women compared to men (30.3% vs 16.2%, p = >.001, Supplementary Figure 1). The highest rates of depression were seen in white women with concomitant cardiovascular disease (41.3%). Similar rates of depression were seen in those taking medication for PsA (n = 386) compared to those who were not (n = 141, 24.1% vs 19.1%, P = .28), which was also true for those taking 2 or more PsA medications.

We then examined correlations between depression and disease measures at baseline. Participants with depression were more likely to be female (62.7% vs 42.0%, P < .01) and older (52.1 years vs 48.1 years, P = .01) (Table 1). Compared to those without depression, patients with depression were more likely to have concomitant anxiety (50.8% vs 8.4%, P < .01). They were also significantly more likely to have cardiovascular disease (including hypertension, hyperlipidemia, coronary artery disease, angina, and history of myocardial infraction and stroke; 41.7% vs 29.7%, P = .02) despite having comparable BMI measurements (28.5 vs 27.8, P = .24). There was no difference in PsA duration between groups.

At baseline, individuals with depression had similar observed tender and swollen joint counts and RAPID3 scores, and a lower BSA (P = .04) compared to those without depression (Figure 1). However, at one year, while both groups had improvement in their tender and swollen joint counts, patients with depression had a significantly higher TJC (P = .004) despite similar SJC, RAPID3, and BSA compared to non-depressed individuals. By year two, although not achieving significance, those with depression had numerically higher TJC yet lower SJC. There was no difference in PsA disease outcomes in patients who were depressed and on anti-depressants compared to those who were depressed and not on anti-depressants (Supplementary Figure 2).

When adjusting for age, sex, race, PsA medication use, and comorbidities in the mixed effects regression models, patients with depression had numerically higher rate of TJC compared to those without depression (RR 1.23, 95%CI .78, 1.94, P = .79) at baseline (Figure 2). This ratio was even higher at year 1

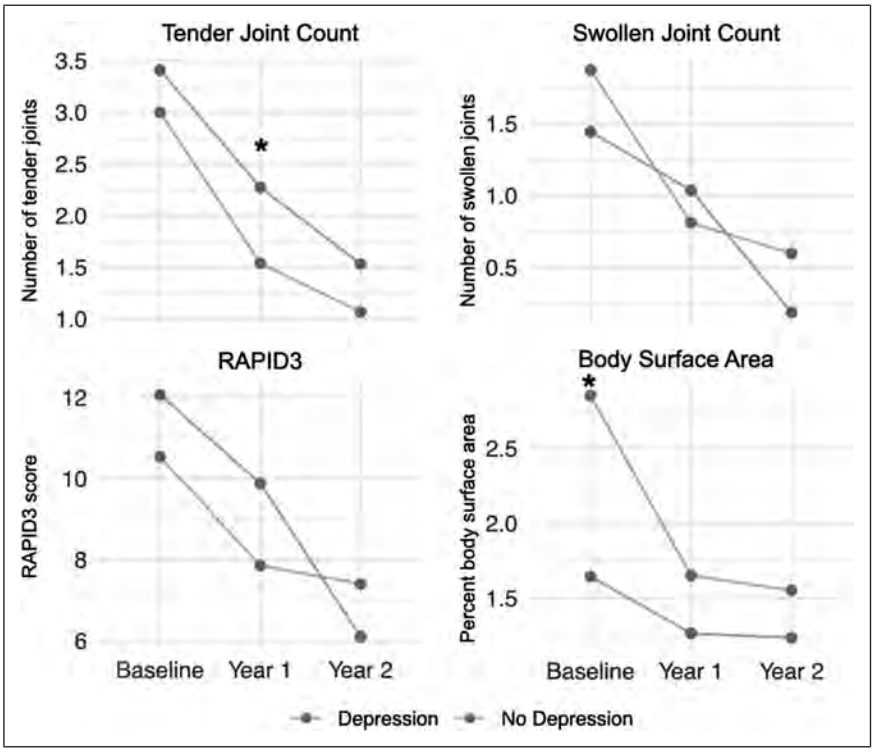

Figure 1. Observed mean PsA outcomes at baseline, year 1, and year 2. Red represents patients with depression, blue represents patients without depression. *P < .05.

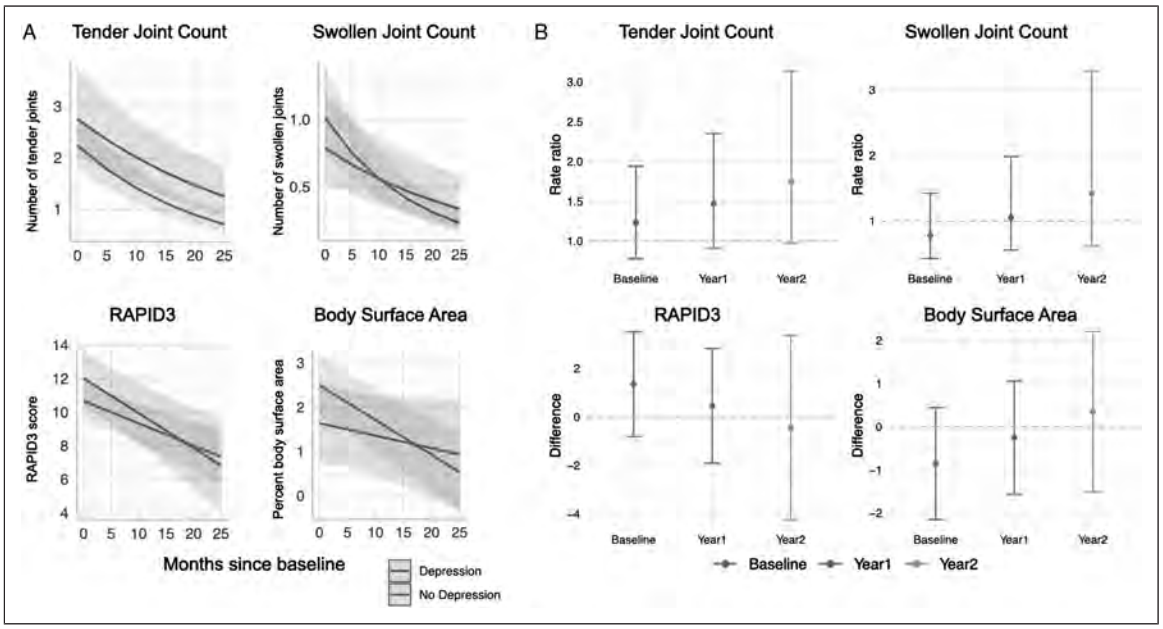

Figure 2. Model predicted means with 95% confidence bands (A), and predicted ratio ratios and estimated differences (B), adjusting for age, sex, race, comorbidities, and medication use.

(RR 1.47, 95%CI .91, 2.35, P = .19) and year 2 (RR 1.75, 95% CI .97, 3.14, P = .07), nearing significance. This same pattern was not seen in the SJCs or in the difference estimates for RAPID3 and BSA.

Discussion

We report on a longitudinal cohort of individuals with PsA seen at a tertiary care, combined-clinic setting in New York City. Observational cohort studies are of particular importance as they can inform on "real world" disease phenotypic characteristics and progression, which differ significantly from populations studied in the setting of controlled clinical trials. As in other recent reports, our cohort is composed by patients with a more oligoarticular, low skin disease involvement presentation. We also note a unique group of patients given its large referral base, urban setting, and diversity. While the NYU PAC population is primarily Caucasian, it has more racial and ethnic variability than any other previously described psoriasis and PsA cohorts.[16]

Importantly, this study emphasizes the high rates of depression and anxiety within the PsA population (22.8% and 18%, respectively). These numbers are in line with those reported by prior studies.[8,17] Of note, our study is the first to report rates of ADHD in an adult PsA population with a prevalence of 4%. This compares to world-wide rates of adults ranging from 1.1% to 4.4%.[18,19] Additionally, those who were depressed were more likely to be female and have cardiovascular disease, both of which are also seen in the general population.[20,21] Furthermore, the depression rates remain higher in women with cardiovascular disease and psoriasis compared to cardiovascular disease alone (40% vs 22.7%).[22] In fact, women with cardiovascular disease and psoriasis (40%) have similar rates of depression to women with cardiovascular requiring hospitalization for a cardiac event (35.7%).

Despite the high prevalence of depression and anxiety[8] and the fact that they have been independently associated with worse quality of life in psoriatic disease, these psychiatric disorders are often overlooked both in outcomes research and in clinical care. Here, we asked whether depression can affect PsA outcome measures. In so doing, we found that even in a population of relatively well controlled patients, over the course of treatment, while all patients improve, those with depression are less likely to see the same magnitude of amelioration in TJC compared to non-depressed patients, despite similar improvements in SJC. This implies that patient reported measures may be more affected by depression than physician observed measures.

Previous studies support our findings. Michelsen at al, looked at 728 patients with PsA and found that those with baseline depression and anxiety had increased patient global assessment of disease activity and joint pain.[9] These differences were largely driven by subjective outcomes, since depression and anxiety were not associated with inflammatory markers and swollen joint count during follow up. Freire et al showed that despite objective improvement on physician-assessed outcomes, patients with depression had increased pain VAS scores despite similar DAS28 and BASDAI scores, indicative of residual pain in these patients despite little objective disease activity and treatment.[17] Additionally, patients with RA and depression also had lower remission rates, driven by differences in pain score and patient global scores.[23]

In rheumatic diseases, depression and catastrophizing (ie, the rumination and magnification of pain intensity) are associated with increased pain sensitivity, pain severity, and self-reported physical limitations.[24] This suggests that depression leads to a worsened subjective disease experience and, therefore, treatment outcomes. Our study supports this hypothesis and extends it to patients with PsA and depression. A possible mechanism behind this phenomenon may be related to how depression can lead to alterations in the central nervous system processing of pain such as through sensitization or the possible amplification of pain-related signals.[24] In individuals with RA, recent studies have shown that increased connectivity between the default mode network and the insula cortex was associated with increased disease activity, tender joints, and higher rates of centralized pain.[25] Additionally, in those with ankylosing spondylitis, functional brain MRI (fMRI) studies have shown that a higher degree of abnormal connectivity between the DMN and the salience network is related to higher pain intensity scores.[26] We propose that in a similar manner, neuroconnectivity in PsA patients is altered by compounded inflammation and psychological stress, triggering the pathways of sensory input and pain perception.

This is of particular importance given that many patients with PsA continue to have residual symptoms despite anti-inflammatory treatment. Even in patients with very low disease activity as defined by physician measures, up to half of them continue to report pain and fatigue.[10] This residual pain, despite seeming control of inflammation, constitutes a significant barrier to achieving remission while the presence of psychologic stress (ie, depression) may be playing a contributing role in the persistence of this non-inflammatory type pain. Therefore, the current therapeutic paradigm of adjusting or escalating immunomodulatory medication may not be sufficient to mitigate pain in its entirety. Rather, patients may require supplementary approaches in treating their depression such as a more effective combination of antidepressant medications, introduction of cognitive behavioral therapy, or mindfulness interventions as co-adjuvant approaches to their standard of care PsA treatments.

