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REVIEW ARTICLE

The Skin and Gut Microbiome in Hidradenitis Suppurativa: Current Understanding and Future Considerations for Research and Treatment

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Abstract

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease comprising painful abscesses, deep nodules, fistulas, and scarring predominantly in the axilla and groin. Bacterial colonization of HS lesions has been well characterized and may lead to chronic infection of lesions. While disease pathogenesis of HS is not fully understood, there is increasing evidence that microbial dysbiosis may be occurring in numerous locations, including the skin and gut. The skin–gut microbiome has been proposed as a mechanism by which inflammatory skin disorders, including HS, can be exacerbated. This is evidenced by HS patients being significantly more likely to develop inflammatory bowel disease as well as the well documented cutaneous manifestations in inflammatory bowel disease. In this review, we discuss the current literature regarding HS skin and gut microbiome research. Furthermore, we discuss further considerations for microbiome research in HS, including the potential role of bacterial metabolites in disease progression and future therapeutic avenues like probiotics.

Key Points

Microbiome studies of hidradenitis suppurativa patients demonstrate dysbiosis of skin and gut flora, with increasing evidence that shifts in microbial byproducts could contribute to the disease process.

Further research is needed to investigate the role of diet, lifestyle modifications, and probiotics on alterations of the microbiome of patients with hidradenitis suppurativa.

1 Hidradenitis Suppurativa (HS)—Etiology and Current Therapies

Hidradenitis suppurativa (HS) is an inflammatory disorder characterized by painful abscesses, deep nodules, fistulas, and scars in intertriginous areas [1]. This painful disorder causes significant distress to those affected and leads to diminished quality of life. HS patients report embarrassment regarding their skin, disruption of leisure or physical activity, and feelings of anxiety or depression [2]. HS lesions develop through follicular hyperkeratosis of the apocrine gland; however, the interplay between the immune system, genetics, environmental factors, and the microbiome are all thought to contribute to the development of HS [3]. The underlying inflammatory process and subsequent colonization of the affected skin by pathogenic bacteria lead to significant alterations in the normal skin flora in HS lesions. In addition, dysregulation of the skin immune response has also been confirmed, including relative reductions of anti-inflammatory regulatory T cells, infiltration of skin by B cells and plasma cells, and upregulation of inflammatory cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β) [4, 5].

Current therapies for HS include topical antibiotics, oral antibiotics, and new investigational therapies that include immunomodulators such as anti-tumor necrosis factor (TNF) antibodies, IL-1 receptor antagonists, and monoclonal antibodies that target the p40 subunit on cytokines

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IL-12 and IL-23 [3, 6–9]. In severe HS or cases that are refractory to medical management, surgical intervention may be required for tunnels and scarring. This includes carbon dioxide laser evaporation, deroofing of lesions, or wide local excision of areas affected by tunnels and scarring [3]. Antibiotics, however, are the current mainstay of treatment during flares, indicating that an infectious process or alteration in microbial populations is likely contributing to the disease process [10]. Generally, tetracyclines are used as first-line systemic antibiotic therapy, given as a 12-week course or long-term management for mild to moderate HS, with clindamycin and rifampin combination therapy being second-line or initial therapy for severe cases of HS [10]. In addition, certain antibiotics commonly used to treat HS not only affect the bacterial population but also promote anti-inflammatory responses in the host. One study demonstrated that rifampicin was able to reduce levels of toll-like receptor 2 (TLR-2) and production of inflammatory cytokines IL-1b, IL-6, IL-8, and TNFα in ex vivo cultures of HS lesional skin explants [11]. Clindamycin has shown similar immunomodulatory effects in studies of acne development including reduced inflammatory cytokines [12]. While the manifestations of HS are predominantly limited to the skin, the inflammatory activation observed in HS patients undoubtedly has systemic effects, including elevated serum levels of C-reactive protein (CRP), IL-17, and increased erythrocyte sedimentation rate (ESR) [13, 14]. Furthermore, systemic antibiotic use is well known to change microbial populations in other sites, including the intestine [15].

