



REVIEW

# Implication of Human Bacterial Gut Microbiota on Immune-Mediated and Autoimmune Dermatological Diseases and Their Comorbidities: A Narrative Review

Roberta Colucci · Silvia Moretti

Received: November 6, 2020 / Published online: January 28, 2021  
© The Author(s) 2021

## ABSTRACT

During the last decade, the advent of modern sequencing methods (next generation techniques, NGS) has helped describe the composition of the human gut microbiome, enabling us to understand the main characteristics of a healthy gut microbiome and, conversely, the magnitude of its disease-related changes. This new knowledge has revealed that healthy gut microbiota allow the maintenance of several crucial physiological functions, such as the ability to regulate the innate and adaptive immune systems. Increasing evidence has pointed out a condition of dysbiosis in several autoimmune/immune mediated dermatological conditions and specific gut microbial signatures have also been reported to correlate with clinical and prognostic parameters of such diseases. Based on a literature search of relevant published articles, this review debates the current knowledge and the possible pathogenic implications of bacterial gut microbiota composition assessed through NGS techniques in systemic lupus erythematosus, atopic dermatitis, psoriasis, and alopecia areata. Evidence of a potential role of specific gut microbiota signatures in modulating the clinical course of such diseases

and their main comorbidities has been also reviewed.

## PLAIN LANGUAGE SUMMARY

The gut microbiota is defined as the collection of microbes (bacteria, fungi, archaea, and viruses) inhabiting the human gut. If healthy, it allows the maintenance of several crucial physiological functions, such as the ability to regulate the immune system. Accordingly, increasing evidence has pointed out a condition of imbalance in the gut microbial community (dysbiosis) in several autoimmune/immune mediated dermatological conditions. Specific gut dysbioses have also been reported to correlate with clinical and prognostic parameters of such diseases.

In this review, the current knowledge and the possible pathogenic implications of bacterial gut microbiota composition assessed through advanced techniques in systemic lupus erythematosus, atopic dermatitis, psoriasis, and alopecia areata are discussed. Furthermore, evidence of a potential role of specific gut microbiota signatures affecting the clinical course and main associated diseases is also reviewed. In this scenario, an increased knowledge of gut microbiota composition and functions in autoimmune/immune mediated dermatological

---

R. Colucci (✉) · S. Moretti  
Section of Dermatology, Department of Health Sciences, University of Florence, Florence, Italy  
e-mail: roberta.colucci21@gmail.com

diseases might suggest additional treatments besides conventional therapies, and predict clinical evolution and comorbidities association.

**Keywords:** Alopecia areata; Atopic dermatitis; Gut microbiota; Psoriasis; Systemic lupus erythematosus

### Key Summary Points

Gut microbiota have been reported to be capable of regulating the innate and adaptive immune systems both locally and systemically.

Increasing evidence has pointed out a condition of imbalance in the gut microbial community (dysbiosis) in several autoimmune/immune mediated dermatological conditions.

Specific gut dysbioses have also been reported to correlate with clinical and prognostic parameters of such diseases.

An improved understanding of gut microbiota in autoimmune/immune mediated dermatoses might suggest additional treatments besides conventional therapies, and predict clinical evolution and comorbidities association.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide and plain language summary, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13547432>.

## INTRODUCTION

The human microbiome is composed of bacteria, eukaryotes, archaea, and viruses inhabiting the human body [1].

The advent of culture-independent approaches such as high-throughput and low-cost sequencing methods (next generation techniques, NGS) has enabled the elucidation of microbial composition in several body areas [1].

In humans, most of the identified microbes can be found in the gastrointestinal tract [2, 3], which contains approximately  $10^{14}$  microbes, collectively defined as the human gut microbiota [1, 2, 4]. Overall, a healthy gut microbiota is mainly dominated by bacteria belonging to two main phyla — Bacteroidetes and Firmicutes [1, 5, 6] — and additionally contains eukaryotes (such as *Candida*, *Malassezia*, and *Saccharomyces*) [1, 7], Archaea (mostly belonging to the *Methanobrevibacter* genus) [1, 8] and viruses (consisting primarily of bacteriophages) [1, 9, 10].

In recent years, increased knowledge of gut microbiota composition and functions has suggested that the well-being of the gut microbiota is crucial in achieving several physiological functions [5, 6]. Among them, food metabolism, nutrient synthesis, protection against pathogens, and maintenance of the integrity of the mucosal barrier are the most important [5, 6].

Another property of the gut microbiota is its capacity to regulate the innate and adaptive immune systems both locally and systemically [2, 6, 11, 12]. Recent findings suggest that such regulation seems to also be exerted epigenetically, directly by gut microbes and their related metabolites, or by nutrients included in plant/animal derived foods, capable of regulating the expression of specific immune-modulating miRNAs. [13]. Accordingly, increasing evidence has pointed out a condition of dysbiosis in several diseases, such as metabolic disorders [14], cancer [15], and autoimmunity [16].

In this scenario, a growing body of investigations performed on both mice and humans has assessed a possible role of gut microbiota in triggering dermatological diseases [17, 18].

**Table 1** Summary of the investigations assessing human gut microbiota composition through NGS methods in SLE, AD, Ps and AA

Authors	Year	Number of patients	Country	Main results
Systemic Lupus Erythematosus (SLE)				
Hevia et al. [21]	2014	20 SLE; 20 controls	Spain	SLE: Diversity of species comparable to controls (Shannon index) ↓ Firmicutes/ Bacteroidetes ratio vs controls
Lopez et al. [31]	2016	37 SLE patients, (20 underwent fecal microbiota sequencing); 36 controls	Spain	Fecal samples of SLE + naïve CD4 + cells → Activation and polarization toward a Th17 phenotype Fecal samples of SLE + naïve CD4 + cells + <i>Bifidobacterium bifidum</i> → T cells activation prevented Controls: ↑ fecal Firmicutes → ↓ IL17 SLE: ↑ fecal Firmicutes → ↑ TH1 cells and IFN-γ
He et al. [23]	2016	45 female SLE; 48 female controls	China	SLE: ↓ Firmicutes/ Bacteroidetes ratio ↑ <i>Rhodococcus</i> , <i>Eggerthella</i> , <i>Klebsiella</i> , <i>Prevotella</i> , <i>Eubacterium</i> , <i>Flavonifractor</i> and incertae sedis ↓ <i>Dialister</i> and <i>Pseudobutyryivibrio</i>
Rodriguez-Carrio et al. [29]	2017	21 SLE; 25 controls	Spain	Controls: Firmicutes/ Bacteroidetes ratio correlates with serum free fatty acids (not observed in SLE) SLE: Altered production of serum short chain fatty acids
Greiling et al. [35]	2018	16 SLE and 2 SCLE; 11 controls	USA	SLE: ↓ Firmicutes/ Bacteroidetes ratio vs controls Sera from human anti-Ro60-positive lupus patients immunoprecipitate commensal Ro60 ribonucleoproteins SLE skin and mucosal Ro60-containing bacteria → activation of Human Ro60 autoantigen-specific CD4 memory T cell clones SLE Germ-free mice monocolonization with a SLE Ro60 ortholog-containing gut commensal → Anti-human Ro60 T and B cell responses + development of glomerular immune complex deposits
Luo et al. [25]	2018	14 active SLE; 17 controls	USA	SLE: Firmicutes/ Bacteroidetes ratio comparable to controls ↑ Abundance of fecal Gram-negative bacteria (Proteobacteria)
Van der Meulen et al. [22]	2019	30 SLE; 39 primary Sjogren syndrome (pSS); 965 controls	the Netherlands	SLE and pSS: ↓ bacterial richness, ↓ Firmicutes/ Bacteroidetes ratio and ↑ Bacteroidetes abundance vs controls SLE: different oral microbiome composition vs pSS
Azzouz et al. [27]	2019	61 female SLE	USA	↓ Bacterial richness, mostly in patients with high SLE disease activity index (SLEDAI) SLE: Fivefold ↑ abundance of <i>Ruminococcus gnavus</i> and Lachnospiraceae family ↑ Fecal calprotectin levels - Serum anti-R. gnavus antibodies → correlation with SLEDAI score, antinative DNA levels and active nephritis

**Table 1** continued

Authors	Year	Number of patients	Country	Main results
Wei et al. [24]	2019	16 SLE; 14 controls	China	SLE: ↑ Proteobacteria and ↓ Ruminococcaceae
Li et al. [26]	2019	40 SLE (19 active and 21 remissive); 20 rheumatoid arthritis; 20 controls	China	SLE: <i>Streptococcus</i> , <i>Campylobacter</i> , <i>Veillonella</i> → positive association with lupus activity SLE: <i>Bifidobacterium</i> → negative association with disease activity
Atopic dermatitis (AD)				
Hong et al. [57]	2010	27 vaginal-delivered infants; 14 caesarean-delivered infants	Singapore	Differences in the relative abundances of <i>Bifidobacterium</i> and Enterobacteriaceae among caesarean-delivered infants with and without eczema
Abrahamsson et al. [54]	2012	20 infants with IgE-associated eczema at 12 months; 20 infants without any allergic manifestation until 24 months of age	Sweden	↓ Intestinal microbial diversity during the first month of life → subsequent atopic eczema
West et al. [53]	2015	10 infants developing IgE associated eczema; 10 infants remaining free of allergic symptoms (controls); 231 atopic pregnant women (whose 178 infants completed the study)	Sweden	Infants developing IgE-associated eczema: ↓ Ruminococcaceae (at 1 week of age) vs controls Inverse correlation between <i>Ruminococcus</i> and TLR2 ligands-induced IL-6 and TNF-α vs controls Inverse association between Proteobacteria and TLR4-induced TNF-α (at 1 week and 1 month of age) vs controls Inverse association between Enterobacteriaceae and TLR4-induced TNF-α and IL-6 (at 1 month of age) vs controls ↓ α-diversity of Actinobacteria (at 1 year) vs controls Mothers whose infants developed IgE-associated eczema: ↓ α-diversity of Bacteroidetes during pregnancy
Orivuori et al. [72]	2015	120 AD infants	Austria, Finland, France, Germany and Switzerland	-↑ Fecal calprotectin at 2 months of age: Predicted asthma and AD by the age of 6 years Correlated with ↓ fecal <i>E. coli</i>
Laursen et al. [58]	2015	114 children of the SKOT1 cohort	Denmark	Furry pets or early life infections do not influence gut microbiota composition Older siblings: ↑ Gut bacterial richness and diversity No association with subsequent atopic skin disorders
Lee et al. [70]	2016	12 AD infants; 12 healthy infants	Korea	AD: ↑ Richness and relative abundance of Bacilli vs controls ↑ Relative abundance of Clostridia: Correlation with AD age of onset (positive) and with blood eosinophils (negative) No association with SCORAD index or total serum IgE
Song et al. [68]	2016	90 AD adults	Korea	AD: ↑ Fecal <i>Faecalibacterium prausnitzii</i> ↓ Serum SCFAs butyrate and propionate