Our study has several limitations, including the relatively short time course of data collection (ie, four years) and the definition of "baseline" visit, which includes patients at different points during their disease journey. Patients are counted as having a diagnosis of depression or anxiety if they presented with an established diagnosis (patient report and/or ICD code) and/or use of psychiatric medication. This study did not capture the current presence or severity at the time the baseline visits or

follow-ups. Additionally, we had a low rate of fibromyalgia (only 6 patients in the cohort), but again this was defined as patient report and/or ICD code and no standardized tools were used.

In summary, despite similar improvements in more objective, physician-assessed outcomes (such as swollen joint count, enthesitis count, and percent of body surface area affected) compared to patients without depression, those with depression were less likely to experience the same amelioration in tender joint count and, to a lesser extent, RAPID3. This discrepancy is likely a manifestation of how depression may affect the way patients experience their PsA and their perception even after systemic therapies. Furthermore, it may explain why despite seemingly adequate inflammatory control and normalized physical exams, some patients continue to complain of pain. Addressing underlying psychiatric comorbidities may bridge this gap between physician assessed measures and patient reported outcomes, and even reduce the need for escalation in therapy as residual pain may actually be inflammation-indepenedent. Therefore, depression should be considered a critical comorbidity when addressing PsA care in both clinical visits and in clinical trial settings. Our future research aims to address whether severity of depression symptoms and/or anti-depressant use can modulate PsA outcomes. This, coupled with investigations on neuroconnectivity dysregulation (as assessed by fMRIs) in PsA patients with comorbid depression as well as the incorporation of pharmacologic or non-pharmacologic modulation of psychiatric comorbidities may lead to improved understanding of residual pain and overall clinical outcomes in PsA.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RHH has served as a consultant for Janssen and UCB. ALN declares that she has served as a consultant for Janssen, UCB, AbbVie, BMS and her immediate family member owns shares of stock in J&J, Eli Lilly, AbbVie, and Pfizer. SR has served as a consultant for AbbVie/Abbott, Amgen, Novartis, Janssen, Pfizer. SA has received grants from Johnson and Johnson. JUS has served as a consultant for Janssen, Novartis, Pfizer, Sanofi, Amgen, UCB and AbbVie; and has received funding for investigator-initiated studies from Janssen and Pfizer.

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Consent

Participants provided written informed consent.

Ethics

Ethics approval was not necessary for the literature review.

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Supplemental Material

Supplemental material for this article is available online.

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Serum Adiponectin Levels as an Independent Marker of Severity of Psoriasis: A Cross-Sectional Analysis

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Abstract

Background: Adiponectin is an adipokine, having anti-inflammatory properties, the levels of which are reduced in metabolic syndrome. In psoriasis, it plays a preventive role by inhibiting the differentiation and proliferation of keratinocytes and decreasing the levels of the signature cytokine, IL-17. **Aims and objectives:** To find a correlation between serum adiponectin levels and the severity of psoriasis and to compare these levels amongst patients with parameters of metabolic syndrome vs those without it. **Materials and methods:** This was a cross-sectional observational study consisting of 60 cases of chronic plaque type psoriasis and 20 controls. Mild, moderate and severe disease was defined based on Psoriasis Area Severity Index (PASI). Serum samples were analyzed for fasting serum adiponectin levels. **Results:** The mean serum adiponectin level among cases (16.07 ± 8.55 μg/ml) was significantly lower than controls (21.65 ± 8.07 μg/ml, $P = .012$). It was not only lower among cases with MetS (14.28 ± 7.95 μg/ml), but also in patients without MetS (17.35 ± 8.83 μg/ml). Serum adiponectin levels were negatively correlated to age, Body Mass Index (BMI), PASI, disease duration and Erythrocyte Sedimentation Rate(ESR). However, only the negative correlation with PASI ($P = .000$), duration ($P = .005$) and ESR ($P = .010$), was statistically significant. **Conclusion:** Serum adiponectin is decreased in psoriasis, independent of metabolic syndrome and is negatively correlated with disease severity and duration. **Limitations:** Analysis on a larger sample size and response to treatment could not be assessed.

Keywords
adiponectin, metabolic syndrome, psoriasis

Introduction

Psoriasis is a chronic inflammatory condition which is associated with metabolic syndrome (MetS).[1-4] Patients of psoriasis are also at risk for type 2 diabetes mellitus, hypertension and coronary artery disease.[5] They have higher prevalence of 'occlusive vascular disease', including myocardial infarction (MI), stroke, thrombophlebitis and pulmonary embolism.[6] Obesity and insulin resistance which are the most important risk factors for MetS are also more prevalent in psoriasis.[7] Studies show a pathologic link between psoriasis and Mets: a common genetic loci (PSORS2-4, CDKAL1, and ApoE4) which increase susceptibility for both,[8,9] psoriatics also have pro-atherogenic lipid profile,[10] obese individuals have increased number of Th1 and Th17 cells[11,12] and increased production of inflammatory cytokines like IL-17, IL22, IL-10 and Interferon (IFN)-γ[13-16] and TNF-α is highly expressed in both psoriasis and obesity and thus contributes to the inflammatory state.[17]

Adipokines are the chemokines secreted by adipocytes in the white adipose tissue (WAT), which are mainly pro-inflammatory, such as leptin, visfatin, resistin and plasminogen activator inhibitor type 1 (PAI-1) and one is adiponectin, which has anti-inflammatory properties.[18] Adiponectin is a collagen-like protein of 247 amino acids that circulates at relatively high serum concentrations (4-26 μg/mL) and regulates the metabolism of lipids and glucose.[19]

Adiponectin levels are inversely correlated with obesity and BMI in the general population.[20] Adiponectin levels are reduced in metabolic syndrome.[1] It reduces insulin resistance and has anti-atherogenic, anti-angiogenic, and

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anti-inflammatory functions.[21] A fall in circulating serum adiponectin levels precedes a reduction in insulin sensitivity, followed by insulin-resistance years later.[1] It is hypothesized that therapy with adiponectin might be advantageous in reversing insulin resistance.[22]

In skin, adiponectin receptors, AdipoR1 and AdipoR2, are expressed in normal human keratinocytes.[23] Adiponectin influences skin homeostasis also, exerting indirect anti-inflammatory effects as mentioned in Table 1. It inhibits both proliferation and differentiation of keratinocytes. It also suppresses involucrin, TGFβ-2 and TGFβ -3 expression, and also decreases IL-6, IL-8, IL-17, IL-22, and TNF-α secretion by human keratinocytes. Adiponectin expression is suppressed by the pro-inflammatory cytokines viz TNF-α and IL-6, which has also been confirmed by increase in levels of adiponectin after treatment with anti-TNF-α and NBUVB therapy. Adiponectin in turn inhibits TNF-α induced IL-6 production.[24,25]

The complexity of adiponectin and its involvement in inflammatory skin diseases needs to be elucidated. In psoriatic patients circulating adiponectin levels are decreased, compared to normal individuals; moreover, there is a fall in these levels with increasing disease severity.[26,27] Figure 1 shows the pathogenic role of serum adiponectin in psoriasis.

Aims and objectives

1. To compare adiponectin levels in psoriasis cases and matched controls
2. To find a correlation between disease severity and Adiponectin levels
3. To compare these levels amongst patients with parameters of metabolic syndrome vs those without it.

Materials and methods

This was a cross-sectional observational study which included individuals with psoriasis and healthy persons visiting the outpatient department of dermatology, Rajindra Hospital, Patiala over a period of 18 months (Jan 2018 to July 2019). The study had total 80 participants: 60 cases and 20 healthy controls with non-inflammatory skin disorders in the age group of 10-80 years. Inclusion criteria: Clinically diagnosed psoriasis, all clinical types of psoriasis within the age group of 10-80 years belonging to both sexes. Exclusion criteria: Patients not willing to take part in the study, non-compliant patients and patients <10 years and >80 years. A complete dermatological examination to ascertain the diagnosis was done along with general physical examination. At the initial

Table 1. Anti-inflammatory Effects of Adiponectin in Skin.

Inhibit TNF-α induced adhesion molecule expression
Inducing IL-10 and IL-1RA by human monocytes, macrophages and dendritic cells
Suppress the production of IFN-γ by lipopolysaccharide (LPS)-stimulated human macrophages (21)
Reduces T-cell proliferation, macrophage phagocytic capability and macrophage TNF-α production (21)
Negative regulator on NK cells, suppressing their IL-2–augmented cytotoxic activity (42)

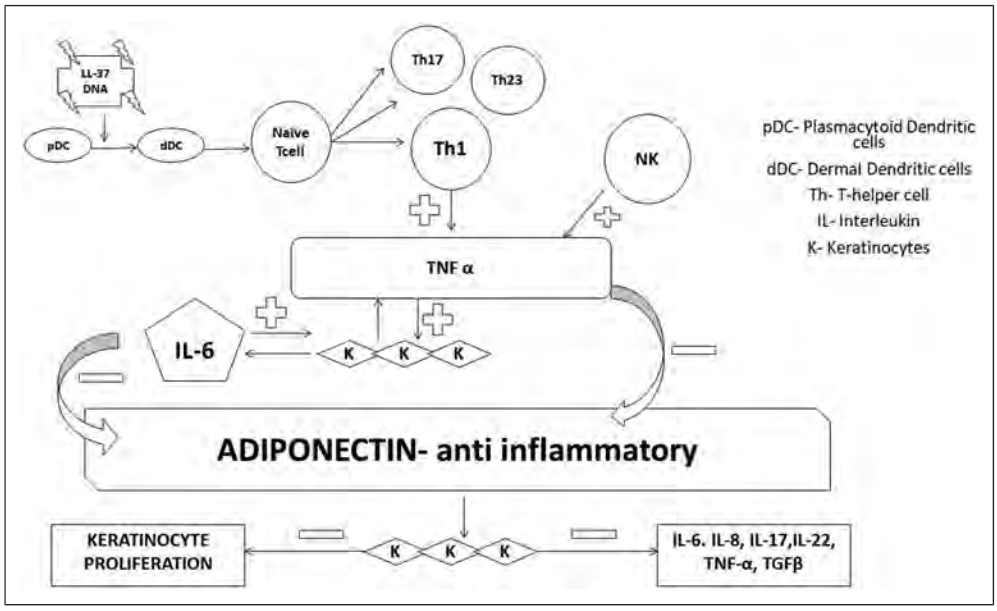

Figure 1. Pathogenic role of serum adiponectin in psoriasis.

Table 2. SAM-NCEP III Criteria for Metabolic Syndrome.

Parameter	Values
Waist circumference	> or = 90 cm for and > or = 80 cm for females
Blood pressure	>130/85 mmHg
Fasting blood glucose	> or = 100 mg/dl
Hypertriglyceridemia	>150 mg/dl
HDL cholesterol	Males <40 mg/dl Females <50 mg/dl
Metabolic syndrome present if >= 2	

Table 3. Comparison of Parameters Between Cases and Controls.

