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The Relationship Between Gut Microbiome Composition and Cardiovascular Risk in Obese Patients: A Cross-Sectional Study

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ABSTRACT

One of the most prevalent comorbidities that may afflict psoriatic people is cardiovascular disease (CVD). Both psoriasis and CVD have both exogenous and endogenous variables contributing to their genesis and progression. There may be a hereditary component between the two conditions, but there are still some unanswered questions about the frequency of CVD in psoriatic individuals. Dysbiosis of the gut microbiota has recently been linked to the onset and progression of both illnesses. For each case, fecal samples were obtained within 24 h of production and were stored at-20 ◦C in sterile containers until use. To reduce possible biases due to environmental effects on the microbiome composition, the study enrolled Caucasian individuals from the same geographic area all of whom had a similar diet and had not received probiotics or antibiotics in the 6 months prior to recruitment. Patients with coronary artery disease have previously been found to have an elevated abundance of Proteobacteria. Our results imply that a greater Proteobacteria abundance in psoriatic patients with CVD may increase the production of inflammatory cytokines, which in turn may contribute to inflammatory processes associated with both psoriasis and CVD. Furthermore, we found that psoriatic patients with CVD had considerably greater proportions of the species Bacteroides ovatus, the genera Coprococcus and Phascolarctobacterium and the family Barne-siellaceae. When the gut microbiome makeup of patients with and without CVD was compared, it was shown that those with the disease had increased prevalence of Phascolarctobacterium and Barnesiellaceae. Barnesiellaceae abundance levels were similar to those of patients without CVD in those receiving biologic therapy among patients with CVD. Overall, our results point to a possible connection between gut microbiome dysbiosis and the co-occurrence of psoriasis and CVD. They also imply that treatment approaches may be able to restore intestinal symbiosis, which could enhance the clinical management of psoriasis and its related comorbidities.

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Key Words

Psoriasis, comorbidities, cardiovascular disease, gut microbiome, biologic therapy, 16S rRNA gene sequencing

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INTRODUCTION

Compared with the general population, psoriatic patients have an increased risk of developing other chronic diseases as comorbidities, including cardiovascular diseases (CVDs). CVDs are one of the most common comorbidities in psoriatic patients, and this may affect the severity of the disease and decrease both the quality of life and the lifespan of psoriatic patients[1].

A combination of several exogenous and endogenous factors, including genetic pre-disposition, is well documented in the etiology and progression of both psoriasis and CVD[2-6]. The presence of systemic inflammation in combination with metabolic abnor-malities might explain the high incidence of CVD in psoriatic patients[1-7].

Genetic and genome-wide association studies have recently allowed for the identifi-cation of a common genetic background of psoriasis and concomitant cardiovascular risk factors, suggesting pleiotropic mechanisms of interactions involving pro-inflammatory pathways[5]. However, other factors besides genetic background may explain the preva-lence of CVD in psoriasis patients.

Gut microbiome dysbiosis is considered as a triggering factor for psoriasis onset as it may promote chronic systemic inflammation. Dysbiosis may indeed contribute to the increase in bacteria promoting the production of harmful compounds involved in the inflammatory response, with a central role in the systemic inflammation of several diseases[8,9].

Significant alterations of the gut microbiome composition were found in psoriatic patients compared with healthy controls, mainly including a reduction in Bacteroidetes and increase in Firmicutes phyla[8].

Cumulative evidence has also demonstrated that the gut microbiome may have a role in the development and maintenance of CVD[10,11]. Compared with healthy controls, patients with CVD showed a peculiar gut microbiome profile, including a reduction in Bacteroidetes and increase in Proteobacteria phyla[12]. Despite the established role of the gut microbiome composition in the development and maintenance of both psoriasis and CVD, a possible link between the gut microbiome composition and the occurrence of CVD in psoriatic patients is still unknown. Dysbiosis can be transient, with the recovery of a new steady state, or persistent, being the background for the development of chronic diseases. Indeed, in recent years, several studies demonstrated the role of gut microbiota and its metabolites in determining the onset and progression of cardiovascular and non-cardiovascular pathologies of the host (e.g., inflammatory bowel disease, colon cancer, hypertension, heart failure and stroke). Many of these products are specific metabolic byproducts of certain bacterial species and the most relevant are short-chain fatty acids (SCFAs), trimethylamine (TMA), bile acids (BAs), coprostanol, phenylacetylglutamine as well as lipopolysaccharide (LPS)., their implication in CVD is of recent interest[13]. Thus, identifying a gut microbiota signature and its related metabolites can be useful for intervening on an undervalued novel cardiovascular risk factor. The objective of this review is to explore the relationship between gut microbiota and cardiovascular risk and CVD and the possible intervention strategies for its modulation, prevention, and treatment.