**Table 1** continued

Authors	Year	Number of patients	Country	Main results
Zheng et al. [61]	2016	50 infants with eczema; 51 healthy infants	China	<p>Controls: ↑ <i>Bifidobacterium</i>, <i>Megasphaera</i>, <i>Haemophilus</i> and <i>Streptococcus</i></p> <p>AD:</p> <p>↑ <i>Escherichia/Shigella</i>, <i>Veillonella</i>, <i>Faecalibacterium</i>, Lachnospiraceae, incertae sedis and <i>Clostridium</i> XIVa (among them <i>Faecalibacterium prausnitzii</i>, <i>Ruminococcus gnavus</i> and <i>Akkermansia muciniphila</i>)</p> <p>↓ <i>Bacteroides fragilis</i> and <i>Streptococcus salivarius</i></p>
Mahdavinia et al. [64]	2017	29 children with AD; 9 control children	Africa	AD → No significant differences of $\alpha$ -diversity + relative abundance for any taxa vs controls
Chua et al. [60]	2018	14 pairs of dizygotic twins, 1 pair of monozygotic twins and 14 unrelated singletons	Taiwan	<p>AD: ↑ Of fecal Lachnospiraceae in (overgrowth of <i>Ruminococcus gnavus</i>)</p> <p>Not AD: ↓ abundance of <i>Ruminococcus gnavus</i></p>
Lee et al. [63]	2018	63 infants with AD; 66 healthy controls	Korea	<p>Comparable OTUs numbers, clusters in PCoA plot, and Shannon diversity between controls and AD samples</p> <p>Controls: ↑ numbers of fecal bacterial cells</p> <p>AD: ↓ expression of genes involved in immune development (PI3K-Akt; NOD-like receptors) associated with ↓ abundance of <i>A. muciniphila</i>, <i>R. gnavus</i>, and Lachnospiraceae</p>
Reddel et al. [62]	2019	19 AD children; 18 healthy controls	Italy	<p>AD: ↑ <i>Faecalibacterium</i>, <i>Oscillospora</i>, <i>Bacteroides</i>, <i>Parabacteroides</i> and <i>Sutterella</i> and ↓ abundance of <i>Bifidobacterium</i>, <i>Blautia</i>, <i>Coprococcus</i>, <i>Eubacterium</i> and <i>Propionibacterium</i> (SCFAs producing bacteria)</p> <p>Ability of a probiotic mixture (<i>B. breve</i> plus <i>L. salivarius</i>) to pass through the gastrointestinal tract and to persist in the gut microbiota (only <i>B. breve</i>)</p>
Park et al. [69]	2020	22 transient and 26 persistent AD children; 84 healthy controls	Korea	<p>Transient AD:</p> <p>↓ Abundance of <i>Streptococcus</i></p> <p>↑ Of <i>Akkermansia</i></p> <p>↓ SCFAs butyrate and valerate levels vs healthy and persistent AD</p> <p>Persistent AD:</p> <p>↓ Abundance of <i>Clostridium</i> and <i>Akkermansia</i></p> <p>↑ <i>Streptococcus</i></p> <p>↓ Gut microbial functional genes related to oxidative phosphorylation</p> <p>SCORAD index:</p> <p>Positive correlation with ↑ abundance of <i>Streptococcus</i></p> <p>Negative correlation with ↑ abundance of <i>Clostridium</i></p>

Psoriasis (Ps)

**Table 1** continued

Authors	Year	Number of patients	Country	Main results
Scher et al. [83]	2015	15 skin Ps; 16 psoriatic arthritis; 17 controls	USA	Ps patients (skin and arthritis) ↓ Diversity of species ↓ Fecal <i>Coprococcus</i> ↑ Fecal protein RANKL and secretory IgA ↓ Fecal heptanoate and hexanoate Psoriatic arthritis patients: ↓ <i>Akkermansia</i> , <i>Ruminococcus</i> , and <i>Pseudobutyryivibrio</i>
Tan et al. [90]	2018	14 Ps vulgaris; 14 controls	China	Ps: ↓ fecal <i>Akkermansia muciniphila</i> and ↑ <i>Clostridium citroniae</i>
Huang et al. [86]	2018	35 Ps patients: 16 vulgaris, 8 pustular, 7 psoriatic arthritis, 4 erythroderma; 27 controls	China	Ps vs controls: altered Firmicutes/ Bacteroidetes ratio Ps patients: association between fecal <i>Veilonella</i> with C reactive protein Ps vs psoriatic arthritis: no gut microbiota differences different fecal microbial profiles according to the severity of Ps
Codoñer et al. [87]	2018	35 Ps; 300 healthy individuals extracted from the human microbiome project	Spain	Ps: Specific enterotype characterized by ↑ <i>Prevotella</i> , <i>Faecalibacterium</i> , <i>Akkermansia</i> and <i>Ruminococcus</i> genera, and by ↓ <i>Bacteroides</i> genus
Chen Y-J et al. [88]	2018	32 Ps patients (4 with psoriatic arthritis); 64 controls	Taiwan	↑ <i>Ruminococcus</i> and ↑ <i>Megasphaera</i> as main discriminants of Ps gut microbiota Over-representation of functional genes and metabolic pathways involving bacterial chemotaxis and carbohydrate transport Under-representation of genes related to cobalamin and iron transport Articular involvement → no influence on the abundance and shaping of gut microbial profile
Shapiro et al. [84]	2019	24 Ps; 22 controls	Israel	Ps: Significant differences in beta diversity ↑ Firmicutes and Actinobacteria phyla; ↑ <i>Ruminococcus gnavus</i> , <i>Dorea formicigenerans</i> and <i>Collinsella aerofaciens</i> ↓ <i>Prevotella copri</i> and <i>Parabacteroides distasonis</i> ↑ Metabolic pathways of lipopolysaccharide function
Hidalgo-Cantabrana et al. [85]	2019	19 Ps; 20 controls	Spain	Ps: ↓ Diversity of species ↑ Bifidobacteriaceae, Coriobacteriaceae, Lachnospiraceae, Clostridiales family XIII, Eggerthellaceae, Peptostreptococcaceae, Ruminococcaceae, Erysipelotrichaceae ↓ Bacteroidaceae, Barnesiellaceae, Prevotellaceae, Tannerellaceae, Burkholderiaceae, Rikenellaceae, Lactobacillaceae, Streptococcaceae, Desulfovibrionaceae, Veillonellaceae, Marinifilaceae, Victivallaceae and Pasteurellaceae

**Table 1** continued

Authors	Year	Number of patients	Country	Main results
Yeh et al. [99]	2019	34 Ps (24 under secukinumab and 10 under ustekinumab therapeutics); 12 controls	Taiwan	Secukinumab treatment: ↑ Proteobacteria, Pseudomonadaceae, Enterobacteriaceae, Pseudomonadales ↓ Bacteroidetes Significant differences in baseline gut microbiome between responders and non-responders Ustekinumab therapy: →↑ <i>Coprococcus</i>
Alopecia Areata (AA)				
Moreno-Arrones et al. [104]	2019	15 AA universalis; 15 controls	Spain	AA: No difference in diversity or richness ↑ <i>Holdemania filiformis</i> , Erysipelotrichaceae, Lachnospiraceae, <i>Parabacteroides johnsonii</i> , Clostridiales vadin BB60 group, <i>Bacteroides eggerthii</i> , Eggerthellaceae and <i>Parabacteroides distasonis</i> Controls: ↑ <i>Phascolarctobacterium succinatutens</i> , <i>Dorea longicatena</i> , Clostridiales family XIII, <i>Phoceae massiliensis</i> , <i>Streptococcus thermophilus</i> , <i>Turicibacter sanguinis</i> and <i>Flavonifractor plautii</i>

*SLE* systemic lupus erythematosus, *SLEDAI* systemic lupus erythematosus disease activity index, *AD* atopic dermatitis, *SCORAD* SCORing atopic dermatitis, *SCFAs* short chain fatty acids, *OTU* operational taxonomic units, *Ps* psoriasis, *AA* alopecia areata

Unfortunately, although a plethora of interesting observational evidence regarding such issues exists, a clear causal role of gut microbes in these diseases has not yet been found.