Characteristic	Cases	Controls	
Age in years	40.48 ± 15.39	44.75 ± 12.44	P = .565
Males	55% (33)	50% (10)	P = .053
Females	45% (27)	50% (10)	
Metabolic syndrome	25 (41.66)	4 (20)	.089
Adiponectin (μg/ml)	16.07 ± 8.55	21.65 ± 8.07	.012[a]
FBS (mg/dl)	119.18 ± 41.41	85.35 ± 11.74	<.001[b]
TG (mg/dl)	158.33 ± 54.44	140.60 ± 34.56	.081
HDL (mg/dl)	47.33 ± 14.81	51.25 ± 9.21	.270
LDL (mg/dl)	119.90 ± 36.52	127.20 ± 26.71	.414
TC (mg/dl)	197.28 ± 37.50	186.45 ± 30.00	.245
ESR (mg/dl)	22.17 ± 13.24	8.15 ± 5.09	<.001[a]

[a]represents statistically significant values.
[b]represents highly significant values.

visit, each patient's age, sex, weight, height and duration of psoriasis, body surface area (BSA), psoriasis area severity index (PASI), nail changes, joint involvement, and family history was recorded. BMI was calculated as weight (kg)/ height (m^2). The cases were divided into mild (PASI < 7), moderate (PASI7-12) and severe (PASI > 12).

South Asian Modified National Cholesterol Education Program III (SAM-NCEP III) criteria was used to diagnose metabolic syndrome in adults, diagnosis of Metabolic syndrome made if >= 2 criteria present (Table 2). Metabolic syndrome in pediatric age group was diagnosed based on criteria by Cooks et al.[28]

Adiponectin level was measured by enzyme linked immunosorbent assay. 8 hours fasting venous blood sample were collected and serum was separated in a centrifuge. Serum was stored at 20°C until processing. Normal values of serum adiponectin range from 4-26 μg/ml.[29]

Statistical analysis: Descriptive statistics was done for all data and were reported in terms of mean and percentages. Continuous variables were analyzed with Mann Whitney U test, t test and Kruskal Wallis test. Correlation was computed using pearson correlation. Categorical variables were analyzed with the help of chi square test. Statistical Significance was taken as P < .05. The data was analyzed using SPSS version 22 and Microsoft Excel.

Results

The study consisted of 80 subjects, 60 patients suffering from psoriasis and 20 healthy controls. The demographics and comparison of various blood parameters between the cases and controls are given in Table 3. The mean serum adiponectin levels in psoriasis group (16.07 ± 8.55 μg/ml) was lower than that in control group (21.65 ± 8.07 μg/ml) and this was statistically significant (P = .012). The mean ESR in psoriasis group (22.17 ± 13.24) was significantly higher than that in control group (8.15 ± 5.09) (P < .001).

PASI score ranged from 1 to 36 and average PASI was 10.97 ± 7.56. In the patient group, 22 (36.67%) had mild psoriasis (PASI<7), 11 (18.33%) had moderate psoriasis (PASI = 7-12) and 27 (45%) had severe psoriasis (PASI > 12). A comparison of parameters according to severity of the disease (PASI) is given in Table 4. The mean value of ESR was17.18 ± 8.57 in mild disease, 17.63 ± 6.45 in moderate disease and 28.07 ± 16.02 in severe disease (P = .004). According to PASI, serum adiponectin was significantly lower in moderate (17.10 ± 6.64 μg/ml) and severe disease (10.85 ± 8.27 μg/ml) as compared to mild disease (21.96 ± 5.26 μg/ml) (P < .001).

Disease parameters were compared between psoriasis cases with MetS and those without MetS (Table 5). In psoriasis group, the average age and PASI was significantly higher in cases with MetS (48.08 ± 14.53 years) (13.72 ± 7.73) as compared to cases without MetS (35.06 ± 13.75 years) (9.00 ± 6.90) (P = .001) (P = .016). Psoriatics with MetS had a higher ESR value (23.0 ± 09.72) than those without MetS (21.57 ± 15.39) (P = .684). Serum adiponectin was lower in cases with MetS (14.28 ± 7.95 μg/ml) when compared to those without MetS (17.35 ± 8.83 μg/ml) (P = .172). When compared with the control group (21.65 ± 8.07 μg/ml) these levels were very significantly lower in psoriasis with MetS (14.28 ± 7.95 μg/ml) (P = .004). Not only this, even the cases without MetS (17.35 ± 8.83 μg/ml) had significantly lower serum adiponectin than that of controls (P = .079). There was no significant difference in serum adiponectin among cases, based on gender (male 15.484 ± 8.59 μg/ml vs female 16.84 ± 8.59 μg/ml).

In this study a correlation of adiponectin levels was established with other blood parameters and disease variables using pearson correlation coefficient. The serum adiponectin levels had significant negative correlation with PASI

Table 4. Disease Parameters According to Severity of Disease.

Parameter	Mild	Moderate	Severe	*P* Value
Duration (years)	4.71 ± 4.63	4.86 ± 8.44	7.83 ± 8.0	*P* = .253
Metabolic syndrome present (number)	4	6	15	.019*
Adiponectin (μg/ml)	21.96 ± 5.26	17.10 ± 6.64	10.85 ± 8.27	<.001*
FBS (mg/dl)	110.55 ± 40.61	116.55 ± 20.54	127.30 ± 47.54	.109
TG (mg/dl)	150.36 ± 71.56	161.27 ± 47.10	163.63 ± 40.61	.084
HDL (mg/dl)	51.45 ± 13.30	38.82 ± 4.87	47.44 ± 3.33	.067
LDL (mg/dl)	122.14 ± 35.91	113.18 ± 33.87	120.81 ± 3.98	.796
TC (mg/dl)	198.64 ± 30.60	190.73 ± 40.49	198.85 ± 42.21	.819
ESR (mg/dl)	17.18 ± 8.57	17.63 ± 6.45	28.07 ± 16.02	.004*
Age (years)	39.18 ± 14.87	42.64 ± 14.04	40.67 ± 16.71	.833
Waist circumference (cm)	85.55 ± 12.97	94.00 ± 15.36	88.19 ± 14.28	.271
Systolic BP	122.91 ± 8.96	126.91 ± 7.18	129.11 ± 8.03	.038*
Diastolic BP	80.18 ± 6.53	82.54 ± 7.33	86.67 ± 6.77	.006*

Table 5. Comparison of Parameters Between Cases With MetS and Without MetS.

Parameter	MetS present (25)	MetS absent (35)	*P* Value
Mean age	48.08 (14.53)	35.06 (13.75)	.001**
Male/female	12/13	21/14	.357
Duration (years)	5.93 ± 6.68	6.30 ± 7.47	.845
Joint involvement present	13	11	.109
Mean BSA	29.36 ± 25.87	21.62 ± 17.83	.175
Mean PASI	13.72 ± 7.73	9.00 ± 6.90	.016*
No. of cases with PASI>12	15	12	.048*
No. of cases with BSA >10%	21	21	.046*
ESR	23.0 ± 09.72	21.57 ± 15.39	.684
Adiponectin (μg/ml).)	14.28 ± 7.95	17.35 ± 8.83	.172

(Pc = -.572, *P* = .000) (Figure 2), duration of disease (Pc = -.355, *P* = .005) (Figure 3) and also negatively correlated to age (Pc = -.019, *P* = .888), BMI (Pc = -.195, *P* = .136) and waist circumference (Pc = -.224, *P* = .086) (Table 6).

Among blood parameters mentioned in Table 7, a significant negative correlation was found with ESR (Pc = -.329, *P* = .010). There was no significant difference in serum adiponectin levels in cases with nail involvement and positive family history (Table 8). However, serum adiponectin levels were higher in cases with psoriatic arthritis.

Discussion

Serum adiponectin levels are known to be low in patients with MetS.[1] With high prevalence of MetS in psoriasis, it becomes crucial to decipher whether the disease itself has a direct relation with serum adiponectin levels. In the present study, average serum adiponectin levels in psoriasis were 16.07 ± 8.55 μg/ml, which was significantly lower than the levels among controls 21.65 ± 8.07 μg/ml (*P* = .012). The values of serum adiponectin were not only significantly lower among cases with MetS (14.28 ± 7.95 μg/ml *P* = .004) when compared with controls (21.65 ± 8.07 μg/ml), but it was also lower among cases without MetS (17.35 ± 8.83 μg/ml, *P* = .079). It was only in 2008 when, for the first time Takahashi et al[30] reported significantly lower mean plasma adiponectin in patients with psoriasis (18.5 μg/mL) compared with healthy controls (29.1 μg/mL, *P* < .05). In 2009, Coimbra et al[31] found significantly lower levels of adiponectin in psoriasis (4130 ng/mL compared to 6122 ng/mL in controls) (*P* = .001). In the same year, Shibata et al compared the levels of total serum adiponectin between healthy males and males with psoriasis and the levels were significantly lower among cases (3.78 ± 1.86 vs 6.38 ± 4.07 μg/mL, *P* = .028).[27] Similar results were found by RC Li et al and Yu Jin et al in 2014.[32,33]

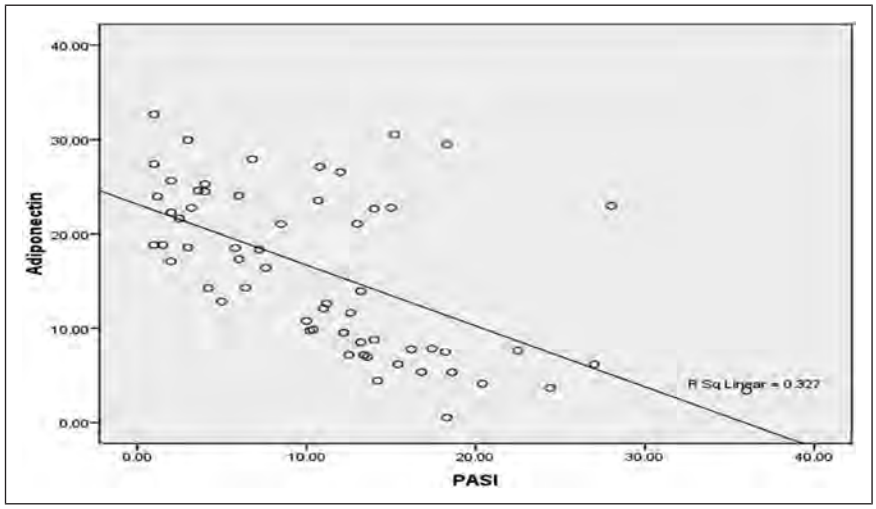

Figure 2. Correlation of serum adiponectin with PASI.