The skin microbiome has long been an interesting target for HS research, and several studies have shown the presence of skin bacterial dysbiosis in HS. Bacterial dysbiosis can refer to loss of beneficial organisms, proliferation of harmful or opportunistic bacteria, and loss of microbial diversity. Affected individuals may have one of the previous microbial disruptions, or a combination of the above factors. It is still unclear whether changes in skin microbial composition, proliferation of pathogenic bacteria in lesions, or a combination are drivers of disease progression in HS. Moreover, studies linking intestinal dysbiosis to pathogenesis or exacerbations of HS are still limited. In this review, we discuss the current literature on the skin microbiome of HS patients, existing literature on the intestinal microbiome of HS patients, and the potential for further research and considerations for treatment in HS.

2 The Skin Microbiome in HS

The microbiome is a diverse collection of bacteria, viruses, fungi, and other microorganisms that colonize a specific area of the human body. The skin acts not only as a barrier but is an interface between host and microbial organisms, and different sites are host to different microbial communities. The skin can generally be divided into the following categories: sebaceous, moist, and dry. In the context of HS, which primarily affects the axilla and groin, the microbial community of interest resides in the moist microenvironment, which is normally dominated by *Corynebacterium* with occasional presence of *Staphylococci* species [16].

As HS is often characterized as a disease of the hair follicle, it is important to consider the niche the hair follicle provides for microbes residing on the skin. Hair follicles are a unique site, well protected from the outside environment, and reach deep in the epidermis, dermis, and subdermal adipose layer and allows for close interaction between the host cells and microbes present within the follicle. The hair follicle is also an immune privileged site, characterized by low expression of MHC class Ia and MHC class II, which allows it to tolerate exposure to antigens without eliciting an inflammatory immune response [17]. As such, hair follicles are important sites of interaction between skin commensal microbes and the immune system that aid in the development and recruitment of regulatory T cells (Treg) within the skin [18, 19]. An animal study found that a subset of skin-resident innate lymphoid cells (ILCs) localized in hair follicles were also found to regulate production of sebum and anti-microbial peptide production. Loss of ILCs led to enlarged sebaceous glands and disrupted commensal bacterial populations [20]. It is likely that dysbiosis of the skin microbiome and the aberrant inflammatory response in HS lesions within hair follicles go hand in hand due to the proximity of skin-resident microbes and skin-resident immune cells. This phenomenon is supported by evidence of altered T-cell populations in HS skin, with substantial infiltration of T helper 17 (Th17) cells and a relative reduction in Treg populations compared with healthy skin [21].

Initial reports identifying bacteria in axillary lesions of HS demonstrated several different bacterial species including *Staphylococcus aureus* and obligate anaerobes [22]. However, this study did not include prolonged cultures and anaerobic transport media, leading to omission of some other microbial species found in other studies. Further studies sampling from deeper portions of HS lesions found a relative abundance of coagulase-negative *Staphylococci* species, which are commonly found as skin commensal bacteria [23, 24]. To explore differences between healthy skin and HS lesions, Ring et al. obtained punch biopsies from lesional and non-lesional sites from HS patients and healthy controls and analyzed bacterial composition by next generation sequencing. This study demonstrated significant differences in the bacterial composition from these three groups. While the study did not find a difference in richness from the three groups, the Shannon Diversity Index, an indicator of taxonomic evenness, was significantly decreased in HS biopsies (lesional and non-lesional) compared with healthy controls.

Secondly, the study also identified increased abundance of obligate anaerobes *Porphyromonas* and *Peptoniphilus* species in HS lesional biopsies compared with both HS non-lesional samples and healthy control [25]. *P. acnes* was more abundant in healthy controls [25].