This review aims to discuss the current knowledge regarding gut microbiota composition in systemic lupus erythematosus (SLE), atopic dermatitis (AD), psoriasis (Ps), and alopecia areata (AA), and analysis of the main gut microbial signatures potentially involved in immune dysregulation, inflammation, or autoimmunity. Possible implications of selected bacteria in affecting the severity, prognosis, and comorbidity risks of the abovementioned diseases are also reviewed.

Different methods including culture, PCR, or EDDGE have been used so far to assess gut microbiota features in such diseases, with inexhaustive or not comparable results. Hence, to achieve a more focused point of view and to properly confront the evidence, we only considered gut microbiome evaluations through next generation sequencing (NGS) which, so far, have been performed with comparable methods (Table 1). A literature search of

PubMed limited to English language articles was performed, and the articles we considered to be relevant were selected and discussed. We limited our review to SLE, AD, Ps, and AA, since these disorders have been evaluated more extensively and in greater depth compared with other dermatological diseases. We excluded dermatoses with a clear microbial pathogenic background. This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

### General Features of Gut Microbiota

SLE is a heterogeneous autoimmune disease involving several organs and displaying a variable clinical course [19], which can be diagnosed according to both clinical and serological criteria established by the 2019 European

League Against Rheumatism/American College of Rheumatology classification [20].

Skin involvement has been identified as a major clinical criterion of this disorder [20] and might present as a malar or generalized maculopapular rash (acute LE), an annular or papulosquamous (psoriasiform) cutaneous eruption (subacute LE), an erythematous-violaceous cutaneous lesion with secondary changes of atrophic scarring, depigmentation and follicular hyperkeratosis/plugging (discoid LE, possibly leading to a scarring alopecia of the scalp), or a non-scarring alopecia. Available investigations on gut microbiota composition in SLE patients do not specify what kind of diagnostic criteria are met in each enrolled subject. Hence, current data on gut microbiota in SLE belong to patients with unspecified and potentially very different types and severities of autoimmune organ involvement.

The most striking evidence of a gut dysbiosis in SLE is provided by several independent studies and consists of a reduced Firmicutes to Bacteroidetes ratio. Such data were first identified by an investigation conducted on a population of Spanish SLE adults [21] and subsequently confirmed by other studies conducted on Dutch [22] and Chinese patients [23, 24].

In addition, specific gut microbiota signatures have been identified in SLE patients at lower taxonomic level. In this context an overall increase of gut Gram-negative bacteria in SLE has been found by some authors [25], while other researchers identified an enrichment of genera *Rhodococcus*, *Eggerthella*, *Klebsiella*, *Prevotella*, *Eubacterium*, *Flavonifractor* and incertae sedis and a depletion of genera *Dialister* and *Pseudobutyrvibrio* [23]. Interestingly, such a signature was outstanding enough to distinguish SLE subjects from controls. It is worth noting that despite the geographical dissimilarity of enrolled patients, almost all studies on gut microbiota in SLE convey specific alterations in the Firmicutes to Bacteroidetes ratio. Such evidence might suggest a potential independence of SLE gut microbiota from diet or habits.

Specific bacterial enrichments have been also recognized as biomarkers of activity in SLE. Accordingly, an enrichment of *Streptococcus*,

*Campylobacter*, and *Veillonella* has been correlated with disease activity, while *Bifidobacterium* was associated with a remission phase [26]. Furthermore, an overall decreased gut bacterial richness has been reported to directly correlate with the SLE disease activity index (SLEDAI) [27], which is a validated measure of SLE activity [28].

The abovementioned dysbiosis and microbial enrichment/depletion might be responsible for the impaired production of short chain fatty acids (SCFAs), mostly acetate and propionate, which has been observed in SLE patients [29]. SCFAs are usually produced under physiological conditions by bacteria as the result of their metabolic and fermentative processes and are involved in gut barrier modulation [30] and inflammatory/immune response regulation. The altered release of SCFAs observed in SLE patients thus suggests possible impairments in the immune system regulation exerted by gut bacteria, likely contributing to the aberrant autoimmune stimulation involved in SLE pathogenesis.

Besides such indirect activation of key immune-pathogenic pathways in SLE, selected gut bacteria also seem to have a direct activating role. An investigation found that naïve CD4+ cells with fecal samples of SLE patients added to them could promote lymphocyte activation and their polarization toward a Th17 phenotype [31], which is a recognised T-cell subset strongly involved in SLE pathogenesis. In addition, a direct correlation was found between fecal Firmicutes abundance and serum Th1 cells and IFN- $\gamma$  in SLE patients, which was not observed in controls [31].

Possible evidence of a direct bacterial pathogenic role comes from a study on gut *Ruminococcus gnavus*, which showed a fivefold increase in gut bacteria in SLE patients compared with controls [27]. Besides such a gut enrichment, SLE patients also have circulating antibodies directed toward B-cell superantigens of the cell wall lipoglycans of a selected strain of this bacterium. Interestingly, such antibodies directly correlated with disease activity, active lupus nephritis and anti-native DNA titers [27]. Such evidence suggests that the gut enrichment by *R. gnavus* in SLE might elicit B-cell activation



and the consequent triggering of pro-inflammatory effects [32, 33].

It is possible that an impaired gut barrier function (leaky gut syndrome) might potentially promote the translocation beyond the gastrointestinal barrier of such selected immunogenic bacteria strains owning epitopes able to cross-react, through molecular mimicry processes, with specific self-antigens, thus eliciting systemic autoimmune pathways [32–34]. Interestingly, high levels of fecal calprotectin [27], which is a marker of intestinal inflammation and mucosal damage, have been recently identified in SLE patients.

In addition, confirmatory evidence of a possible molecular mimicry process derives from an *in vitro* investigation by Greiling et al. [35] showing that sera from SLE patients positive for autoantibodies directed toward the RNA binding protein Ro60 (anti-nuclear antibodies anti-Ro60) also undergo T- and B-cell activation and a pro-inflammatory cytokine release after *in vitro* stimulation by selected commensal bacteria [34]. Among such reactive microbes, the authors identified intestinal *Bacteroides thetaiotaomicron*, a bacterium with high sequence similarity to human Ro60 protein (Ro60 ortholog) [35]. This research provides evidence of a cross-reactivity phenomenon between bacterial and human epitopes.

The dysbiosis and specific gut microbiota signatures identified so far might also contribute to understanding the recognized female predominance of SLE [36, 37]. It has been demonstrated in mice that gender strongly affects specific gut microbial genetic and metabolic pathways involved in immune regulation, with an immune-stimulating role exerted by estrogens and an opposite action carried out by androgens in the mice model [38, 39]. In this scenario, specific gut microbiota signatures might correlate with the strongest hyper-reactive immune responses, and consequently result in the strongest susceptibility toward autoimmunity in females versus males [38, 40]. As to the differences in gut microbiota composition in SLE in females vs males, this has been addressed so far only in mice. As expected, differences in gut microbiota composition of female rodents compared with males were

associated with an increased progression of the disease in females [40].

### Future Directions

The lack of investigations aiming to evaluate gut microbiota features in SLE patients with different kinds and severities of organ involvement might raise some concerns, since different organ damage might lead to different autoantibody patterns. Only one study selectively assessed SLE patients with major renal involvement, and identified that the presence of a specific gut microbiota signature and the occurrence of specific antibodies directed toward selected pathobionts (i.e., *R. gnavus*) were strong predictors of nephritis development [27]. Investigation of a selection of different SLE patients is required in order to explain the different degree and variability of organ involvement in SLE [27]. The identification of selected causal bacteria able to drive a specific organ involvement might have a possible predictive role, hence changing the current screening protocols in SLE. Further, besides the gut microbiota analysis, increased attention should be given to the microbiota of other body sites [41, 42]. For example, acute flares (malar rash) in SLE patients have been reported to predict an early subclinical respiratory tract inflammation, hence allowing the early detection of unfavorable lung involvement in SLE [42]. It is unclear how a specific gut or lung microbiota composition might contribute to such auto-inflammatory skin and lung conditions. Nonetheless, an increased knowledge of the interplay between gut microbiota, other organ microbiota, and the skin might help identify specific microbial signatures of different body sites, potentially predicting early multi-organ involvement.

In the light of all the abovementioned issues, studies independently addressing gut microbiota composition in females or males, or in SLE patients with different organ involvement, are needed.

## ATOPIC DERMATITIS (AD)

### General Features of Gut Microbiota

AD is a chronic inflammatory skin disorder usually affecting children, characterized by persistent itching and skin manifestations specific for each age [43]. Less frequently, AD can even last to, or begin in, adulthood [44]. AD may be associated with an increased level of IgE [45]. This parameter allows the classification of AD into intrinsic (normal IgE, non-allergic) and extrinsic (high IgE level, allergic and more severe) [45]. Patients with extrinsic AD seem to have an increased risk of developing the so-called atopic march, a well-defined succession of diseases starting from atopic dermatitis and food allergy (infancy) and later developing into allergic asthma and allergic rhinitis (childhood) [45]. AD derives from an intricate interaction between genes and environment. Pathogenetically, abnormalities of intercellular lipids, filaggrin, and tight junctions cause a breaking of the skin barrier, ultimately developing into skin inflammation [46]. Even if it is widely recognized that Th2 cells and their related cytokines play a major role in AD inflammation, mostly in the acute phase, recent findings suggest an adjunctive switch of the T response toward a type 1/Th17 phenotype, especially in the chronic phase of AD [47, 48]. The earliest suggestions of a potential interaction between microbes and AD came from the hygiene hypothesis [49, 50]. Given the increased prevalence of allergic disorders in modern Westernized populations, this theory postulates that poor microbial exposure early in life could result in impaired immune priming, and subsequently an increased risk of developing allergic or autoimmune disorders later in life. In this scenario, due to the known ability of gut microbes to modulate immune responses toward pathogens and tolerance, a eubiotic gut microbiota during early childhood might promote adequate immune tolerance and prevent allergic over-sensitizations [51].