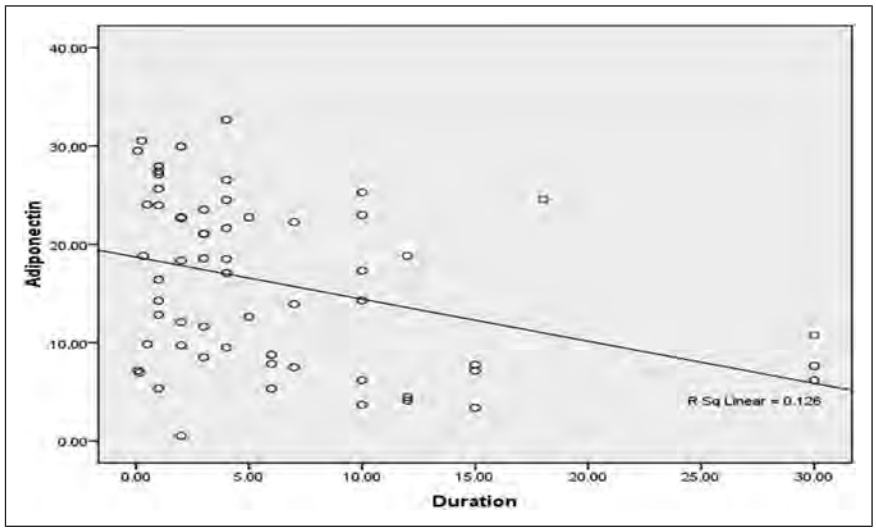

Figure 3. Correlation of serum adiponectin with duration of disease.

Table 6. Correlation of Serum Adiponectin Levels With Disease Parameters.

Pearson correlation	Age	BMI	PASI score	Duration	Waist circumference
Adiponectin	−.019	−.195	−.572**	−.355**	−.224
Sig. (2-tailed)	.888	.136	.000	.005	.086

Table 7. Correlation of Serum Adiponectin With Blood Parameters.

Pearson correlation	FBS	TG	HDL	LDL	TC	ESR
Adiponectin	−.087	−.196	.137	−.200	−.180	−.329*
P(Sig. 2-tailed)	.511	.134	.296	.126	.170	.010

Table 8. Serum Adiponectin Level and in Cases With Nail Changes, Psoriatic Arthritis and Family History.

Parameter	Present	Absent	*P*-value
Nail involvement	16.00 ± 8.43	16.17 ± 8.85	.938
Psoriatic arthritis	18.01 ± 8.94	14.78 ± 8.14	.153
Family history	15.13 ± 9.18	16.20 ± 8.54	.759

After establishing lower levels of this anti-inflammatory adipokine in psoriasis, we compared these values according to the severity of the disease. Average serum adiponectin levels were significantly higher in cases with severe diseases based on PASI score. Using pearson correlation coefficient a significant negative correlation of serum adiponectin levels with PASI and with ESR was established. Takahashi et al[30] also reported a negative correlation of serum adiponectin with PASI (Spearman test: $r = -.34$, $P < .05$). Yu Jin et al reported a negative correlation of serum adiponectin with PASI score and BMI.[33] In a study from Poland, Baran et al[34] performed a multivariate analysis to find a significantly negative correlation of serum adiponectin with PASI, BMI and CRP. In some studies a negative correlation with IL-6 and TNF-α shows the negative correlation with disease severity.[27,30] The present study in Indian patients corroborates that a lower level of serum adiponectin correlates with a more severe and longer duration of disease.

Similar to a study by Yu Jin et al, there was no significant difference of adiponectin levels in psoriasis cases with nail involvement or family history of psoriasis in our study.[33] In a study by Eder L et al, they reported higher levels of serum adiponectin and HOMA-IR values in psoriatic arthritis when compared to chronic plaque type psoriasis.[35] Similar to these findings, in our study also adiponectin levels were higher in cases with psoriatic arthritis although not meeting the level of significance. Several studies have demonstrated that adiponectin also has pro-inflammatory effects, increasing the production of pro-inflammatory factors such as MMP-3, MMP-9, CCL-2, IL-8, and IL-6.[36-38] It has been hypothesized that this dual function of adiponectin is isoform-specific: high molecular weight adiponectin increases IL-6 production in human monocytes, whereas MMW isoform decreases LPS-mediated IL-6 secretion and also induces IL-10 release.[39] A study of increased joint damage in RA patients, suggest the pro-inflammatory effects is particularly present in the joints.[40]

Fasting blood sugar, serum triglycerides, serum low density lipoproteins and total serum cholesterol were all negatively correlated to serum adiponectin and serum high density lipoproteins had a positive correlation with it in the present study. However, none of these were statistically significant. Thus, a pro-atherogenic lipid profile correlates with lower levels of serum adiponectin. A recent study by Yan H et al showed a negative correlation of serum adiponectin levels with intimal-medial thickening, suggesting higher occurrence of atherosclerosis in psoriasis patients with low levels of serum adiponectin.[41]

Conclusion

To summarize, serum adiponectin levels are decreased in psoriasis irrespective of presence of MetS and low level of serum adiponectin is a marker of severe and longer duration of disease in psoriasis patients.

Limitations

Analysis on a larger sample size and effect of therapy on serum adiponectin levels could not be carried out.

Author Contributions

AK, KK and DC are the Principal Investigators who conceived the study. AK, SG and DC designed the study; SG and PC contributed to the literature searches and review; AK, KK, SG and DC were involved in data collection; AK, SG and PC carried out data analysis; AK, DC and SG wrote the manuscript; KK, PC and DC provided the critical revision of the manuscript for important intellectual content; all authors have read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CME Credit

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https://www.eeds.com/em/7140

Consent

Written informed consent was taken from all the subjects who participated in the study.

Ethical Approval

Institutional review board of Baba Farid University of Health Sciences, Faridkot, Punjab, India (BFUHS/2k19p-TH/14770).

Guarantor

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Review

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Decrypting Skin Microbiome in Psoriasis: Current Status

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Abstract

Background: Psoriasis is an autoimmune, chronic, inflammatory skin condition of multifactorial etiology. Recent studies in human skin microbiome research have revealed the dysbiosis in lesional skin of psoriatic patients, as well as have established the association of dysbiosis in the elicitation of inflammatory response of psoriatic skin.

Objective: The present review aimed to recapitulate the insights of psoriasis lesional skin microbiome studies published in the last 2 decades, and to determine the most important bacterial genera that can be deployed as psoriatic skin microbial signature for therapeutic intervention.

Methods: To achieve the stated objectives, full-text analysis of literature selected through systematic search of digital literature databases has been carried out following PRISMA guidelines.

Results: Literature analysis suggests differential abundance of specific bacterial genera in the lesional psoriatic skin (LPS) compared to normal skin (NS) of psoriasis patients and skin from healthy subjects. These bacterial genera collectively can be utilized as potential biomarker for constructing lesional psoriatic skin specific microbial signature, and to explore the role of bacterial species in maintaining the skin homeostasis. The analysis further revealed that multiple bacterial species instead of a single bacterial species is important for understanding the psoriasis etiogenesis. Furthermore, decreased microbiome stability and increased diversity might have role in the exacerbation of lesions on skin of psoriatic patients.

Conclusion: Considering the importance of human skin microbiome dysbiosis in psoriasis, research efforts should be carried out to develop new therapeutic measures in addition to current therapies by exploiting the human and host-skin-associated microbial genomic and metabolomic knowledge.

Keywords
psoriasis, human skin microbiome, inflammation, psoriasis etiology, skin

Introduction

Psoriasis is a chronic autoimmune skin inflammation triggered by interplay of multiple factors such as stress, lifestyle, diet, infection, genetic, epigenetic or immunologic.[1] It is characterised by plaque, erythrodermic, guttate or pustular lesions on the skin. The regional prevalence of psoriasis varies from .09%[2] to 11.4%[3] according to global estimates,[4] whereas median and derived mean prevalence are 3.0 and 3.4% respectively, according to expert estimates.[5,6] It is associated with other metabolic and systemic inflammatory disorders such as inflammatory bowel disorder (IBD), obesity, psoriatic arthritis or cardiovascular disorders. Psoriasis vulgaris is most common type of psoriasis affecting 85%-95% of psoriatic patients.[7] Psoriasis has a negative encroachment on the quality of life of the individual with psoriasis experience (such as physical discomfort, itching, self-consciousness about appearance or impairment on physical appearance, fear of public rejection, low self-esteem and depression) as well as on society, based on the severity of the psoriasis outbreak. The complete cure or reversal of psoriasis is not possible as most of the therapeutic measures are available for managing symptoms only.[7] It may be due to lack of in depth understanding of psoriasis etiology based on cumulative effects of multiple factors.

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The microbiome colonized on and in the human body have been known to play an important role in maintaining homeostasis and disruption in their composition or functionality, induces dysregulation of the immune system.[8] Moreover, microbial dysbiosis has critical role in modulation of inflammatory pathways and thus, have potential for clinical manifestation and treatment of various chronic inflammatory diseases.[9] Since the last decade, scientific community has exploited the microbiome to demonstrate the potential of gut microbiome in the incidences of chronic diseases including cancer, type2 diabetes.[10,11]

Human skin constructs a physical barrier through cornification of keratinocytes to regulate injury and microbial insults in the human body. The commensal microbial organisms including bacteria, fungus, virus or bacteriophage harboured on the skin have special adaptations to live on human skin and are collectively known as skin microbiota. Skin microbiota is dominated by bacterial communities to Firmicutes, Actinobacteria, Bacteroidetes and Proteobacteria at phylum level.[12] Microbiota composition depends on the micro-environment of skin sites such as moisture content, body temperature, pH value.[13] Moreover, skin microbiota disturbance is known to have potential to trigger immune dysregulation and thus, significantly contribute towards pathological conditions of skin diseases.[14] Interestingly, attempts like manipulation of skin microbiome in atopic dermatitis[9,14] open new avenues in alternative medicine. Therefore, there is considerable attentiveness towards developing potential application of skin microbiota in clinical and therapeutical methods for psoriasis. Moreover, to address "good" microbes for maintenance of healthy skin state and modulation of skin inhabitants of psoriasis, further research is needed.

Several studies have been carried out to investigate the organisation and potential of skin microbiota in the exacerbation of psoriasis in the last 2 decades. However, the understanding of defined microbial signature and critical mechanism of global skin metabolism regulation in psoriasis on basis of skin microbiome is still at its basal level. Moreover, the data from e-literature appears chaotic in terms of relative abundance of microbiota at genera level. This might be because of the variability in the sampling methods, environment, geographical location, experiment, and downstream computational and statistical analysis. Several reviews have been published in the last decade for skin microbiota of psoriasis that had given emphasis on the microbial community, molecular technique(s) used for sequencing or cloning and sampling techniques in separate instances.[3,15-19] The present review is aimed to systematically analyse the published studies related to skin microbiota from psoriasis patients and summarise the most recent reliable observations. This review attempts to elaborate the common pattern of microbial community of skin at "Genera" taxa level in addition to deployed empirical molecular and computational method. Moreover, it will describe the importance of skin microbiota manipulation in addition to current therapeutics of psoriasis.

Methods

The present systematic analysis was carried out as per the systematic guidelines of preferred reporting items for systematic reviews and meta-analysis (PRISMA).[20] The schematic framework of the methodology deployed by the present meta-review analysis is shown in Figure 1.