Cumulative evidence has also demonstrated that the gut microbiome may have a role in the development and maintenance of CVD[14,15]. Compared with healthy controls, patients with CVD showed a peculiar gut microbiome profile, including a reduction in Bacteroidetes and increase in Proteobacteria phyla[16]. Despite the established role of the gut microbiome composition in the development and maintenance of both psoriasis and CVD, a possible link between the gut microbiome composition and the occurrence of CVD in psoriatic patients is still unknown.

In this study, we characterized and compared the gut microbiome composition in psoriatic patients with and without CVD to investigate whether gut dysbiosis might influence the occurrence of CVD in psoriatic patients, with possible clinical relevance.

MATERIALS AND METHODS

Every patient who took part in the trial signed an informed consent form that included a thorough explanation of the study methodology and was approved by the Sree Mookambika Institute of Medical Sciences, Kanyakumari, local ethics committee. The Declaration of Helsinki's guiding principles were followed when conducting the study.

For each patient, the primary clinical-pathological and personal data were gathered, such as sex, age at enrolment and diagnosis, length of disease, body mass index (BMI), kind and severity of psoriasis and use of biological anti-psoriatic therapy.

Faecal samples were collected for every case within a day of production and kept in sterile containers at -20°C until needed. In order to minimise potential biases resulting from environmental influences on the composition of the microbiome, the study included White participants from the same region who had a comparable diet and had not taken probiotics or antibiotics in the six months before to enrolment.

Using the commercially available InviMag Stool DNA Kit/KF96, faecal bacterial DNA was isolated and subjected to 16s rRNA gene sequencing on the Illumina MiSeq platform for analysis. QIIME2 version 2019 and DADA2 software were used to process the sequencing data., the information that was previously given included the number of reads that passed quality filters, as well as the raw and clean data for each sample. Following filtering by length and quality and purification from chimeric sequences, each sample was assigned an operational taxonomic unit (OTU). The OTU table was then subjected to rarefaction analysis to normalise samples at the lowest number of reads, as previously mentioned. The corresponding author may obtain the sequencing data upon justifiable request.

The diversity in the gut microbiome makeup of psoriatic individuals with and without CVD was ascertained by bioinformatics analyses.

As previously mentioned, taxonomy was assigned using the Greengenes v[13-8]. database and the DeSeq2 programme of R/Bioconductor was used to determine the difference in microbial abundance between the two groups.

The χ2 test was used for categorical variables and the Wilcoxon rank-sum test for numerical variables in the statistical analysis of the clinical-pathological aspects in the case series. At p<0.05, the results were deemed statistically significant.

RESULTS AND DISCUSSIONS

Table 1: The Personal and Clinical-Pathological Data of the 38 Psoriatic Patients Included in the Study are Shown in

Clinical-Pathological Features	Total Patients N = 38 (%)	Patients with CVD N = 27 (%)	Patients without CVD N = 21 (%)	P-Value 1
Sex				
Male	24 (63.1%)	19 (70.3%)	16 (76.1%)	
Female	14 (36.8%)	8 (29.6%)	5 (23.8%)	0.198
Age at enrollment	60.6	68.3	49.7	0.001
(mean ± standard error)	(±3.6)	(±2.7)	(±5.4)	
Age at diagnosis	31.7	37.2	23.6	0.049
(mean ± standard error)	(±3.1)	(±4.2)	(±3.5)	
Duration of the disease	22.3 years	23.0 years	20.8 years	1.000
(mean ± standard error)	(±3.5)	(±4.8)	(±4.0)	
BMI (mean)	29.1 (±0.8)	31.2 (±2.3)	26.4 (±2.3)	0.002
Type of psoriasis				
Plaque	32 (84.2%)	25 (92.5%)	16 (76.1%)	
Guttate	3 (7.8%)	2 (7.4%)	2 (9.5%)	
Arthropathic	3 (7.8%)	0 (0.0%)	3 (14.2%)	0.173
Degree of psoriasis				
Mild	5 (13.1%)	3 (11.1%)	5 (23.8%)	
Moderate	14 (36.8%)	10 (37.0%)	7 (33.3%)	
Severe	19 (50.0%)	14 (51.8%)	9 (42.8%)	0.559
Biological treatment				
Treated 2	11 (28.9%)	8 (29.6%)	9 (42.8%)	
Untreated	27 (71.0%)	19 (70.3%)	12 (57.1%)	0.702

Notably, an increased abundance of Proteobacteria was previously reported in patients with coronary artery disease. Our findings suggest that a higher abundance of Proteobacteria in psoriatic patients with CVD might contribute to inflammatory processes related to both psoriasis and CVD by means of increasing the production of inflammatory cytokines.

In addition, we observed a significantly higher proportion of the family Barne-siellaceae, the genera Coprococcus and Phascolarctobacterium and the species Bacteroides ovatus in psoriatic patients with CVD (Table 2).