Subsequent investigations using quantitative real-time PCR and/or denaturing gradient gel electrophoresis (DGGE) pointed out differences

regarding the kind and the abundance of bacteria inhabiting the gut of AD subjects, compared with healthy controls, hence suggesting a potential role for gut microbiota composition in AD development [51, 52].

The advent of metagenomics undeniably provided clear and exhaustive evidence of an altered gut microbiota composition in AD patients.

A condition of gut dysbiosis seems to be an early and long-lasting event in AD-prone children, capable of triggering the immune activation and cytokine release involved in the subsequent development of AD clinical signs.

Such an event has been demonstrated by an NGS study by West et al. [53] on pregnant atopic women and their offspring. The authors analyzed and correlated baseline gut microbiota (at 1 week, 1 month, and 1 year) of such infants with specific markers of innate immune responses at 6 months of age (assessed as cytokine production from peripheral blood mononuclear cells after activation with specific microbial ligands for TLR2 (Pansorbin) and TLR4 (lipopolysaccharide) and with the development of IgE-associated eczema at 2.5 years of age [53]. A dysbiosis and an immune activation were found in atopic patients, sustained by a reduced relative abundance of Ruminococcaceae at 1 week in infants developing a future IgE-associated eczema, and an increased IL-6 and TNF- $\alpha$  release after TLR2-ligands stimulation, [53]. Additionally, an inverse association between a Proteobacteria abundance (at 1 week and at 1 month) and an Enterobacteriaceae enrichment (at 1 year) with TLR4-induced TNF- $\alpha$  secretion was also found [53]. A further investigation confirmed a long-lasting gut bacterial impairment consisting of a reduced microbial diversity in AD children [54].

Some factors are capable of shaping gut microbiota composition early in life. Among them, the delivery mode (cesarean versus vaginal) [55], the kind of feeding [56], the maternal gut microbiota composition during pregnancy [53, 55, 57] and the presence of an older sibling [58, 59] are worth mentioning. Interestingly, a protective role of vaginal delivery and breastfeeding toward AD development has been discovered in children, while a reduced diversity

and abundance of gut bacteria in pregnant mothers whose infants subsequently developed atopy has been identified [53, 55, 57]. The presence of an older sibling seems to not affect AD risk in children [58, 59]. The studies assessing gut microbiota in AD should consider all the above reported potential confounding factors in the enrollment process.

Specific bacteria have also been identified as potential sustainers of a gut dysbiosis in AD. The most frequently identified bacteria by several independent studies as enriched in AD children are *Faecalibacterium* and *Ruminococcus gnavus* [60–62], whose ability to elicit pro-inflammatory and immuno-sensitizing responses, as shown in mice [60], suggests a potential pathogenic role. A depletion of *Bifidobacterium*, a bacterium capable of releasing SCFAs with anti-inflammatory properties, has also often been identified in AD children [61, 62].

Supplementary bacteria have been less frequently identified as increased in pediatric AD [61, 62] (Table 1), while others have been found to be decreased [61, 63] (Table 1).

Among them, *Akkermansia muciniphila* depletion in AD children has been reported to directly correlate with a modified expression of functional genes involved in immune system regulation [63]. Such genes belong to the phosphoinositide 3-kinase-protein kinase B (PI3K-Akt) signaling pathway, implicated in epithelial cell and dendritic cell survival, and to the nucleotide-binding oligomerization domain (NOD)-like receptors signaling, involved in gut microbiota homeostasis. Such gene regulation might result in aberrant antigen processing and presentation, hence potentially favoring immune sensitization. In addition, since *Akkermansia muciniphila* is involved in mucus degradation, its depletion in AD might promote an increased mucus layer thickness, which makes nutrients (such as glycans) less available for other potentially beneficial microbes, hence encouraging a bacterial dysbiosis [63].

Perturbations in gut microbiota composition have not been found so far in AD children coming from rural Africa [64]. Indeed, the unique study performed on such atopic infants showed no differences in bacterial richness and abundance of species, as compared to non-

atopic African children. The authors suggest that AD in African children might be more likely due to genetically predisposing backgrounds or to skin barrier impairments, than to a gut dysbiosis. More in-depth evaluations are needed to clarify such an association.

Overall, except for the above reported investigation, studies performed so far in AD agree with the findings of early alterations in gut microbiota composition or enrichment/depletion of bacteria involved in mucus layer homeostasis. Such alterations might lead to dysbiosis, gut inflammation, and increased permeability, potentially enabling the transit to blood circulation of pro-sensitizing toxins, bacteria, or antigens which could reach the skin and trigger sensitization processes by the immune system, hence contributing to a subsequent development of AD [50, 65, 66].

In addition, specific microbes might release circulating neurotransmitters capable of modulating local skin processes involved in itch and inflammation [65].

So far, most investigations have focused on gut microbiota composition in AD children, since this disorder mostly affects prepuberal ages and usually disappears in adults [43]. However, recently an increased incidence of adult AD has been reported [67]. AD adults exhibited a gut dysbiosis with increased *Faecalibacterium prausnitzii* [68] and reduced SCFAs, as previously reported in infants [61, 62].

Such evidence suggests a potential shared pathogenic gut microbial signature, which seems to be independent of age.

### Correlations with Clinical Parameters and Comorbidities

Selected enrichment or depletion of specific bacteria in AD has been reported to correlate with the clinical course, the severity of the disease, and serological or fecal markers of hypersensitization/inflammation.

An enrichment of *Akkermansia* (genus) and a depletion of *Streptococcus* have been associated with a transient clinical course in AD children while, conversely, an *Akkermansia* and *Clostridium* depletion, and a *Streptococcus* enrichment,

have been linked to a persistent AD [69]. In addition, the SCORAD index, which is the main clinical score assessing AD severity [69], has been found to correlate with an increased abundance of *Streptococcus* and a decreased abundance of *Clostridium*. Also, bacterial metabolites might play a role in affecting the clinical course of AD, since low anti-inflammatory SCFAs levels (butyrate and valerate) have been reported to correlate with a persistent AD [69].

As for serological or fecal markers in pediatric AD, a correlation between a depletion of gut *Clostridia* and blood eosinophils [70] has been identified, while increased levels of fecal calprotectin, marker of increased intestinal inflammation [71], have been detected in AD children [72]. Such a fecal biomarker was also associated with a reduced abundance of gut *Escherichia coli* at the age of 2 months in those infants subsequently developing AD at the age of 6 years [72], and directly correlated with the severity of pediatric AD [73].

Although inconclusive, these findings suggest the need for further studies aiming to assess a potential role of specific microbial signatures or metabolic products as biomarkers for severity and prognosis.

As previously mentioned, AD might be associated with respiratory or gastrointestinal disorders characterized by selective hypersensitizations to common antigens. [45, 74]. Whether the altered skin barrier in AD allows an increased penetration of allergens resulting in gastrointestinal or respiratory allergy, or whether an altered gut or airway barrier facilitates an increased spectrum of hypersensitizing disorders, including AD, is still under debate [75]. It is possible that in AD patients an altered gut epithelial barrier and a dysbiosis might contemporarily predispose to the onset of gastrointestinal sensitization. Indeed, a leaky gut condition, which implies an increased penetration by food antigens, might result in phagocytosis of the food antigens by macrophages and their consequent exposure to T cells in draining lymph nodes, thus leading to a Th2 activation, as suggested by some authors [75]. Moreover, a condition of gut dysbiosis could contribute to a direct immune system

dysregulation, facilitating the immune pathways at the basis of gut and lung immune system sensitization. Such allergic processes might be sustained by an impaired activation of microbial functional genes involved in immune regulation, by the loss of possible tolerogenic bacteria, or by an altered balance of microbial derived SCFA levels with a consequent reduction of Tregs activity and immunosuppressive cytokines. [50, 65, 66].

Celiac disease has also been recognized as a frequent comorbidity of AD [76].

A leaky gut syndrome and a gut microbiota dysbiosis sustained by an increase of *Bacteroidetes* (among them *Escherichia coli* and *Staphylococcus* genus) and a depletion of *Bifidobacterium* genus, have been widely recognized in such disease [77, 78], similarly to what has been described in AD by NGS and some quantitative real-time PCR studies [51, 52].

In this scenario, a shared increased gut permeability and a potential common underlying gut microbiota signature might be responsible of the co-occurrence of AD and celiac disease. In addition, both AD skin and celiac intestinal mucosa show an increased expression of the long isoform thymic stromal lymphopoietin (TSLP), an immune mediator strongly implicated in immune sensitization and capable of driving the development of Th2 cells, CD4 + T cells, B cells, and Tregs [79]. Interestingly, some bacteria such as *E. coli* (increased in both AD and celiac disease) and *Salmonella* have been found to be able to directly activate the expression of TSLP in intestinal epithelial cell lines [80]. It is unknown whether patients who show AD and celiac disease have a distinctive gut microbial signature, different from subjects having only one. However, it might be possible that the enrichment of a specific bacterium able to activate TSLP or other still unknown pathogenic immune pathways might predispose patients to the concomitant development of both AD and celiac disease.

### Future Directions

Future research into AD should investigate whether specific gut microbiota signatures can

differentiate AD patients having an atopic march, or celiac diseases, from patients without such clinical evolution. An increased knowledge of such issues could potentially have a predictive role and might suggest potential measures capable of preventing hypersensitization in patients identified as at risk of developing allergic comorbidities.