Search Strategy

Ten search engines (*viz,* Pubmed, Science Direct, Web of Science, Google Scholar, Biological Abstract, Scifinder, WorldCat, Chemical Abstracts, SciELO, and Scopus) have been chosen initially for searching electronic literature. However, Biological Abstract, Scifinder, chemical abstracts, and Scopus have not been found freely accessible, and therefore, were not used. A systematic search was carried out via Pubmed, Science Direct, Web of Science, Google Scholar, WorldCat, and SciELO literature search engine with time interval from 2006 to 2022 to identify the records. The query keywords or medical subject headings (MeSH) "microbiome" and "metagenome" amalgamated with "Psoriasis" have been used to identify the records containing information for skin microbiota composition. English language filter has been applied while scanning digital literature database through the advanced search option. The list of selected records has been retrieved and saved in bibliography format for further investigation.

Study Selection and Inclusion/Screening

The list of selected records was imported into the Mendeley Desktop version 1.19.8 and duplicates were removed. The titles and abstracts of articles of selected records have been reviewed independently to identify the studies that fit the selection criteria for full-text evaluation. Selection criteria include articles that focus on (i) Human as host; (ii) Psoriasis disease; (iii) comparison of the microbiome from lesional psoriatic skin (LPS) and normal skin of psoriatic patients and skin from healthy control (NS); (iv) culture-independent molecular techniques. The articles published as book chapter, encyclopaedia, editorial, reviews or meta-reviews were excluded from the meta-review analyses. Records that meet the selection criterion with article type "original research", "clinical report" and "translational research" were considered for further review process.

Data Extraction

The information like first author; year of publication; title of publication; type of study; area of the study where it was conducted; subject information (healthy or control, age, gender); sample information (technique of sampling, site of sampling and number of samples); information of platform and technique used for microbiota analyses; shift in skin microbial diversity and major findings of the studies have been extracted from the full text of selected literature. Initially, all

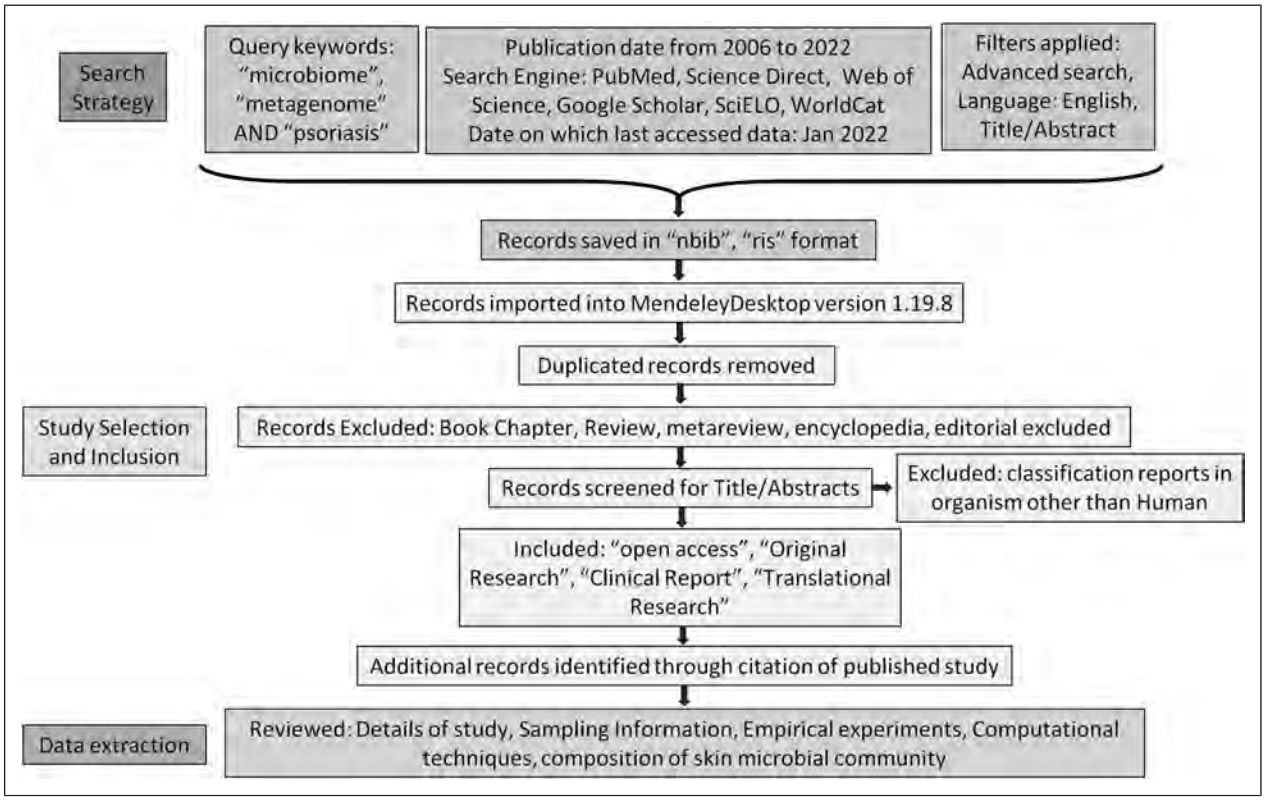

Figure 1. Schematic framework of methodology used for selection of literature for the purpose of meta-review analysis. Firstly (Search strategy), selected keywords (psoriasis, microbiome and metagenome) were used to search the records in the digital databases. In the second step (Study selection and inclusion), redundancy of the records is removed and records were reviewed for title and abstracts to meet the inclusion criteria. Finally (Data extraction), full text analysis of selected records was carried out.

the data were recorded into the excel sheet and then analysed for finding the skin microbial signature of the psoriasis.

Construction of Word Cloud

The word cloud has been constructed from word Art (wordart.com) web server to find the representative taxa at genera level. A list of all genera found to be abundantly present in the lesional psoriatic skin have been imported into the word Art web server with default parameters.

Ethics

This study is a review of hypotheses that have been put forth by publicly available published studies. This study does not employ animal or human/patient-based samples for analyses.

Results and Discussion

Human skin is harboured by billions of microbial organisms, including bacteria, fungus, virus, and bacteriophage, that can be beneficial or pathogenic depending upon the cumulative effect of multiple factors including environment, geography and host etc. Traditionally, the information on these microorganisms is retrieved using culture dependent methods which are time consuming and labour intensive. Moreover, the microbes that are fastidious (are highly sensitive or require excessive delicacy) and underrepresented (show extreme slow or little growth in media) in the cultures of mixed microbial communities, cannot be recovered for the microbial analyses using culture dependent techniques. Over the last 2 decades, advanced sequencing technologies and culture-independent molecular techniques (such as PCR-based clone analyses, 16S rRNA gene sequencing and shotgun metagenome sequencing), have been extensively utilised for microbiome analysis (identification and characterisation) in context to various disease etiology including psoriasis.[21] The present review summarises those studies that emphasise on the skin or cutaneous microbiota from the psoriatic patients.

With the searching of digital literature databases such as Pubmed, Science Direct, Web of science, Google Scholar, WorldCat, and SciELO, a total of 523 records (Table 1) have been imported into the Mendeley Desktop and duplicate records removed later on.

After importing into the Mendeley Desktop, and removing the duplicates, a total of 205 articles have been considered for reviewing of the title and abstracts. After reading the title and abstracts, only 69 studies are considered based on the selection criteria as mentioned in the methodology section. Among 69

Table 1. Number of Literature Records From Various Digital Literature Databases.

Digital Literature Database	Web Address	Psoriasis and Microbiome	Psoriasis and Metagenome
Pubmed	https://pubmed.ncbi.nlm.nih.gov/	178	3
Science Direct	https://www.sciencedirect.com/search	49	1
Web of Science	https://www.webofscience.com/wos/woscc/basic-search	132	3
Google Scholar	https://scholar.google.com	52	1
WorldCat	https://www.worldcat.org	102	1
SciELO	https://scielo.org/en/	0	0

peer-reviewed articles, only "original research" or "clinical report" and "translational research" publications are considered for further reviewing. Later on, 4 studies were included based on citations of these selected publications, thus, a total of 21 studies were assessed for the full text review. After assessing the full text, 1 more study also has been excluded as it explains more about faecal microbiota translational research in psoriasis-like inflammation in mice and did not accord with the objective of present meta-study. Therefore, we reviewed twenty research articles (PMID: 33796091,[21] 24451201,[22] 18648509,[23] 29199351,[24] 26811697,[25] 16891514,[26] 25510344,[27] 32945341,[28] 31619666,[29] 32852562,[30] 30185226,[15] 30985920,[31] 29559344,[32] 26659932,[33] 22065152,[34] 28649415,[35] 24018484,[36] 31247199,[37] 31228520,[38] 32486022[16]) thoroughly that focus on skin microbiota dysbiosis of the lesional and normal psoriatic skin.

Methodologies Incorporated to Measure Microbiota of Lesional Psoriatic Skin

From the full-text reviewing of 20 studies, swabbing and biopsies were found to be the 2 main techniques deployed for collecting the skin microbiome samples. Out of 20 studies, only 1 study[34] used biopsies for collecting microbiome samples while others used swabbing techniques with a variety of buffer solutions such as sterile ST (.15 m NaCl with .1% Tween-20)[22,23] or liquid Amies.[24] The variation in the swabbing techniques and areas of sample collection for experiment might be the reason for showing the differential abundance in these reports. Out of 20 selected studies, three studies are focussed on fungal microbiota,[16,26,27] 1 on bacteriophage community,[37] 13 on bacterial[15,21-25,30-34,36,38]and 3 on whole microbial community including fungus, bacteriophage and bacteria.[28,29,35] The variable regions of 16S rRNA such as V1-V3 or V3-V5 are very important to define the diversity of microbial community in samples. Most of the studies have targeted V1-V3 or V3-V5 for sequencing and identify the diversity at different taxa levels in skin samples (Table 2). The molecular technique is either PCR cloning, pyrosequencing or amplicon sequencing or shotgun metagenome sequencing for finding the microbial signature of non-culturable microbial community in psoriatic skin samples. The common bioinformatics software deployed for downstream computational analysis for finding OTUs (Operational Taxonomic Units) are QIIME,[39] RDP Classifier,[40,41] Greengenes,[42] SILVA,[43] UCLUST,[44] USEARCH,[45] and PICRUSt.[46] Species richness & evenness and alpha & beta diversity indices are calculated for investigating the microbial pattern in different skin types.

Skin Microbiota Inhabiting the Lesional Psoriatic Skin

Full-text of selected records has been thoroughly and systematically reviewed and it shows the dysbiosis of microbial community on the lesional psoriatic skin. The genera of differentially abundant microbes on lesional psoriatic skin from the selected studies have been tabulated in Table 3.