Taxonomic Group	Abundance Status	log2 Fold Change	Adjusted *p*-Value
p__Bacteroidetes; c__Bacteroidia; o__Bacteroidales; f__[Barnesiellaceae]	Higher in psoriatic patients with CVD	−24.34886704	2.06×10^{-12}
p__Firmicutes; c__Clostridia; o__Clostridiales; f__Lachnospiraceae; g__Coprococcus	Higher in psoriatic patients with CVD	−23.4934486	8.34×10^{-12}
p__Firmicutes; c__Clostridia; o__Clostridiales; f__Veillonellaceae; g__Phascolarctobacterium	Higher in psoriatic patients with CVD	−24.97162307	3.64×10^{-15}
p__Bacteroidetes; c__Bacteroidia; o__Bacteroidales; f__Bacteroidaceae; g__Bacteroides; s__ovatus	Higher in psoriatic patients with CVD	−23.82969219	6.41×10^{-13}
p__Firmicutes; c__Clostridia; o__Clostridiales	Higher in psoriatic patients without CVD	24.26865586	8.71×10^{-11}
p__Bacteroidetes; c__Bacteroidia; o__Bacteroidales; f__Rikenellaceae; g__Alistipes; s__finegoldii	Higher in psoriatic patients without CVD	24.55698275	6.41×10^{-13}
p__Firmicutes; c__Clostridia; o__Clostridiales; f__Lachnospiraceae; g__Roseburia; s__faecis	Higher in psoriatic patients without CVD	24.62161750	6.41×10^{-13}

A higher abundance of Barnesiellaceae and Phascolarctobacterium, known to produce elevated quantities of short-chain fatty acids associated with both hypercholesterolemia and hypertriglyceridemia, was previously reported in CVD patients compared with healthy controls[17,18]. Our findings suggest that a higher prevalence of Barnesiellaceae and Phasco-larctobacterium might be considered as risk factors for developing CVD in psoriatic patients. Previous studies showed controversial associations of Barnesiellaceae and Phascolarcto-bacterium with metabolic status (measured as BMI), as some studies reported higher levels in higher BMI patients and others reported an inverse correlation[19-22]. These contrast-ing results may be due to other additional features that may act as confounding factors. In our series, psoriatic patients with CVD were significantly older and had a significantly higher BMI compared with psoriatic patients without CVD. Given the relatively small number of patients analyzed, we cannot rule out the possible effects of age and BMI as confounding factors for the observed associations. On the other hand, our observations may hint at a possible link between gut microbiome composition and metabolic factors, for example, a high BMI, suggesting a possible concurrent role of gut microbiome alterations and traditional cardiovascular risk factors in psoriatic patients.

Consistent with these previous studies, we found diferences in gut microbiota according to metabolic status in overweight and obese individuals. At the genus level, Oscillospira within the family Ruminococcaceae and Clostridium within the family Clostridiaceae were signifcantly more abundant in metabolically healthy subjects. Some Oscillospira species can likely secrete important short chain fatty acids (SCFAs)15 which are a source of energy for the host and can produce a signal through membrane receptors to integrate metabolic functions[23]. SCFAs have benefcial efects on body weight control,

infammatory status and insulin sensitivity, as well as glucose and lipid homeostasis. Animal studies suggest that SCFAs and succinate have important roles in the prevention and treatment of obesity-associated insulin resistance. Clostridium is a butyrate-producing bacterium. Previous studies showed a signifcant decrease in butyrate-producing bacteria, including Clostridium, in individuals with type 2 diabetes mellitus (T2DM) compared to healthy individuals. Tese results suggest that butyrate-producing bacteria aford protection against T2DM. Butyrate improves colon mucosal barrier function. Moreover, butyrate exhibits immunomodulatory efects and exhibits anti-infammatory properties by down regulating pro-infammatory cytokines[24].

This study has a few limitations. First, it is a pilot study on a small cohort of patients., thus, it was not possible to exclude the possible influence of confounding factors for the observed associations. On the other hand, the analyzed cohort was collected through stringent inclusion criteria in order to minimize environmental biases. Another possible limitation is represented by data analysis. It is well known that microbiome data analysis is a computational challenge, and a standardization of the best pipeline is currently lacking. The analysis pipeline, whose results are shown here, is based on evidence from previous results and evidence from recent methodological comparisons[25,26].

Further studies using multiple functional and computational approaches are needed to confirm our observations regarding the gut microbiome dysbiosis and the possible functional relationship among dysregulated taxa in the risk of CVD in psoriatic patients.

CONCLUSIONS

Moreover, our results suggested that biological therapy may have an effect on the composition of the gut microbiome, an observation that merits additional investigation. Therefore, therapeutic and preventive measures targeted at reestablishing the gut microbiome's symbiosis may prove to be effective in the treatment of psoriasis and its related comorbidities. In terms of treating and preventing related diseases, greater research on bigger patient cohorts will shed light on how biological medicines affect the makeup of the gut microbiome and bacteria that may be crucial to the host's cardiovascular health.

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