## PSORIASIS (PS)

### General Features of Gut Microbiota

Ps is a chronic systemic and inflammatory skin disorder characterized by erythematous plaques sheltered by silvery scales appearing in specific pathognomonic body sites. Its pathogenesis depends on a close interaction between the immune system, environmental factors, and genetic background. From a molecular point of view, the identifying feature of Ps is the infiltration of the skin by activated T cells capable of stimulating the proliferation of keratinocytes [81]. Such an event is the consequence of a complex, and in part yet unknown, synergism of pathways involving inflammation, cell signaling, antigen presentation, and transcriptional regulation [82].

A close scrutiny of the gut microbiota composition in Ps has begun only in recent times and most of the studies concern the most common type of Ps, which is Ps vulgaris. Gut microbiota in Ps seems to be actually dysbiotic, since it has been reported to be characterized by a reduced microbial diversity [83–85] and a reduced Bacteroidetes to Firmicutes ratio [86]. In addition, specific gut microbiota signatures characterized by a depletion of *Coprococcus* [83] and *Akkermansia muciniphila* [83], and an enrichment of *Faecalibacterium* [87], *Ruminococcus* [84, 87, 88], *Megasphaera* [88] *Actinobacteria* [84], *Dorea formicigenerans* [84], and *Colinsella aerofaciens* [84], have been collectively identified by different independent studies performed with comparable methods.

From a functional point of view, specific metabolic pathways with pro-inflammatory effects are elicited by some of the above reported gut microbiota in Ps. The reduction of

*Coprococcus* indeed correlates both with a fecal reduction of heptanoate and hexanoate, which are beneficial SCFAs, and an increase of the pro-inflammatory protein RANKL and the secretory IgA, which are markers of intestinal and systemic inflammation [83].

In the same study, such alterations have also been identified in a subgroup of psoriatic patients developing arthritis [83], a rheumatological condition affecting 30% of patients with Ps [89]. Psoriatic arthritis additionally shows a depletion of beneficial *Pseudobutyrvibrio*, *Ruminococcus* and *Akkermansia muciniphila* [83]. The latter has also been identified by another study on Ps patients without articular involvement, even if with a lower abundance [90]. Other studies, in contrast, did not observed any significant difference in gut microbiota composition in psoriatic arthritis, compared with Ps vulgaris [86, 88].

The enrichment by Firmicutes and Actinobacteria (phyla), and *Dorea formicigenerans* and *Colinsella aerofaciens* (species) [84] correlates with a noticeable increase in metabolic pathways involved in lipopolysaccharide (LPS) function. Interestingly, LPS has been reported to be involved in gut inflammation, and its increase correlates with insulin resistance and diabetes mellitus, which are frequently encountered Ps comorbidities [84].

Gut microbiota studies also identified markers of mucus layer and intestinal barrier impairment in psoriatic patients. Among them, the reduced abundance of intestinal *Akkermansia muciniphila* [83, 90] is noteworthy. As previously reported, this bacterium is crucial for gut intestinal barrier homeostasis and eubiosis, since it contributes to the mucus layer thickness and glycosylation pattern, which in turn strongly affect the abundance and kinds of resident microbes [91].

In addition, a significant serological increase in claudin-3, a protein released after intestinal epithelial barrier damage which is involved in tight junction function and assembly [92, 93], and an increase in serological intestinal fatty acid binding protein (I-FABP), which is a marker of enterocyte damage [93], have both been reported in Ps [94, 95].

Both markers of intestinal barrier impairment and specific microbial enrichment/depletion have been reported to directly correlate with clinical parameters of Ps. Namely, the increase of plasma I-FABP correlates with the well-known index of Ps severity, PASI [95], while an increase in *Veillonella* correlates with an increase in blood C-reactive protein [86], which is a marker of systemic inflammation usually increased in Ps [96].

A leaky gut syndrome resulting from increased gut permeability might also be responsible for a potential bacterial translocation from gut to bloodstream [97, 98]. Indeed, bacterial DNA fragments, mostly belonging to *E. coli*, have been identified in psoriatic patients. Interestingly, they have been found to correlate with a systemic inflammation, characterized by increased circulating levels of IL-1 $\beta$ , IL-6, IL-12, tumor necrosis factor, and interferon  $\gamma$ , and a more severe course of psoriasis [97]. Such research provides proof of a potential bacterial trigger for a systemic inflammatory response and a modulation of clinical course in Ps [97]. In this scenario, increased permeability markers and specific microbial signatures collectively provide proofs of a general state of microbiota-driven inflammation in Ps, suggesting a possible pathogenic role for gut microbiota in Ps pathogenesis.

### Correlations with Clinical Parameters and Comorbidities

The assessment of potential correlations between specific microbial profiles and Ps clinical course and severity is ongoing, but still inconclusive.

At present, only an increased abundance of Bacteroidetes and a depletion of Firmicutes seem to directly correlate with PASI. Further, a reduced abundance of the beneficial gut microbe *Bifidobacterium* has also been identified in patients with severe Ps [86].

However, there is no consensus at present on a distinctive gut microbiota signature in Ps. Dissimilar patient enrollment criteria might explain the contrasting results which have been reported so far. In addition, biologic treatment

for Ps might modify gut microbiota composition, as demonstrated by a recent study by Yeh et al. [99] showing a persistent modification of gut microbiota after secukinumab (anti-IL17) and ustekinumab (anti-IL 12/23) therapy. Such significant changes in gut microbiota composition nonetheless seem of great interest, since they have been reported to predict the response to treatment [99].

Given its strong association with Ps, obesity might be a confounding factor in evaluating gut microbiota in Ps, and studies should consider this potential confounding factor in patient enrollment processes.

### Future Directions

At present, there is a lack of evaluations of Ps patients with comorbidities, as compared to Ps patients without comorbidities. Nonetheless, an enrichment of selected bacteria is shared by psoriasis and its main comorbidities. For example, the reduced abundance of *Akkermansia muciniphila* observed in psoriasis is a common finding in obesity too [100]. Also, features of a leaky gut syndrome (i.e., altered intestinal barrier and permeability) have been found in psoriasis, and resemble those identified in inflammatory bowel diseases, which interestingly are other known comorbidities of Ps.

Hence, besides a common shared genetic background, a similar gut microbiota signature and an increased gut permeability might contribute to the concomitance of Ps and its main comorbidities. Further studies should also assess the effects of conventional systemic therapeutic options for Ps in shaping gut microbiota composition, because the consequent microbial changes might affect the therapeutic outcome.

In this scenario, an increased knowledge of gut microbiota composition in psoriatic patients might guide the therapeutic choices for this disease and hypothetically might help prevent the onset of its associated comorbidities, through interventions capable of modulating gut microbiota.

## ALOPECIA AREATA (AA)

### General Features of Gut Microbiota

AA is a common form of alopecia characterized by non-cicatricial hair loss on the scalp, beard, body, eyebrows, and eyelashes due to an autoimmune attack directed toward hair follicles. Its pathogenesis involves the local activation of Th1 and Th17 pathways leading to the release of pro-inflammatory cytokines, with consequent peribulbar inflammation resulting in hair loss [101].

The first evidence of a potential role of gut microbiota composition in modulating the immunological pathways involved in AA pathogenesis derived from the anecdotal observations of Rebello et al. [102] on patients under fecal transplantation for gastrointestinal disease treatment. The authors reported two cases of young adults affected by active AA refractory to conventional treatments, who underwent fecal transplantations for concomitant *Clostridium difficile* colitis and Crohn disease, respectively [102]. Both patients, besides an expected successful outcome of their gastrointestinal disorders, experienced a moderate hair regrowth, which persisted after a long follow-up.

Other authors recently reported a comparable observation deriving from an elderly patient who experienced a complete and persistent hair regrowth following fecal transplantation for noninfectious diarrhea [103].

At present only one investigation has assessed gut microbiota composition in AA through next generation sequencing methods [104]. The authors performed a cross-sectional study involving 15 patients with AA universalis, which is the more severe form of AA characterized by a complete hair loss on scalp and body. The analysis of the relative abundance of species in the examined groups pointed out among other species an interesting enrichment of *Erysipelotrichaceae*, capable of triggering a pro-inflammatory cytokine release, and of *Lachnospiraceae*, which have been already reported as increased in some autoimmune comorbidities

of AA (AD, sclerosing cholangitis and ankylosing spondylitis) [60, 61, 104].

Furthermore, a depletion of bacteria in the order *Clostridiales* that produce SFCAs was also observed, suggesting a potential loss of the anti-inflammatory abilities exerted by such bacteria [104].

The choice of enrolling only AA universalis patients is noteworthy, since the possible identification of the abovementioned gut bacterial signature in other less severe kinds of AA might be suggestive of an unfavorable development toward a universalis form.

### Future Directions

AA is frequently associated with autoimmune, immune-mediated, nutritional, or psychiatric disorders. The most frequently found comorbidities are AD, vitiligo, autoimmune thyroiditis, vitamin D deficiency, celiac disease, anxiety, and depression [105–108]. Even if gut microbiota features have been assessed so far in all the above-reported comorbidities [66, 78, 109–111], except vitiligo, there is a lack of research assessing gut microbiota composition in AA patients with associated disorders. Hence, potentially causal microbial signatures shared by AA and its main comorbidities are yet to be elucidated.

Further in-depth evaluations on a larger number of patients with AA are needed to confirm the abovementioned results.