Bacterial Microbiota of Lesional Psoriatic Skin. Among the phyla level, *Firmicutes* are the most prevalent in the lesional psoriatic skin (LPS) whereas *Actinobacteria* is more abundant in normal skin (NS) types.[23,34] However, another report suggested the enrichment of both phyla *Firmicutes* and *Actinobacteria* in lesional psoriatic skin.[22] The lesional psoriatic skin has been found to be rich and more even in diversity as compared to the normal skin of psoriatic patients and healthy control.[23] At genera level, *Propionibacterium* sp. is the common genera with different proportions in both skin types (less abundance in lesional psoriatic skin) in the study by Gao et al.[23] In another report, the commonest genera were *Streptococci* (32% in lesional psoriatic and 26% in normal skin types); *Staphylococci* (5% in lesional psoriatic and 16% in controls) and *Propionibacterium* (.0001669% in lesional psoriatic, .0254% in controls) in the both skin types.[34] However, Tett et al[35] displayed the association of increased abundance of *Staphylococcus* sp with lesional psoriatic skin, whereas, at species level, Chang et al[15] reported the enriched relative abundance of *Staphylococcus aureus* and underrepresentation of *Staphylococcus epidermidis* in the lesional psoriatic skin. Moreover, significant abundance of *Campylobacter jejuni* pathogen has been reported from lesional psoriatic skin.[28] In addition, *Xanthomonas* (Keratolytic) and *Corynebacterium* genera are associated with lesional psoriatic skin according to the report by Martin et al.[33] From a recent study, *Capnocytophaga, Leptotrichia, Abiotrophia* and *Tannerella* are known to play an important role in the severity of lesional psoriatic skin.[30] In another report, *Prevotella* and *Staphylococcus* were suggested to have association with lesional psoriatic skin whereas *Anaerococcus* and

Table 2. Summary of Sampling Techniques and Molecular Techniques Deployed by Studies.

S.No	PMID	Author	Sampling Technique	Organism Focussed	Variable Region	Sequencing Technique	Platform	Computational Techniques	Statistical Techniques
1	16891514	Paulino et al	Swab	Fungus	18S rDNA and 5.8S rDNA/ ITS2	PCR cloning	PCR	NCBI GenBank, BLASTN, ClustalX, Mega2 (JC, NJ), EstimateSv7	Richness: Nonparametric richness estimator, Chao1 DPCoA (Double-principal coordinate analysis and cluster analysis), EstimateSv7
2	18648509	Gao et al	Swab	Bacteria	16S rDNA	PCR cloning	PCR	RDP II, Bellerophon, GenBank, BLAST, SLOTUs, NAST at Greengenes, Mega V4.0 (JC-NJ)	DPCoA for sample diversity and relationship amongst samples, UniFrac
3	22065152	Fahlen et al	Biopsies	Bacteria	V3-V4 16S rRNA gene	16S rRNA pyrosequencing	454-FLX GS-100	Ribosomal database project (RDP), BLAST, MEV,	Shannon diversity index, *t* test, FastUnifrac, PCoA, vegan
4	24018484	Statnikov et al	Swab	Bacteria	V1-V3 & V3-V5 16S rRNA gene	16S rRNA high-throughput DNA sequencing	Roche 454-FLX	RDP classifier	Generalised Local Learning (GLL), Fisher's Z-test, SVM-RFE, Kruskal-Wallis non-parametric one-way ANOVA test, random forest
5	24451201	Alekseyenko et al	Swab	Bacteria	V1-V3 16S rRNA gene	16S rRNA high-throughput DNA sequencing	Roche 454-FLX	QIIME, UCLUST, RDP classifier, PyNAST, Greengenes, FASTTREE, ChimeraSlayer,	UniFrac beta diversity indices, Kruskal-Wallis non-parametric one-way ANOVA, rarefactions for richness and shannon diversity indices, Principal Coordinates Analysis (PCoA),vegan, ade4
6	25510344	Takemoto et al	Swab	Fungus	D1 and D2 26S rRNA	Pyrosequencing	454 GS FLX	QIIME, UCLUST, RDP classifier	Shanon diversity index, Student's *t* test, UniFrac, PCoA
7	26659932	Martin et al	Swab	Bacteria	V1-V2 16S rRNA	16S rRNA sequencing	Roche 454 FLX	QIIME, UCLUST, RDP classifier,	Kruskal-Wallis one-way analysis of variance for taxonomy, R

(continued)

Table 2. (continued)

S.No	PMID	Author	Sampling Technique	Organism Focussed	Variable Region	Sequencing Technique	Platform	Computational Techniques	Statistical Techniques
8	28649415	Tett et al	Swab	Total microbiota	NA	Shotgun metagenomics	Illumina HiSeq-2000	FastqMcf, MetaPhlAn2, HUMAnN, USEARCH, strain-level profiling with de-novo SPAdes, MLST, PanPhlAn	Species evenness Gini-Simpson index, diversity indice rarefaction curve, richness Bray-Curtis distance matrix, Welch's *t* test
9	29199351	Assarson et al	Swab	Bacteria	16S rDNA	16S metagenomic sequencing	Illumina MiSeq	CLC genomic Workbench, Greengenes, MUSCLE	Chao 1 bias-corrected, Shannon diversity index, Simpson's index, and phylogenetic diversity, ANOVA UniFrac, Bray-Curtis and Jaccard, PCoA, PERMANOVA (CLC)
10	29559344	Loesche et al	Swab	Bacteria	V1-V3 16S rRNA	16S rRNA sequencing	Illumina MiSeq	Quantitative insights into microbial ecology	OTU richness, shannon diversity, beta diversity, Wilcoxon or Kruskal-Wallis tests, vegan
11	30185226	Chang et al	Swab	Bacteria	V1-V3 16S rRNA	16S rRNA sequencing	Illumina MiSeq	FLASH, UCLUST, PyNAST, GreenGenes, ChimerSlayer, QIIME, Kendall	chao1 index, Shannon's and Simpson's diversity index, Mann-kendall, UniFrac, Kruskal-Wallis one-way ANOVA,
12	31619666	Fyhrquist et al	Swab	Total microbiota	16S rRNA	16S RNA and shotgun metagenomics	Roche/454 & Illumina HiSeq	QIIME, Greengenes, ChimeraSlayer, ClustalW2, PICRUSt, iTOL (tree of life)	Kruskal−Wallis test, Mann−Whitney U test
13	30985920	Langan et al	Swab	Bacteria	16S rRNA	16S rRNA sequencing	Illumina MiSeq	USEARCH, MOTHUR, SILVA, FASTTREE,	Alpha diversity (Chao1) and Bray-Curtis dissimilarity index (beta diversity), vegan
14	32486022	Koike et al	Swab	Fungus	ITS1-F	Fungal ITS1 deep sequencing	Illumina MiSeq	Merged using PEAR, UCLUST, RDP Classifier, QIIME	Relative abundance

(continued)

Table 2. (continued)

S.No	PMID	Author	Sampling Technique	Organism Focussed	Variable Region	Sequencing Technique	Platform	Computational Techniques	Statistical Techniques
15	32852562	Assarson et al	Swab	Bacteria	V3-V4 16S rRNA	16S rRNA sequencing	Illumina MiSeq	CLC genomics, SILVA, MUSCLE	Kruskal-Wallis one-way analysis of variance, UniFrac, PERMANOVA, PCoA
16	32945341	Wang et al	Swab	Total microbiota	NA	Shotgun metagenomics	HiSeq 1500	IDBA-UD, DIAMOND, MEGAN,	Relative abundance, alpha and beta diversity
17	31247199	Wang et al	Swab	Bacteriophage and bacteria	NA	Shotgun metagenomics	Illumina HiSeq 1500	IDBA-UD, DIAMOND, MEGAN,	Shannon diversity indices, PCoA Bray-Curtis distances, vegan, ggplot2, Lme4
18	33796091	Chen et al	Swab	Bacteria	V3-V4 16 rRNA	16S rRNA sequencing	Illumina NovaSeq 6000	FLASH, Trimmomatic, UCHIME, SSU rRNA database, QIIME,	Alpha and beta diversity, linear discriminant analysis coupled with effect size (LEfSe), PCA, OPLS-DA, Metstat
19	26811697	Drago et al	Curette	Bacteria	V2-V3	16S rRNA	Ion torrent PGM seq	Ion Reporter software workflow, BLAST, MicroSEQ ID db	Student *t* test
20	31228520	Quan et al	Cotton swab	Bacteria	V3-V4	PCR & 16S rRNA sequencing	MiSeq	Trimmomatic, FLASH, USEARCH, RDP Classifier, MOTHUR	UniFrac, R, Kruskal-Wallis test, ROC curve with Medcalc, Spearman correlation, Wilcoxon matched-pairs signed rank test

Propionibacterium with normal skin.[31] Also, Assersson et al[24] demonstrated the abundance of *Staphylococcus* at genera level in the lesional psoriatic skin as compared to normal skin.[24] Furthermore, lower abundance of *Cutibacterium* and higher abundance of *Corynebacterium* in the lesional psoriatic skin has been presented in another study.[38] Furthermore, Chen et al demonstrated the association of a pathobiont, *Vibrio,* with psoriasis for the first time.[21] Thus, all studies evidenced the change in the composition of skin microbial load in lesional psoriatic skin as compared to the normal skin of psoriatic patients and healthy controls, however, with disparity and inconsistency in the findings through all selected studies. Moreover, the cause-effect relationship (ie, disease causes microbial dysbiosis or dysbiosis is responsible for disease) of impaired microbial community in lesional psoriatic skin remains to be elusive. In addition, conserved or defined microbial patterns or signatures of lesional psoriatic skin have not been observed among the selected studies. Furthermore, the microbial communities inhabiting the skin have been found to be weakly correlated with the disease-related gene expression in psoriasis.[21] However, the role of variation in relative abundance or composition diversity of microbiota to modulate the skin immune system to harbour or as specialised adaptation of pathogenic microbiota which in turn exacerbate the severity of psoriatic lesional scales/skin remains to be deduced. Further, research has to be carried out to unravel the mechanism by which these microorganisms disintegrate or break the skin immune barrier to exacerbate or aggravate the psoriasis lesions. Therefore, elucidation of the potential of skin microbiome in etiology of psoriasis is yet to be dug deep.

Fungal Microbiota of Lesional Psoriatic Skin. Among the selected 3 studies that discuss the fungal microbiome, none has suggested the difference between the fungal microbiome of lesional psoriatic skin and normal skin.[16,26,27] All the 3 studies suggested that *Malassezia* sp is prevalent in both normal and

Table 3. Most Prevalent/Abundant Taxa at Genera Level Reported by Different Studies.