A larger study of 82 HS patients included a total of 102 samples to examine the lesional microbiome through bacterial culture and metagenomics. Two microbiological profiles were identified from lesions; one profile was predominated by *Staphylococcus lugdunensis* and the other characterized by mixed aerobic/anaerobic microbes including *Peptoniphilus*, *Prevotella*, *Fusobacterium*, *Porphyromonas*, *Actinomyces* and *Viridans streptococci* [26]. A separate study sampling from HS tunnels in the axilla and groin with next generation sequencing recapitulated the previous findings and identified *Porphyromonas*, *Corynebacterium*, *Staphylococcus*, *Prevotella*, and *Acinetobacter* species from HS patients [27]. *Porphyromonas* and *Peptoniphilus*, the two commonly identified species in HS lesions from the described studies, are commonly found in necrotizing soft tissue infections [28]. *Porphyromonas* can form biofilms, which may promote persistent colonization in HS skin lesions [29]. Biofilm formation is common in HS lesions, possibly due to anatomical changes such as tunnel formation, dilation of hair follicles, and accumulation of keratin debris [30, 31]. It is likely that biofilm formation contributes to recurrence of HS lesions and the difficulty with antibiotic treatment. Biofilms provide an environment for increased resistance gene exchange, reduced antimicrobial penetrance, as well as increased tolerance of bacteria to antimicrobial agents [32, 33]. As with management of other local wounds with biofilm formation, it has been proposed that early surgical excision of HS lesions and high doses of local antibiotics may be beneficial in treatment [34, 35]. Although *Porphyromonas* is classically thought to be part of the oral microbiome and implicated in gingivitis and gingival epithelial dysfunction, it has also been found to be increased in vulvar lichen sclerosis, a chronic inflammatory skin disorder [36, 37]. It would be reasonable to hypothesize that HS lesions are predisposed to colonization by these microbes, contributing to chronic inflammation, tunneling, and scarring. *Peptoniphilus* species are correlated with impaired wound healing in diabetic foot ulcers, which may add to the persistence of HS lesions [38]. Anaerobic species *Peptoniphilus*, *Porphyromonas*, and *Fusobacterium* are often found in secondary infections of the skin, including atopic dermatitis, poison ivy dermatitis, and pustular psoriasis [39–42]. In sum, these studies demonstrate increased colonization of HS lesions by bacteria found in skin and soft tissue infections with relatively low pathogenicity.

To identify whether dysbiosis contributes to HS exacerbations, a pilot study of 12 HS patients and five healthy volunteers by Naik et al. explored the relationship between microbial colonization of the skin and disease severity through 16s rRNA sequencing with swabs from the axilla, gluteal crease, inguinal crease, and inframammary fold. The results established a relative decrease in the skin commensal bacteria and increase in anaerobes of HS lesional and non-lesional skin compared with healthy volunteers. Relative abundance of commensal microbes negatively correlated with HS severity, and relative abundance of anaerobes positively correlated with HS severity as measured by Hurley stage [43]. These preliminary results show that the skin flora of HS patients diverges significantly from healthy volunteers, even within non-lesional HS samples, and that HS severity is associated with greater microbial population disturbances. This also suggests that microbial dysbiosis is not limited to HS lesions but may be an underlying risk factor in the development of HS. Further studies by Riverain-Gillet et al. confirmed that HS skin microbiota differed significantly from healthy patients by both culture and 16s rRNA sequencing. Culture results showed a similar predominance of *Staphylococcus* species in control skin of HS patients and healthy volunteers; however, a significant decrease in *Staphylococcus epidermidis and Staphylococcus hominis* was identified in the skin folds (axilla, gluteal cleft, groin) of HS patients. 16s rRNA sequencing demonstrated two predominant clusters of microbes in HS patients and healthy controls. One was mostly composed of anaerobes including *Prevotella*, *Porphyromonas*, and *Peptoniphilus*, and the other cluster comprised aerobic bacteria such as *Staphylococcus* and *Micrococcus* [44]. As reported previously, a significantly higher proportion of HS samples (61%) was associated with the anaerobic cluster compared with healthy samples (22%). However, these results demonstrate that presence of the anaerobic microbes associated with HS is not enough to elicit disease in all patients, as this microbial profile was also identified in healthy subjects. This suggests that other factors, such as immune dysregulation, genetic factors, or environmental factors may also play a role in development of HS in addition to dysbiosis. Various genetic mutations involved in follicular keratosis, such as Notch signaling, and inflammasome formation have been proposed as contributors to HS [45]. Disruption of immune signaling, in particular IL-12/IL-23 cytokine signaling pathway and regulation of Th17 cells, is another possible predisposing risk factor for the development of HS [46, 47].