In addition, due to the frequent relapses in AA and the difficulties of achieving and maintaining satisfactory hair regrowth through conventional treatments, investigations assessing potential prognostic microbial biomarkers and indicators of response to therapies would be advisable as well. Finally, future investigations should assess gut microbiota features in AA patients with associated disorders, with the aim of elucidating gut microbiota signatures potentially predisposing to an increased risk in developing comorbidities.

## CONCLUSIONS

Metagenomic evaluations of gut microbiota rapidly raised the interest of dermatologists because an increasing number of evaluations pointed out alterations suggestive of an impaired gut microbiota composition in common autoimmune and immune-mediated skin diseases such as SLE, AD, Ps and AA (Table 1). A growing body of evidence from studies on gut microbiota composition in such diseases also suggests that specific microbial signatures could be sources of biomarkers and an alternative strategy for clustering patients.

A major limitation of the reported metagenomic evaluations is the limited size of evaluated patient populations and possible influences of diet, gender, age, environment, and ethnicity in shaping gut microbiota. Such conditions, coupled with the fact that available results have been reported at different taxonomic levels, make several studies not comparable and could provide uncertain findings.

In addition, due to their observational design, most of the reported studies lack an *in vitro* or *ex vivo* confirmatory model, which could contribute to providing a possible causal role of selected bacteria.

A further limitation is the methodological choice of assessing fecal samples, which can only supply evidence for the superficial gut microbiota of the lumen, and not for the mucosal gut microbiota, which could be interesting and relevant in terms of immune modulation as well.

Nevertheless, apart from several limitations, the reported impairment of gut microbiota composition in immune-mediated and autoimmune dermatological diseases is noteworthy.

The identified depletion of beneficial bacteria with recognized immunomodulatory and inflammatory properties and the reduction of intestinal anti-inflammatory microbial metabolites, such as SCFAs, suggest a possible causal role of gut microbiota in promoting the onset and maintenance of the abovementioned dermatological diseases.

Moreover, the presence of markers of altered intestinal permeability suggests a potential ability of selected bacteria to translocate and trigger specific responses involved in autoimmunity and allergic sensitization [50, 65, 66, 98]. Interestingly, distinctive gut microbiota signatures and dysbiosis are shared between AD, Ps, SLE, and common gastrointestinal associated diseases, such as coeliac diseases, inflammatory bowel diseases, or leaky gut syndrome.

Altogether, the reported findings strengthen the previously hypothesized existence of a gut-skin-axis [112], in which intestinal bacteria and their metabolites can modulate skin function, immune system, and endocrine and nervous apparatus through a strict and intricate bi-directional interplay.

Future studies on this issue should assess an increased number of patients, focus on different ethnicities, and might investigate males and females independently. Gut microbiota composition, given the ability of some bacteria to produce and metabolize hormones, and of some hormones in turn able to modulate microbiota composition, could contribute to an explanation of the gender bias in the incidence of some autoimmune dermatological diseases, such as SLE [37, 38, 107–116].

In addition, the assessment of circulating bacterial fragments in autoimmune and immune-mediated skin disorders should be improved, because further investigation might explain how a specific gut microbiota composition might have a role in determining distant pathogenic effects on the skin.

Furthermore, a deeper evaluation of the effects of selected diet in patients affected by autoimmune and immune-mediated skin disorders should be performed, due to the known ability of specific gut microbes to allow the metabolism and absorption of dietary nutrients. In this context, since animal or plant derived nutrients (i.e., resveratrol, quercetin, vitamin D) have been reported to modulate the immune system, inflammation, cell proliferation and differentiation epigenetically [13, 117, 118], possible differences in the inter/intra-individual composition of gut microbiota might lead in turn to variations in nutrient absorption or



metabolism. Such conditions could explain the different outcomes of selected diets or supplementations in SLE and Ps [119–123]. The presence of a specific gut microbiota composition might also help identify those patients that would benefit from a selected diet or nutrient supplementation [119, 123].

Finally, a more comprehensive evaluation of gut microbiota that also assesses the fungal gut microbiota should be performed, given the intestinal abundance of these eukaryotes and their ability to affect bacterial gut microbiota composition and to modulate immune responses, both locally and systemically.

## ACKNOWLEDGEMENTS

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Authorship Contributions.** Roberta Colucci and Silvia Moretti had the idea for the article, Roberta Colucci and Silvia Moretti performed the literature search, Roberta Colucci performed data analysis, Roberta Colucci drafted and Silvia Moretti critically revised the work.

**Disclosures.** Roberta Colucci and Silvia Moretti have nothing to disclose.

**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the author.

**Data Availability.** The manuscript has no associated data.

**Open Access.** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

1. Lloyd-Price J, Abu-Ali G, Curtis HC. The healthy human microbiome. *Genome Med.* 2016;8:51.
2. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J.* 2017;474:1823–36.
3. Hugon P, Dufour J-C, Colson P, Fournier PE, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. *Lancet Infect Dis.* 2015;15:1211–9.
4. Qin J, Li R, Raes J, Arumugam M, Solvsten K, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature.* 2010;464:59–65.
5. The Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012;486:207–14.
6. Selber-Hnatiw S, Rukundo B, Ahmadi M, Akoubi H, Al-Bizri H, Aliu AF. Human gut microbiota toward an ecology of disease. *Front Microbiol.* 2017;8:1264.
7. Rizzetto L, De Filippo C, Cavalieri D. Richness and diversity of mammalian fungal communities shape innate and adaptive immunity in health and disease. *Eur J Immunol.* 2014;44:3166–81.
8. Horz HP. Archaeal lineages within the human microbiome: absent, rare or elusive? *Life (Basel).* 2015;5:1333–45.

9. Loke P, Lim YA. Helminths and the microbiota: parts of the hygiene hypothesis. *Parasite Immunol.* 2015;37:314–23.
10. Scarpellini E, Ianiro G, Attili F, Bassanelli C, De Santis A, Gasbarrini A. The human gut microbiota and virome: potential therapeutic implications. *Dig Liver Dis.* 2015;47:1007–12.
11. Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. *BMC Immunol.* 2017;18:2.
12. Zárate-Bladés HR, Caspi RR. Regulation of Autoimmunity by the Microbiome. *DNA Cell Biol.* 2016;35:455–8.
13. Kocic H, Damiani G, Stamenkovic B, Tirant M, Jovic A, Todorovic D, et al. Dietary compounds as potential modulators of microRNA expression in psoriasis. *Ther Adv Chronic Dis.* 2019;10:2040622319864805.
14. Brial F, Le Lay A, Dumas ME, Gauguier D. Implication of gut microbiota metabolites in cardiovascular and metabolic diseases. *Cell Mol Life Sci.* 2018;75:3977–90.
15. Rea D, Coppola G, Palma G, Barbieri A, Luciano A, Del Prete P, et al. Microbiota effects on cancer: from risks to therapies. *Oncotarget.* 2018;9:17915–27.
16. Kosiewicz MM, Dryden GW, Chhabra A, Alard P. Relationship between gut microbiota and development of T cell associated disease. *FEBS Lett.* 2014;588:4195–206.
17. Polkowska-Pruszyńska B, Gerkowicz A, Krasowska D. The gut microbiome alterations in allergic and inflammatory skin diseases—an update. *J EADV.* 2020;34:455–64.
18. Salem I, Ramser A, Isham N, Ghannoum MA. The gut microbiome as a major regulator of the gut-skin axis. *Front Microbiol.* 2018;9:1459.
19. Kuhn A, Bonsmann G, Anders HJ, Herzer P, Tenbrock K, Schneider M. The diagnosis and treatment of systemic lupus erythematosus. *Dtsch Arztebl Int.* 2015;112:423–32.
20. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Rmasey-Goldman R, et al. European league against rheumatism/American college of rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol.* 2019;71:1400–12.
21. Hevia A, Milani C, Lopez P, Cuervo A, Arbolea S, Duranti S, et al. Intestinal dysbiosis associated with systemic lupus erythematosus. *MBio.* 2014;5:e01548-e1614.
22. Van der Meulen TA, Harmsen HJM, Vila AV, Kurilshikov A, Liefers SC, Zhernakova A, et al. Shared gut, but distinct oral microbiota composition in primary Sjögren's syndrome and systemic lupus erythematosus. *J Autoimmun.* 2019;97:77–87.
23. He Z, Shao T, Li H, Xie Z, Wen C. Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. *Gut Pathog.* 2016;8:64.
24. Wei F, Xu H, Yan C, Rong C, Liu B, Zhou H. Changes of intestinal flora in patients with systemic lupus erythematosus in northeast China. *PLoS ONE.* 2019;14:e0213063.
25. Luo XM, Edwards MR, Mu Q, Yu Y, Vieson MD, Reilly CM, et al. Gut microbiota in human systemic lupus erythematosus and a mouse model of lupus. *Appl Environ Microbiol.* 2018;84:e02288-e2317.
26. Li Y, Wang HF, Li X, Li HX, Zhang Q, Zhou HW, et al. Disordered intestinal microbes are associated with the activity of systemic lupus erythematosus. *Clin Sci (Lond).* 2019;133:821–38.
27. Azzouz D, Omarbekova A, Heguy A, Schwudke D, Gisch N, Rovin BH, et al. Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal. *Ann Rheum Dis.* 2019;78:947–56.
28. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI: a disease activity index for lupus patients. *Arthritis Rheum.* 1992;35:630–40.
29. Rodríguez-Carrio J, López P, Sánchez B, González S, Gueimonde M, Margolles A, et al. Intestinal dysbiosis is associated with altered short-chain fatty acids and serum-free fatty acids in systemic lupus erythematosus. *Front Immunol.* 2017;8:23.
30. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes.* 2016;7:189–200.
31. López P, de Paz B, Rodríguez-Carrio J, Hevia A, Sánchez B, Margolles A, et al. Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. *Sci Rep.* 2016;6:24072.
32. Silverman GJ, Azzouz DF, Alekseyenko AV. Systemic lupus erythematosus and dysbiosis in the microbiome: cause or effect or both? *Curr Opin Immunol.* 2019;61:80–5.
33. Bunker JJ, Drees C, Watson AR, Plunkett CH, Nagler CR, Schneewind O, et al. B cell superantigens in the human intestinal microbiota. *Sci Transl Med.* 2019;11:9356. <https://doi.org/10.1126/eaau9356>.