S. No	PMID	Authors	Most Prevalent/Abundant Taxa at Genera Level
1	16891514	Paulino et al	*Malassezia*
2	18648509	Gao et al	*Anaerococcus, Corynebacterium, Flavobacteriaceae, Gemella, Kocuria, Micrococcus, Propionibacterium, Rothia, Staphylococcus, Streptococcus*
3	22065152	Fahlen et al	*Acinetobacter, Corynebacterium, Prevotella, Propionibacterium, Staphylococcus, Streptococcus*
4	24018484	Statnikov et al	Classification studies (similar data as reported by Alekseyenko et al, 2013)
5	24451201	Alekseyenko et al	*Corynebacterium, Cupriavidus, Dermacoccus, Flavisolibacter, Geobacillus, Lactobacillus, Methylobacterium, Propionibacterium, Ralstonia, Schlegelella, Staphylococcus, Streptococcus, Uruburuella*
6	25510344	Takemoto et al	*Aspergillus, Candida, Cladosporium, Cryptococcus, Magnaporthe, Malassezia, Meyeroyzma, Rhodotorula, Toxicocladasporium*
7	26659932	Martin et al	*Acinetobacter, Alicyclobacillus, Anaerococcus, Brevibacterium, Chryseobacterium, Corynebacterium, Enhydrobacter, Finegoldia, Kocuria, Micrococcus, Paracoccus, Peptoniphilus, Prevotella, Propionibacterium, Pseudomonas, Rhodobacter, Staphylococcus, Streptococcus, Wautersiella, Xanthomonas*
8	28649415	Tett et al	*Acinetobacter, Brevibacterium, Corynebacterium, Dermatophilacea, Enhydrobacter, Escheria, Escherichia, Finegoldia, Gardnerella, Malassezia, Micrococcus, Propionibacterium, Pseudomonas, Rothia, Staphylococcus, Streptococcus, Veillonella*
9	29199351	Assarson et al	*Acinetobacter, Actinomyces, Anaerococcus, Clostridium, Conchiformibius, Corynebacterium, Dermacoccus, Enhydrobacter, Finegoldia, Gardnerella, Lactobacillus, Megasphaera, Micrococcus, Paracoccus, Peptoniphilus, Prevotella, Propionibacterium, Pseudomonas, Staphylococcus, Streptococcus*
10	29559344	Loesche et al	*Acinetobacter, Agrobacterium, Anaerococcus, Bacillus, Corynebacterium, Enhydrobacter, Finegoldia, Gemellales, Micrococcus, Propionibacterium, Peptoniphilus, Pseudomonas, Staphylococcus, Streptococcus*
11	30185226	Chang et al	*Acinetobacter, Alloiococcus, Anaerococcus, Brevibacterium, Comamonas, Corynebacterium, Dermabacter, Enhydrobacter, Finegoldia, Flavobacterium, Gallicola, Helcocccus, Hyphomicrobium, Janibacter, Kocuria, Lactobacillus, Larkenella, Marinicella, Micrococcus, Mycobacterium, Novosphingobium, Paracoccus, Pedobacter, Peptoniphilus, Peptostreptococcus, Prevotella, Propionibacterium, Pseudomonas, Roseomonas, Rothia, Sphingomonas, Staphylococcus, Streptococcus, Vogesella, Williamsia*
12	31619666	Fyhrquist et al	*Acinetobacter, Actinomyces, Anaerococcus, Blautia, Bradyrhizobium, Burkholderia, Coprococcus, Corynebacterium, Dermabacter, Enhydrobacter, Finegoldia, Fusobacterium, Kocuria, Lactobacillus, Leptotrichia, Micrococcus, Paracoccus, Pelomonas, Peptoniphilus, Peptostreptococcus, Phyllobacterium, Prevotella, Propionibacterium, Ralstonia, Rothia, Staphylococcus, Streptococcus, Variovorax*
13	30985920	Langan et al	*Acidovorax, Acinetobacters, Anaerococcus, Brochothrix, Corynebacterium, Leuconostoc, Micrococcus, Pelomonas, Propionibacterium, Staphylococcus, Stenotrophomonas, Streptococcus, Unclassified, Undibacterium*
14	32486022	Koike et al	*Bjerkandera, Cerrena, Earliella, Lentinus, Malassezia, Steccherinum, Sterenum*
15	32852562	Assarson et al	*Acidovorax, Acinetobacter, Allorhizobium-Neorhizobium-Pararhizobium-Rhizobium, Anaerococcus, Citricoccus, Corynebacterium 1, Cutibacterium, Finegoldia, Fusobacterium, Gemella, Granulicatella, Enhydrobacter, Haemophilus, Lawsonella, Macrococcus, Micrococcus, Moraxella, Neisseria, Peptoniphilus, Prevotella 7, Pseudomonas, Staphylococcus, Streptococcus, Tepidimonas, Veillonella, Conchiformibius, Lactococcus, Lautropia, Peptostreptococcus*
16	32945341	Wang et al	*Acinetobacter, Campylobacter, Cutibacterium, Flavobacterium, Moraxella, Mycobacterium, Propionibacterium, Pseudomonas, Sphingomonas, Staphylococcus*
17	31247199	Wang et al	*Acinetobacter phage* Presle, *Bacillus phage* SP-10, *Bordetella virus* BPP1, *Burkholderia virus* BcepC6B, *Enterobacteria phage* Sfl, *Haemophilus phage* Aaphi23, *Mycobacterium phage* DrDrey, *Pseudomonas phage* O4,*Rhodoferax phage* P26218, *Salmonella phage* vB_SenS-Ent2
18	33796091	Chen et al	*Anaerococcus, Acinetobacter, Bacillus, Bifidobacterium, Brachybacterium, Brevindimonas, Candidatus_Competibacter, Chryseobacterium, Citrobacter, Cutibacterium, Deinococcus, Delftia, Enhydrobacter, Enterobacter, Enterococcus, Erysipelatoclostridium, Erwinia, Ferruginibacter, Gardnerella, Corynebacterium, Lactobacillus, Luteimonas, Lysobacter, Mangrovibacter, Massilia, Micrococcus, Paracoccus, Pseudoclavibacter, Pseudomonas, Romoutsia, Salinicoccus, Serratia, Staphylococcus, Thermomonas, Vibrio, Zoogloea*
19	26811697	Drago et al	*Prevotellaceae, Clostridiaceae, Lactobacillaceae, Rhodobacteraceae, Oxalobacteraceae, Desulfovibrionaceae, Bacteroidaceae, Veillonellaceae, Corynebacteriaceae, Moraxellaceae, Pasteurellaceae, Ruminococcaceae, Staphylococcocaceae, Propionibacteriaceae, Halomonadaceae, Neisseriaceae, Lachnospiraceae, Streptococcaceae, Micrococcaceae, Enterobacteriaceae, Camplylobaceriaceae*
20	31228520	Quan et al	*Propionibacterium (Cutibacterium), Corynebacterium, Streptococcus, Deinococcus, Brevundimonas, Micrococcus*

lesional skin types. However, the distribution of fungal species is largely found to be host-specific but stable over a time period.[26] Fungal microbiome is independent in lesional psoriatic skin (Psoriatic Patients) and normal skin of psoriasis patients and healthy controls.[26] No correlation between PASi score and skin *Malassezia* colonisation level is consistent in all studies. However, the fungal microbiome is more diverse in psoriatic patients than in healthy control.[26] Koike et al suggested that *Malassezia* sp is abundant in all groups of lesional psoriatic skin, normal skin of psoriasis patients and normal skin of healthy person.[16] In contrast, colonisation of fungal species including *Malassezia* sp and *Candida* sp is shown to be directly related to aggravation of skin inflammation.[47]

Bacteriophage Microbiota of Lesional Psoriatic Skin. Surprisingly, only 1 study demonstrated the diversity of bacteriophage in the skin of the psoriatic population. The ten most predominant bacteriophages (including *Acinetobacter* phage Presle, *Bacillus* phage SP-10, *Bordetella* virus BPP1, *Burkholderia* virus BcepC6B, *Enterobacteria* phage Sfl, *Haemophilus* phage Aaphi23, *Mycobacterium* phage DrDrey, *Pseudomonas* phage O4, *Rhodoferax* phage P26218, *Salmonella* phage vB_SenS-Ent2) were found to be decreased in their normalised abundance in the psoriatic skin in comparison to healthy skin.[37] This study also suggested the potential of phage population influencing the microbial diversity on the health of normal and lesional psoriatic skin. This study shows the suppression in the abundance of genera *viz, Acinetobacter* and *Pseudomonas* by differential abundance of *Acinetobacter phage* Presely and *Pseudomonas* phage O4 in normal and lesional psoriatic skin. However, no change in alpha diversity of phage population has been observed in lesional psoriatic skin of psoriatic patients and normal skin. More research has to be carried out to evaluate the bacteriophage dysbiosis in the lesional psoriatic skin to reduce the probability of biased inferences.

Microbiota of Lesional Psoriatic Skin at "Genera" Level

The published literature reported substantial difference in diversity of microbiota, their relative abundance and evenness of lesional psoriatic skin and normal skin. However, variation in the taxa of represented genera from lesional psoriatic skin to normal is small. For example, the most common genera that differ in their abundance in lesional psoriatic skin as compared to normal skin are *Propionibacterium* sp,[23] *Streptococci, Staphylococci* and *Propionibacterium*,[34] *Xanthomonas* and *Corynebacterium*,[33] Staphylococcus[35] *Staphylococcus aureus* and *Staphylococcus epidermidis*,[15] *Staphylococcus*,[24] *Prevotella* and *Staphylococcus*,[31] *Campylobacter jejuni*,[28] *Capnocytophaga, Leptotrichia, Abiotrophia a*nd *Tannerella*,[30] and *Vibrio*.[21] Therefore, it is clear from the previous published studies that microbial communities exhibit alterations of considerable importance on lesional psoriatic skin as compared to normal skin. Microbiomes of lesional psoriatic skin and normal skin show a few discriminative characteristic features. Therefore, to find the representative lesional psoriatic microbial taxa, a word cloud was constructed from all the overrepresented microbial taxa at genera level from lesional psoriatic skin published in the selected studies (Table 3). *Staphylococcus, Corynebacterium, Propionibacterium, Acinetobacter, Anaerococcus* are the most congruous reported bacterial taxa at genera level among published literature (Figure 2). In addition, *Malassezia* fungal taxon is consistently reported by all 3 fungal microbiome studies at genera level. Moreover, *Staphylococcus* sp, *Corynebacterium* sp*, Propionibacterium* sp and *Malassezia* sp have also been used as the top taxonomic discriminatory species by random forest analysis.[35]

A color-coded map was constructed for the top 20 (*Staphylococcus, Corynebacterium, Propionibacterium, Acinetobacter, Anaerococcus, Micrococcus, Streptococcus, Pseudomonas, Enhydrobacter, Finegoldia, Lactobacillus, Prevotella, Peptoniphilus, Paracoccus, Cutibacterium, Kocuria, Rothia, Brevibacterium, Gardnerella, and Moraxella*) microbial genera reported by at least 2 studies to show the variation in their relative abundance in psoriatic lesional skin samples compared to the normal skin samples (Figure 3). The color-coded map shows the variation in the findings of relative abundance of microbial genera. For example, *Staphylococcus* sp reported to increase in relative abundance in lesional psoriatic skin as compared to normal skin by all studies except 3.[24,25,34] Similarly, observation of relative abundance of *Corynebacterium, Propionibacterium, Acinetobacter, Anaerococcus* sp and other genera varies among the studies reviewed. Therefore, variability in the findings among studies raises concerns about chaotic microbiota in lesional psoriatic skin and can also depend on the microenvironment of skin *viz*, moist, sebaceous or dry skin. However, these twenty microbial genera might be used in the preclinical and therapeutic studies for checking the onset and exacerbation of psoriatic lesions as taxonomic discriminative features and might be able to discriminate the lesional psoriatic skin from normal skin types.