Schneider et al. also demonstrated loss of skin microbial diversity in HS patients. This effect was present on lesional and non-lesional skin. Furthermore, the authors used a computational approach to investigate the functional significance of skin microbial dysbiosis and demonstrated differences in propanoate and retinol metabolism, as well as vitamin and amino acid metabolic pathways [48]. Similarly, a study of HS lesional and non-lesional controls demonstrated alteration of tryptophan metabolism

in skin from active HS lesions compared with controls. Guenin-Macé et al. found that HS lesional skin had overactivation of the kynurenine pathway, leading to overall reduced tryptophan on HS lesional skin [49]. Interestingly, a key enzyme in the kynurenine pathway, Indoleamine 2,3-dioxygenase (IDO1), is stimulated in the presence of bacteria in the gut and has been linked to inflammatory bowel disease (IBD) [50]. While the source of abnormal tryptophan metabolism could not be traced to a bacterial or human origin in this study, the authors propose that induction of the kynurenine pathway leads to increased recruitment of inflammatory cells in HS patients. These results suggest that dysbiosis extends to the skin metabolome and warrants further exploration on the functional aspect of microbial dysbiosis. While bacterial changes have been the main focus of biome studies in HS, recent work has also explored the skin mycobiome and its contribution to disease. Of note, serologic anti-*Saccharomyces* IgG and IgA antibodies were more frequently detected in HS patients than in healthy controls in a multi-center study [51]. Ring et al. also sought to characterize the skin mycobiome of HS patients. This pilot study of 30 HS patients and 24 healthy controls did not find any significant difference in the skin mycobiome through 18s rRNA sequencing, including *Malassezia* or *Saccharomyces* species [52].

One difficulty with studying the skin microbiome is the different sampling techniques used in studies. Multiple sampling techniques are used, including swabs and deeper punch biopsies. While each of these individual methods has been documented and validated for skin microbiome research, each technique will introduce variability when comparing studies [53, 54]. Standardized skin and sample preparation is paramount for detecting accurate changes in the microbial populations of the skin [55]. Additionally, due to the skin's direct interface with the outside environment, there can be temporal changes in the flora or transient organisms present at the time of sampling [56, 57]. Future studies of HS lesions may be able to reduce variability or these confounding factors by taking multiple samples over time to conduct a longitudinal study. In addition to possible bias being introduced through collection methods, results from 16s ribosomal sequencing studies are influenced by primer choice, PCR cycle length, and DNA isolation technique and preparation. A systematic review by Williams et al. highlighted five next generation sequencing studies of the HS skin microbiome in which three sequenced the V3–V4 hypervariable region, one sequenced V1–V2, and one the V1–V3 region [58]. As the sequencing methods of these studies differ, it is difficult to pool conclusions from these studies. However, patterns of skin dysbiosis have held true across multiple studies as described above. Further standardization of collection and sequencing methods for microbiome studies in HS are needed to fully elucidate the role dysbiosis may play in development or progression of HS.

3 The Gut Microbiome in HS

The intestinal tract is host to the largest reservoir of bacteria in the human body, with over 10^{12} bacteria per gram of luminal contents [59, 60]. Under normal conditions, the microbiome is crucial for fermentation of complex carbohydrates, production of short chain fatty acids (SCFAs), development of a healthy immune system, and outcompeting invasive or harmful bacterial species [61–65]. Dysbiosis of the intestinal microbiome has been linked to numerous disease states, including IBD, obesity, rheumatoid arthritis, type 2 diabetes mellitus, and psoriasis [66–74]. There are multiple mechanisms by which intestinal microbial dysbiosis can affect extraintestinal sites like the skin. This includes regulating the balance between T-cell subtypes, the leakage of harmful bacterial products such as lipopolysaccharide (LPS) or bacteria from the intestinal lumen to extraintestinal sites, and downstream activation of inflammatory processes [75–78].