34. Kim JK, Kwok SK, Choe JY, Park SH. Recent advances in our understanding of the link between the intestinal microbiota and systemic lupus erythematosus. *Int J Mol Sci.* 2019;20:4871.
35. Greiling TM, Dehner C, Chen X, Hughes K, Iniguez AJ, Boccitto M, et al. Commensal orthologs of the human autoantigen Ro60 as triggers of autoimmunity in lupus. *Sci Transl Med.* 2018;10:eaan2306.
36. Krasselt M, Baerwald C. Sex, symptom severity, and quality of life in rheumatology. *Clin rev allerg Immunol.* 2019;56:346–61.
37. Christou EAA, Banos A, Kosmara D, Bertias GK, Boumpas DT. Sexual dimorphism in SLE: above and beyond sex hormones. *Lupus.* 2019;28:3–10.
38. Markle JCM, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Rolle-Kampczyk U, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science.* 2013;339:1084–8.
39. Johnsona BM, Gaudreaux MC, Gudia R, Browna R, Gilkesonb G, Vasua C. Gut microbiota differently contributes to intestinal immune phenotype and systemic autoimmune progression in female and male lupus-prone mice. *J Autoimmun.* 2020;108:102420.
40. Vemuri R, Sylvia KE, Klein SL, Forster SC, Plebanski M, Eri R, et al. The microgenderome revealed: sex differences in bidirectional interactions between the microbiota, hormones, immunity and disease susceptibility. *Semin Immunopathol.* 2019;41:265–75.
41. König MF. The microbiome in autoimmune rheumatic disease. *Best Pract Res Clin Rheumatol.* 2020;34:101473.
42. Damiani G, Pigatto PDM, Marzano AV, Rizzi M, Santus P, Radovanovic D, et al. Malar rash is a predictor of subclinical airway inflammation in patients with systemic lupus erythematosus: a pilot study. *Clin Rheumatol.* 2019;38:2541–6.
43. Kapur S, Watson W, Carr S. Atopic dermatitis . *Allergy Asthma Clin Immunol.* 2018;14:52.
44. Megna M, Patruno C, Balato A, Rongioletti F, Stingeni L, Balato N. Italian Adult Atopic Dermatitis Study Group. An Italian multicentre study on adult atopic dermatitis: persistent versus adult-onset disease. *Arch Dermatol Res.* 2017;309:443–52.
45. Yang L, Fu J, Zhou Y. Research progress in atopic march. *Front Immunol.* 2020;11:1907.
46. Nakahara T, Kido-Nakahara M, Tsuji G, Furue M. Basics and recent advances in the pathophysiology of atopic dermatitis. *J Dermatol.* 2020. <https://doi.org/10.1111/1346-8138.15664>.
47. Clayton K, Vallejo A, Sirvent S, Davies J, Porter G, Reading IC, et al. Machine learning applied to atopic dermatitis transcriptome reveals distinct therapy-dependent modification of the keratinocyte immunophenotype. *Br J Dermatol.* 2020. <https://doi.org/10.1111/bjd.19431>.
48. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol.* 2012;130:1344–54.
49. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299:1259–60.
50. Kim JE, Kim HS. Microbiome of the skin and gut in atopic dermatitis (AD): understanding the pathophysiology and finding novel management strategies. *J Clin Med.* 2019;8:444.
51. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. *Allergy.* 2007;62:1223–36.
52. Penders J, Thijs C, van den Brandt PA, Kummeling I, Snijders B, Stelma F. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut.* 2007;56:661–7.
53. West CE, Ryden P, Lundin D, Engstrand L, Tulic MK, Prescott SL. Gut microbiome and innate immune response patterns in IgE-associated eczema. *Clin Exp Allergy.* 2015;45:1419–29.
54. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol.* 2012;129:434–40.
55. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA.* 2010;107:11971–5.
56. Ho NT, Li F, Lee-Sarwar KA, Tun HM, Brown BP, Pannaraj PS, et al. Meta-analysis of effects of exclusive breastfeeding on infant gut microbiota across populations. *Nat Commun.* 2018;9:4169.
57. Hong P-Y, Lee BW, Aw M, Shek LPC, Yap GC, Chua KY, et al. Comparative analysis of fecal microbiota in infants with and without eczema. *PLoS ONE.* 2010;5:e9964.

58. Laursen MF, Zachariassen G, Bahl MI, Bergström A, Høst A, Michaelsen KF, et al. Having older siblings is associated with gut microbiota development during early childhood. *BMC Microbiol.* 2015;15:154.
59. Madsen AL, Schack-Nielsen L, Larnkjaer A, Mølgaard C, Michaelsen KF. Determinants of blood glucose and insulin in healthy 9-month-old term Danish infants; the SKOT cohort. *Diabet Med.* 2010;27:1350–7.
60. Chua HH, Chou HC, Tung YL, Chiang BL, Liao CC, Liu HH, et al. Intestinal dysbiosis featuring abundance of *Ruminococcus gnavus* associates with allergic diseases in infants. *Gastroenterology.* 2018;154:154–67.
61. Zheng H, Liang H, Wang Y, Miao M, Shi T, Yang F. Altered gut microbiota composition associated with eczema in infants. *PLoS ONE.* 2016;11:e0166026.
62. Reddel S, Del Chierico F, Quagliariello A, Giancristoforo S, Vernocchi P, Russo A, et al. Gut microbiota profile in children affected by atopic dermatitis and evaluation of intestinal persistence of a probiotic mixture. *Sci Rep.* 2019;9:4996.
63. Lee MJ, Kang MJ, Lee SY, Lee E, Kim K, Won S, et al. Perturbations of gut microbiome genes in infants with atopic dermatitis according to feeding type. *J Allergy Clin Immunol.* 2018;141:1310–9.
64. Mahdavinia M, Rasmussen HE, Engen P, Van den Berg JP, Davis E, Engen K, et al. Atopic dermatitis and food sensitization in South African toddlers: role of fiber and gut microbiota. *Ann Allergy Asthma Immunol.* 2017;118:742–743.e3.
65. Lee S-Y, Lee E, Park YM, Hong A-J. Microbiome in the gut-skin axis in atopic dermatitis. *Allergy Asthma Immunol Res.* 2018;2018(10):354–62.
66. Petersen EBM, Skov L, Thyssen JP, Jensen P. Role of the gut microbiota in atopic dermatitis: a systematic review. *Acta Derm Venereol.* 2019;99:5–11.
67. Sacotte R, Silverberg JI. Epidemiology of adult atopic dermatitis. *Clin Dermatol.* 2018;36:595–605.
68. Song H, YooY HJ, Na YC, Stanley KH. *Faecalibacterium prausnitzii* subspecies-level dysbiosis in the human gut microbiome underlying atopic dermatitis. *J Allergy Clin Immunol.* 2016;137:852–60.
69. Park YM, Lee SY, Kang MJ, Kim BS, Lee MJ, Jung SS, et al. Imbalance of gut *Streptococcus*, *Clostridium*, and *Akkermansia* determines the natural course of atopic dermatitis in infant. *Allergy Asthma Immunol Res.* 2020;12:322–37.
70. Lee E, Lee SY, Kang MJ, Kim K, Won S, Kim BJ, et al. Clostridia in the gut and onset of atopic dermatitis via eosinophilic inflammation. *Ann Allergy Asthma Immunol.* 2016;117:91–92.e1.
71. Aadland E, Fagerhol MK. Faecal calprotectin: a marker of inflammation throughout the intestinal tract. *Eur J Gastroenterol Hepatol.* 2002;14:823–5.
72. Orivuori L, Mustonen K, de Goffau MC, Hakala S, Paasela M, Roduit C, et al. High level of fecal calprotectin at age 2 months as a marker of intestinal inflammation predicts atopic dermatitis and asthma by age 6. *Clin Exp Allergy.* 2015;45:928–39.
73. Seo SC, Ahn SH, Ri S, Yoon Y, Byeon JH, Kim SH, et al. Elevated fecal calprotectin levels are associated with severity of atopic dermatitis in children. *Asian Pac J Allergy Immunol.* 2018;36:82–7.
74. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol.* 2003;112:S118–127.
75. Zhu TH, Zhu TR, Tran KA, Sivamani RK, Shi VY. Epithelial barrier dysfunctions in atopic dermatitis: a skin-gut-lung model linking microbiome alteration and immune dysregulation. *Br J Dermatol.* 2018;179:570–81.
76. Shalom G, Kridin K, Raviv KO, Freud T, Comaneshter D, Friedland R, et al. Atopic dermatitis and celiac disease: a cross-sectional study of 116,816 patients. *Am J Clin Dermatol.* 2020;21:133–8.
77. Cardoso-Silva D, Delbue D, Itzlinger A, Moerkens R, Withoff S, Branchi F, et al. Intestinal barrier function in gluten-related disorders. *Nutrients.* 2019;11:2325.
78. Cukrowska B, Sowińska A, Bierła JB, Czarnowska E, Rybak A, Urszula G-CU. Intestinal epithelium, intraepithelial lymphocytes and the gut microbiota—key players in the pathogenesis of celiac disease. *World J Gastroenterol.* 2017;23:7505–7511.
79. Varricchi G, Pecoraro A, Marone G, Criscuolo G, Spadaro G, Genovese A, et al. Thymic stromal lymphopoietin isoforms, inflammatory disorders, and cancer. *Front Immunol.* 2018;9:1595.
80. Fornasa G, Tsilingiri K, Caprioli F, Botti F, Mapelli M, Meller S, et al. Dichotomy of short and long thymic stromal lymphopoietin isoforms in inflammatory disorders of the bowel and skin. *J Allergy Clin Immunol.* 2015;136:413–22.
81. Nair PA, Badri T. Psoriasis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
82. Grän F, Kerstan A, Serfling E, Goebeler M, Muhammad K. Current developments in the immunology of psoriasis. *Yale J Biol Med.* 2020;93:97–110.

83. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, et al. Decreased bacterial diversity characterizes an altered gut microbiota in psoriatic arthritis and resembles dysbiosis of inflammatory bowel disease. *Arthritis Rheumatol.* 2015;67:128–39.
84. Shapiro J, Cohen NA, Shalev V, Uzan A, Koren O, Maharshak N. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. *J Dermatol.* 2019;46:595–603.
85. Hidalgo-Cantabrana C, Gómez J, Delgado S, Requena-López S, Queiro-Silva R, Margolles A, et al. Gut microbiota dysbiosis in a cohort of patients with psoriasis. *Br J Dermatol.* 2019;181:1287–95.
86. Huang L, Gao R, Yu N, Zhu Y, Ding Y, Qin H. Dysbiosis of gut microbiota was closely associated with psoriasis. *Sci China Life Sci.* 2019;62:807–15.
87. Chen YJ, Ho HJ, Tseng CH, Lai ZL, Shieh JJ, Wu CY. Intestinal microbiota profiling and predicted metabolic dysregulation in psoriasis patients. *Exp Dermatol.* 2018;27:1336–43.
88. Codoñer FM, Ramírez-Bosca A, Climent E, Carrión-Gutiérrez M, Guerrero M, Pérez Orquín JM, et al. Gut microbial composition in patients with psoriasis. *Sci Rep.* 2018;8:3812.
89. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. *N Engl J Med.* 2017;376:957–70.
90. Tan L, Zhao S, Zhu W, Wu L, Li J, Shen M, et al. The *Akkermansiamuciniphila* is a gut microbiota signature in psoriasis. *Exp Dermatol.* 2018;27:144–9.
91. Ouwerkerk JP, de Vos WM, Belzer B. Glycobiome: bacteria and mucus at the epithelial interface. *Best Pract Res Clin Gastroenterol.* 2013;27:25–38.
92. Garcia-Hernandez V, Quiros M, Nusrat A. Intestinal epithelial claudins: expression and regulation in homeostasis and inflammation. *Ann N Y Acad Sci.* 2017;1397:66–79.
93. Grootjans J, Thuijls G, Verdam F, Derikx JP, Lenaerts K, Buurman WA. Non-invasive assessment of barrier integrity and function of the human gut. *World J Gastrointest Surg.* 2010;2:61–9.
94. Sikora M, Chrabaszcz M, Maciejewski C, Zaremba M, Waśkiel A, Olszewska M, et al. Intestinal barrier integrity in patients with plaque psoriasis. *J Dermatol.* 2018;45:1468–70.
95. Sikora M, Stec A, Chrabaszcz M, Waskiel-Burnat A, Zaremba M, Olszewska M, et al. Intestinal fatty acid binding protein, a biomarker of intestinal barrier, is associated with severity of psoriasis. *J Clin Med.* 2019;2(8):1021.
96. Beygi S, Lajevardi V, Abedini R. C-reactive protein in psoriasis: a review of the literature. *J Eur Acad Dermatol Venereol.* 2014;28:700–11.
97. Ramírez-Bosca A, Navarro-López V, Martínez-Andrés A, Such J, Francés R, Horga de la Parte J, et al. Identification of bacterial DNA in the peripheral blood of patients with active psoriasis. *JAMA Dermatol.* 2015;151:670–1.
98. Visser MJ, Kell DB, Pretorius E, et al. Bacterial dysbiosis and translocation in psoriasis vulgaris. *Front Cell Infect Microbiol.* 2019;9:7.
99. Yeh NL, Hsu CY, Tsai TF, Chiu HY. Gut microbiome in psoriasis is perturbed differently during secukinumab and ustekinumab therapy and associated with response to treatment. *Clin Drug Investig.* 2019;39:1195–203.
100. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al. *Akkermansiamuciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut.* 2016;65:426–36.
101. Lepe K, Zito PM. Alopecia Areata. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
102. Rebello D, Wang E, Yen E, Lio PA, Kelly CR. Hair growth in two alopecia patients after fecal microbiota transplant. *ACG Case Rep J.* 2017;2017(4):e107.
103. Xie WR, Yang XY, Xia HH, Wu LH, He XX. Hair regrowth following fecal microbiota transplantation in an elderly patient with alopecia areata: a case report and review of the literature. *World J Clin Cases.* 2019;7:3074–81.
104. Moreno-Arrones OM, Serrano-Villar S, Perez-Brocal V, Saceda-Corralo D, Morales-Raya C, Rodrigues-Barata R, et al. Analysis of the gut microbiota in alopecia areata: identification of bacterial biomarkers. *J Eur Acad Dermatol Venereol.* 2020;34:400–5.
105. Lim CP, Severin RK, Petukhova L. Big data reveal insights into alopecia areata comorbidities. *J Invest Dermatol Symp Proc.* 2018;19:S57–61.
106. Miller R, Conic RZ, Bergfeld W, Mesinkovska NA. Prevalence of comorbid conditions and sun-induced skin cancers in patients with alopecia areata. *J Invest Dermatol Symp Proc.* 2015;17:61–2.
107. Kuty-Pachecka M. Psychological and psychopathological factors in alopecia areata. *Psychiatr Pol.* 2015;49:955–64.

108. Mohan GC, Silverberg JL. Association of vitiligo and alopecia areata with atopic dermatitis: a systematic review and meta-analysis. *JAMA Dermatol*. 2015;151:522–8.
109. Fenneman AC, Rampanelli E, Yin YS, Ames J, Blaser MJ, Fliers E. Gut microbiota and metabolites in the pathogenesis of endocrine disease. *Biochem Soc Trans*. 2020;48:915–31.
110. Naderpoor N, Mousa A, Gomez Arango LF, Barrett HL, Nitert MD, de Courten B. Effect of vitamin D supplementation on faecal microbiota: a randomised clinical trial. *Nutrient*. 2019;11:2888.
111. Pusceddu MM, Del Bas JM. The role of the gut microbiota in the pathophysiology of mental and neurological disorders. *Psychiatr Genet*. 2020;30:87–100.
112. O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: a paradigm with therapeutic implications. *BioEssays*. 2016;38:1167–76.
113. Gomez A, Luckey D, Taneja V. The gut microbiome in autoimmunity: sex matters. *Clin Immunol*. 2015;159:154–62.
114. Shamriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. *Autoimmunity Rev*. 2016;2016:859–69.
115. Yurkovetskiy L, Burrows M, Khan AA, Graham L, Volchkov P, Becker L, et al. Gender bias in autoimmunity is influenced by microbiota. *Immunity*. 2013;39:400–12.
116. Markle JGM, Frank DN, Mortin-Toth S, Robertson CE, Feazel LM, Kampczyk UR, et al. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science*. 2013;339:1084–8.
117. Kumari A, Bhawal S, Kapila S, Yadav H, Kapila R. Health-promoting role of dietary bioactive compounds through epigenetic modulations: a novel prophylactic and therapeutic approach. *Crit Rev Food Sci Nutr*. 2020;21:1–21.
118. Behrouzi A, Ashrafi F, Mazaheri H, Lari A, Nouri M, Riazi Rad F, et al. The importance of interaction between MicroRNAs and gut microbiota in several pathways. *Microb Pathog*. 2020;144:104200.
119. Adawi M, Damiani G, Bragazzi NL, Bridgwood C, Pacifico A, Conic RRZ et al. (2019). The Impact of intermittent fasting (ramadan fasting) on psoriatic arthritis disease activity, enthesitis, and dactylitis: a multicentre study. *Nutrients* 11:601.
120. Barrea L, Balato N, Di Somma C, Macchia PE, Napolitano M, Savanelli MC, et al. Nutrition and psoriasis: is there any association between the severity of the disease and adherence to the Mediterranean diet? *J Transl Med*. 2015;13:18.
121. Damiani G, Watad A, Bridgwood C, Pigatto PDM, Pacifico A, Malagoli P, et al. The impact of Ramadan fasting on the reduction of PASI score, in moderate-to-severe psoriatic patients: a real-life multicenter study. *Nutrients*. 2019;11:277.
122. Castaldo G, Pagano I, Grimaldi M, Marino C, Molettieri P, Santoro A, et al. Effect of very-low-calorie ketogenic diet on psoriasis patients: a nuclear magnetic resonance-based metabolomic study. *J Proteome Res*. 2020. <https://doi.org/10.1021/acs.jproteome.0c00646>.
123. Constantin MM, Nita IE, Olteanu R, Constantin T, Bucur S, Matei C, et al. Significance and impact of dietary factors on systemic lupus erythematosus pathogenesis. *Exp Ther Med*. 2019;17:1085–90.