Microbiota of Lesional Psoriatic Skin at "Species" Level

Microbiota of lesional psoriatic skin at "species" level shows alteration in relative abundance as compared to normal psoriatic skin. After reviewing the full text of 20 studies, 59 bacterial species *viz, Acinetobacter baumannii, Acinetobacter johnsonii, Acinetobacter lwoffii, Actinomyces, Agrobacterium, Alloiococcus otitis, Brevibacterium unclassified, Brevibacterium unclassified, Burkholderia sp., Campylobacter jejuni, Corynebacterium kroppenstedtii, Corynebacterium pseudogenitalium, Corynebacterium pyruviciproducers, Corynebacterium simulans, Corynebacterium striatum, Corynebacterium tuberculostearicum, Cutibacterium acnes, Dermatophilacea unclassified, Enhydrobacter aerosaccus, Escherichia coli, Finegoldia magna, Gammaproteobacteria bacterium, Gardnerella vaginalis, Jonquetella anthropi, Kocuria palustris, Lactobacillus iners, Malassezia globosa, Micrococcus luteus, Moraxella osloensis,*

Figure 2. Word Cloud for the microbial taxa at genera level found to be differentially abundant in lesional psoriatic skin in comparison to healthy skin (Healthy control and non-lesional skin of psoriatic patients). Fungus (a) and Bacteria (b).

	Gao et al. 2008	Fahlén et al. 2012	Alekseyenko et al. 2013	Drago et al., 2015	Tett et al, 2017	Chang et al. 2018	Fyhrquist et al. 2019	Langan et al. 2019	Assarsson et al. 2020	Quan et al. 2020	Chen et al. 2021	Wang et al. 2020	Martin et al. 2015 (therapy)	Assarsson et al. 2018 (therapy)	Loesche et al. 2018 (therapy)
Staphylococcus	Increase	Decrease	NSC	Decrease	Increase	Increase	Increase	Increase	Increase	No data	Altered	Increase	Increase	Decrease	Increase
Corynebacterium	Increase	Decrease	NSC	Increase	No data	Increase	Increase	Increase	Increase	Increase	Altered	No data	Decrease	Decrease	Altered
Propionibacterium	Decrease	Decrease	NSC	Decrease	No data	Decrease	Decrease	Decrease	Decrease	Decrease	Altered	Increase	Decrease	NSC	Decrease
Acinetobacter	Decrease	Increase	No data	No data	No data	NSC	Decrease	Decrease	Increase	No data	Altered	Increase	Increase	NSC	Decrease
Anaerococcus	Increase	NSC	No data	No data	No data	Increase	Increase	NSC	Increase	No data	Altered	No data	No data*	Increase	NSC
Micrococcus	NSC	Decrease	No data	Decrease	No data	Decrease	Decrease	Decrease	Decrease	Increase	Altered	No data	Decrease	Increase	Decrease
Streptococcus	Increase	Increase	NSC	Increase	No data	NSC	Increase	Decrease	Decrease	Decrease	No data	No data	Increase	Decrease	Increase
Pseudomonas	Increase	No data*	No data	No data	No data	Increase	No data	No data	Increase	No data	Altered	Decrease	No data*	Increase	NSC
Enhydrobacter	Decrease	No data	No data	Increase	No data	No data*	Decrease	No data	Decrease	No data	Altered	No data*	NSC	Increase	Increase
Finegoldia	Decrease	No data*	No data	No data	No data	Increase	Increase	No data	Increase	No data	No data	No data	Decrease	Increase	Altered
Lactobacillus	Decrease	No data*	No data	Increase	No data	NSC	Decrease	No data	No data	No data	Altered	No data	No data	Increase	No data
Prevotella	Decrease	No data*	No data	Increase	No data	Decrease	Increase	No data	Decrease	No data	No data	No data	NSC	Increase	No data
Peptoniphilus	Increase	No data*	No data	No data	No data	Increase	Increase	No data	Increase	No data	No data	No data	No data*	Increase	NSC
Paracoccus	Decrease	No data*	No data	No data	No data	No data*	NSC	No data	No data	No data	Altered	No data	NSC	Decrease	No data
Cutibacterium	Decrease	Decrease	NSC	Decrease	No data	Decrease	Decrease	Decrease	Decrease	Decrease	Altered	No data*	Decrease	NSC	Decrease
Kocuria	Increase	No data	No data	No data	No data	Decrease	NSC	No data	No data	No data	No data	No data	No data	No data	No data
Rothia	Increase	No data	No data	No data	No data	No data*	Increase	No data	No data	No data	No data	No data	No data	No data	No data
Brevibacterium	NSC	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Gardnerella	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	NSC	No data	No data	Decrease	No data
Moraxella	Decrease	No data	No data	Increase	No data	No data*	Decrease	No data	Decrease	No data	Altered	No data*	NSC	Increase	Increase

Figure 3. Color-coded map showing the increase and decrease in relative abundance of specific taxa at genera level. The red color represents increase in abundance, blue represents decrease in abundance, yellow represents no significant change in abundance, mustard represents altered taxa abundance but without information on increase or decrease in abundance, and transparent cell shows that no data or information available for those taxa. No data* refer to inference could not be made based on the available data. NSC refers to no significant change observed in relative abundance.

Propionibacterium acnes, Paracoccus sp., Pelomonas sp., Peptoniphilus sp., Peptostreptococcus anaerobius, Phyllobacterium sp., Prevotella sp., Propionibacterium acnes, Propionibacterium granulosum, Pseudomonas aeruginosa, Pseudomonas fluorescens, Pseudomonas fragi, Ralstonia sp., Roseateles depolymerans, Rothia dentocariosa, Rothia mucilaginosa, Sphingobacteriia bacterium, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus aureus, Staphylococcus caprae/capitis, Staphylococcus hominis, Staphylococcus lugdunensis, Staphylococcus pettenkoferi, Staphylococcus

warneri, Streptococcus agalactiae, Streptococcus mitis/oralis/pneumoniae, Streptococcus salivarius, Variovorax paradoxus, Veillonella spp and 3 fungal species *viz, Malassezia restricta, Malassezia globosa, Malassezia sympodialis* are found to be differentially rich in their relative abundance in the lesional psoriatic skin as compared to normal skin.

Role of Skin Microbiota in Psoriasis Etiogenesis

The skin microbiome varies according to the microenvironment of skin sites ie, dry, moist and sebaceous and is known to affect the skin homeostasis and onset of inflammatory response.[17] No direct correlation has been observed between psoriasis pathogenesis and skin dysbiosis[48] even though the presence of instances of microbiota alteration in lesional psoriatic skin has been reported. Interestingly, immunity against skin commensal fungi (*Candida albicans*, *Malassezia furfur* and *Trichophyton mentagrophytes)* was found to aggravate the psoriasiform or skin inflammation through TH17 cell dependent manner.[47] Despite the known facts of interplay of skin microbiome in exacerbation of psoriasis condition, there is requirement of scrupulous analysis for lesional psoriatic skin microbiota to gain the better understanding of role of inhabitant bacteria, phages and micro-eukaryotes in the enhanced pathology of psoriasis.

The comprehensive and systematic analysis of the published literature suggests the trend of impaired microbial community in lesional psoriatic skin. Although single OTU is not capable to deduce the psoriasis pathogenesis, but differential relative abundance and evenness of multiple genera: *Staphylococcus, Corynebacterium, Propionibacterium, Acinetobacter, Anaerococcus, Micrococcus, Streptococcus, Lactobacillus* and *Finegoldia* can be used to construct the microbial fingerprint or signature as therapeutic biomarker for the psoriasis skin condition. Moreover, finding the etiology is arduous for a multifactorial disease like psoriasis from the skin microbiome alone due to several confounding factors such as location and environment of the body site, treatment, gender, race, ethnicity and skin condition. Moreover, most of the studies deployed solely marker-based amplicon sequencing genomic approaches for microbiome analysis instead of whole shotgun metagenomics because of the low cost of the earlier approach. Furthermore, the computational techniques deployed for downstream analysis and data representation could have contributed to the variability in the published findings. Therefore, incorporating the integrative analysis of 'omics' data from different approaches such as whole genome shotgun metagenomic, amplicon sequencing taxonomic, proteomic, metabolomic and transcriptomic with account of multiple suggested factors is necessary. Furthermore, to determine the functional capacity of microbiota, taxonomic annotation at strain level is needed. The task of identification of microbial signatures associated with specific disease is cumbersome and challenging. In addition, most of the studies focus on the investigation of the composition of skin microbiota[16,22-24,26-28,31-34,36,38] and rarely attempt to infer the causality of skin microbiota variation in psoriasis exacerbation.[21] Therefore, more studies with functional-based analysis are needed in addition to the taxonomic based analysis. New approaches should be developed to solve the causal role of skin microbiota in psoriasis ectogenesis and to infer the biomarkers of therapeutic interventions. Moreover, host-microbiome interaction studies need to investigate at molecular, genetic, as well as clinical level to develop diagnostic, preventive and therapeutic measures based on skin microbiota in case of precision medicine for psoriasis. Accordingly, the scientific community is striving towards getting better at these challenges and developing more robust analytical methods for finding correlation of microbiota in chronic diseases.

Conclusion

Bacterial genera *viz., Staphylococcus, Corynebacterium, Propionibacterium, Acinetobacter, Anaerococcus, Micrococcus, Streptococcus, Pseudomonas, Enhydrobacter, Finegoldia, Lactobacillus, Prevotella, Peptoniphilus, Paracoccus, Cutibacterium, Kocuria, Rothia, Brevibacterium, Gardnerella, and Moraxella* are reported to be differentially abundant on the lesional psoriatic skin in comparison to normal psoriatic and healthy skin by at least 2 studies. Despite the supporting evidence of skin microbiota alterations in psoriasis, the potential mechanism of psoriasis exacerbation because of dysbiosis is still unclear. Further efforts are required to infer the mechanistic role of skin microbiota in maintaining the skin homeostasis by considering the impact of factors such as the race, ethnicity, physicochemical condition of body sample, lifestyle, environment and geographical location, and psoriasis heterogeneity. Moreover, only diversity analysis of skin microbiota may not be the right approach to uncover the etiogenesis of psoriasis. Therefore, thorough studies are required to understand and validate the role of dysbiosis as a bystander or driver or amplifier of impaired immune response in psoriasis. This can be achieved by an in-depth understanding of the host-skin-associated microbial metabolites in combination with the microbiome analysis. With an increased mechanistic understanding of skin microbiome in skin inflammation, research efforts can be applied to develop new therapeutic measures in the foreseeable future in addition to current therapies for psoriasis.

Appendix

Abbreviations

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
Normal skin (NS)	healthy subject's skin and non-lesional psoriatic skin from psoriasis patients
Lesional psoriatic skin (LPS)	lesional skin from psoriasis patients
Normal psoriatic skin (NPS)	non-lesional skin of patients suffering from psoriasis

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Ethical Approval

The study is a review of hypotheses that have been put forth by publicly available published studies. This study does not involves any animal or human/patient-based samples for analyses.

Patient Consent

The study did not use any human or animal(s). Therefore, did not require any patient consent.

Disclosure

No writing assistance was deployed during the writing of this manuscript.

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