HS is associated with several comorbid conditions. Of particular note, IBD is four to eight times more prevalent in patients with HS compared with the general population, with Crohn's disease being more common than ulcerative colitis [79–82]. HS and IBD share common disease pathways, including genetic predisposition, inappropriate activation of TNFα, involvement of Th17 cells and IL-23, as well as microbial dysbiosis [21, 83, 84]. As in the case of IBD, it is possible that intestinal microbial changes in HS patients polarize T cells into a Th17 phenotype and contribute to the pathology observed in HS [21]. IBD also exhibits cutaneous manifestations of disease, including erythema nodosum and pyoderma gangrenosum. Interestingly, a handful of studies have also demonstrated alterations to the intestinal microbiome of HS patients; however, there is still further research needed to elucidate the potential connection between intestinal dysbiosis and development or exacerbation of HS [85–87]. There is increased interest in the role of the gut microbiome in numerous inflammatory disease processes, and the gut–skin axis has been proposed as a mechanism by which dysbiosis in the intestinal lumen can influence pathologic processes in the skin [88].

In a pilot case study of three HS patients, Kam et al. evaluated the intestinal microbiome compared with three healthy controls by 16s rRNA polymerase chain reaction (PCR). This study also evaluated the diversity and evenness of microbial species by the Shannon Index [85]. The Shannon Diversity Index is an index frequently used in microbial studies to indicate the diversity of a population: the higher the Shannon Diversity Index, the higher the microbial community diversity. As a general rule, increased microbial

diversity is reported to be beneficial in the skin microbiome [89]. HS patients had significantly reduced Shannon Diversity Index compared with healthy controls. When comparing specific bacterial species present in the two groups, the authors also noted a significant decrease in the relative prevalence of *Firmicutes* species in HS patients compared with healthy controls. A decreased ratio of *Firmicutes* in the intestinal microbiome has previously been reported to be associated with obese or overweight individuals [90]. The study also found increased *Bilophila* and *Holdemania* species in HS patient samples compared with healthy controls. *Bilophila* is a microbial species that mainly colonizes the gastrointestinal tract and is highly bile resistant. It is also reported to be increased in the intestinal microbiome of subjects who consume animal products and high-fat diets [68, 91]. *Bilophila wadsworthia* has also been reported to induce colitis in mouse models [92]. A study of fecal microbial composition in ulcerative colitis patients also demonstrated that *Bilophila* species were more abundant in the active inflammatory phase of colitis compared with the remission phase or in healthy patients [93]. *Holdemania* abundance was correlated with impaired glucose and lipid metabolism in a study of patients with obesity and metabolic syndrome [94]. Interestingly, *Holdemania* species were also enriched in the gastrointestinal microbiota of patients with alopecia areata [95]. A larger exploratory study with 17 HS patients and 20 healthy controls found that analysis by linear discriminant analysis effect size (LEfSe) revealed significant differences in the bacterial taxa between HS fecal samples and healthy controls. This method characterizes genomic features that differentiate between healthy controls and HS patients. Of note, anaerobic *Robinsoniella* species were detected in 59% of HS fecal samples and none were detected in healthy samples [87].

A study of 59 HS patients compared with 30 controls looked at the skin, nasal, and intestinal microbiome in the same sample of patients. This study also found that the overall fecal microbiome was altered in HS patients compared with healthy controls with decreased α-diversity, or the number of microbial species identified. The same patient sample also demonstrated decreased α-diversity within skin and nasal microbiome [96]. It is plausible that some HS patients will experience microbial dysbiosis only in the skin or the gut; however, due to the chronic nature of HS and persistent inflammation, most patients are likely to experience dysbiosis in both body sites. Additionally, this study identified increased *Ruminococcus gnavus* in the fecal samples from HS patients, which is a species commonly identified in patients with IBD [97, 98]. *R. gnavus* has been reported to produce an inflammatory polysaccharide capable of stimulating toll-like receptor 4 (TLR-4) to induce production of inflammatory cytokines, which may contribute to development of disease [99].

The intestinal microbiome is a producer of SCFAs such as acetate, propionate, and butyrate through fermentation [100]. Butyrate is known to promote expansion of Tregs and has shown to reduce inflammation in mouse models of contact hypersensitivity and imiquimod-induced psoriasis [101, 102]. As such, intestinal bacteria producing SCFAs may be of significance in regulating inflammation within the skin. One study exploring fecal samples from patients with psoriasis, HS, IBD, concomitant psoriasis and IBD, and concomitant HS and IBD demonstrated that HS alone did not lead to significant shifts in *Faecalibacterium prausnitzii*, a commensal bacteria known to produce butyrate [103, 104]. However, samples isolated from patients with concomitant HS and IBD were depleted of protective species *F. prausnitzii*. This study also demonstrated no difference in *E. coli* abundance between healthy and HS patients, indicating that these two bacterial species may not necessarily contribute to HS alone in the absence of IBD [103]. Further studies looking at fecal or circulatory levels of SCFAs may be warranted in HS patients to understand the role they may play in progression of disease.

While pathogenic bacterial species themselves can cause inflammation, byproducts or metabolites from certain bacterial species may also contribute to disease progression. Trimethylamine N-oxide (TMAO) is one such bacterial metabolite that has been studied as a biomarker for cardiovascular disease, metabolic syndrome, and IBD [105–107]. TMAO is a metabolite derived from gut microbial metabolism and associated with inflammation. Targeting and reducing TMAO production has shown benefits in mouse models of chronic kidney disease and atherosclerosis [108, 109]. One study explored the effect of intestinal bacterial metabolites in HS patients. In a case-control study of HS and control patients, Barrea et al. investigated the circulatory levels of TMAO [110]. The study demonstrated increased levels of TMAO in circulation of HS patients, as well as a correlation of increasing levels of circulatory TMAO with HS Sartorius score when adjusted for body mass index (BMI) as well as waist circumference. Patients with Hurley grade 2 HS also had significantly increased circulatory TMAO compared with those with Hurley grade 1. Other inflammatory skin conditions, including psoriasis, have also demonstrated elevated levels of circulatory TMAO in patients [69]. It is plausible that TMAO is increased in circulation due to disrupted intestinal barrier function and intestinal dysbiosis [69]. In concert with bacterial metabolites, the dispersal of harmful bacterial byproducts, such as toxins, must also be considered in future studies of HS patients. While there are currently no studies exploring circulating levels of toxins such as LPS in HS, a study of psoriasis patients demonstrated higher levels of lipopolysaccharide binding protein (LBP), an indicator of serum LPS concentration, in psoriasis patients with concomitant metabolic syndrome. No difference in LBP was

observed between healthy patients and psoriasis patients without metabolic syndrome [111]. Obesity and insulin resistance are associated with HS and have been found to correlate with increased serum LBP [112, 113]. Microbial dysbiosis may not be the only underlying factor in inflammatory conditions such as HS, but rather, bacterial pathways leading to production of harmful metabolites or toxins contribute to worsening inflammation. Additional studies of activated bacterial pathways isolated from the intestinal microbiome of HS patients could elucidate further information, such as whether bacterial toxins or other byproducts can be associated with or contribute to development of HS.

In a similar vein, one study examined whether bacterial DNA could be detected in peripheral blood of patients with active HS flares as an indicator of disruption of the skin or gut epithelial barrier. Of the 50 HS patients included in the study, bacterial DNA as detected by 16S rRNA PCR followed by partial sequencing analysis was detected in 17 HS patients (34%) compared with two controls (4%). In addition, TNF-α, IL-1β, and IL-17A levels detected by enzyme-linked immunosorbent assay (ELISA) were also increased in HS patients. Additionally, 82% of the bacteria identified in HS patients were Gram negative species. While the bacteria identified could originate from HS skin lesions, Gram negative bacteria are most commonly identified in the intestinal tract microflora. The authors of this study did not specify the origin of bacterial DNA found in HS patients, however it is plausible the source could be intestinal in nature [114]. Dysbiosis observed in HS patients may be present in the skin, gut, or both sites. Future studies of microbial populations in multiple organ systems of HS patients would provide a more complete picture of systemic effects of dysbiosis. Patterns of microbial dysbiosis observed in populations of HS patients can provide useful information regarding antibiotic treatments, as individual patients may vary in their response to therapies based on the microbial populations present.

4 Further Considerations

There is increasing evidence of the importance of the microbiome in disease development and progression. HS is highly co-morbid with other disorders associated with intestinal microbial dysbiosis, including metabolic syndrome and obesity, which likely influences the dysbiosis observed in HS patients. Metabolic syndrome, insulin resistance, and obesity are all associated with chronic inflammatory processes that have repeatedly been linked to intestinal microbial dysbiosis [72, 115]. As an example, a 'healthy' fecal microbiome has been demonstrated to improve insulin resistance by decreasing inflammatory activation through LPS/toll-like receptor 4 (TLR4) signaling and increased circulation of beneficial SCFAs [115, 116]. Allogenic gut microbial transplantation from lean donors to patients with metabolic syndrome showed improved insulin sensitivity 6 weeks after infusion of microbiota, demonstrating the vast systemic effects of the intestinal microbiome on the host [117]. While microbial dysbiosis is an important factor in metabolic syndrome, insulin resistance, and obesity, it is still poorly understood whether these conditions predispose patients to intestinal dysbiosis or whether dysbiosis occurs first. In the context of HS, high BMI was a predictor of poor response to antibiotic therapy in a study comparing oral clindamycin oral monotherapy and clindamycin combined with rifampicin in patients with moderate to severe HS [118]. It is possible that obesity-related microbial dysbiosis may contribute to poor antibiotic response.

Insulin resistance has also been repeatedly found to be increased in patients with HS compared with control subjects [119, 120]. As a result, metformin, an oral antihyperglycemic, has been useful as an adjuvant therapy in HS with a favorable side-effect profile and the added benefit of improving insulin resistance [121–123]. There is also evidence that metformin treatment exerts its beneficial effects through modulating the intestinal microbiota. Wu et al. demonstrated that transfer of fecal samples from metformin-treated human donors to germ-free mice led to improved glucose tolerance [124]. High BMI, a risk factor for development of diabetes, is also correlated with increased risk of HS as well as poor response to therapy [118, 125]. Presence of metabolic syndrome and hemoglobin A1C (HbA1c) levels were also found to be inversely correlated with severity of HS in a cross-sectional study of 50 patients [126]. When treating HS patients, these findings support a multi-pronged approach to target not only HS lesions, but also the addition of therapies like metformin and lifestyle interventions including weight loss. These interventions may work in concert to improve dysbiosis.

Lifestyle modifications, especially through diet, can be of great importance in diversifying the gut microbiome and promoting expansion of beneficial bacteria. Clinical trials of low fat/high fiber diets and low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diets in IBD patients have shown promising results in preventing dysbiosis and inflammation [127, 128]. Of note, a high-fat diet was shown to induce follicular hyperkeratosis and neutrophilic folliculitis in a mouse model, which is commonly observed in HS lesions [129]. The importance of dietary interventions in HS treatment has been identified in previous literature. A survey of HS patients identifying alleviating and exacerbating foods found that the most cited exacerbating foods were sweets, breads, pasta, rice, dairy, and high-fat foods [130]. In a case-controlled cross-sectional study of 41 HS and 41 control patients, HS patients had a lower adherence to the Mediterranean diet [131]. A sample of HS patients who eliminated dairy from their diet

prevented progression of lesions [132]. Although the mechanism is unclear, a study following 185 HS patients on a yeast exclusion diet led to 70% of participants noting improvement in skin lesions [133]. These results were obtained via a self-administered questionnaire with no clinical assessment by a physician or consideration of prior and concomitant HS treatments during the study, including antibiotics, and therefore more rigorous studies with appropriate controls are required to verify these results. Additionally, there are currently no studies associating diet and intestinal dysbiosis in HS patients and this presents another area for further investigation.

Probiotics are another consideration for the treatment of inflammatory disorders such as HS. Of note, topical probiotics have been of interest in numerous skin conditions as a possible therapeutic. Sequential application of donor skin microbiome is able to successfully modulate recipient skin flora [134]. Topical probiotic administration has been studied in atopic dermatitis with some success in symptom reduction [135, 136]. Oral probiotic administration has also been investigated in atopic dermatitis. A mouse model of atopic dermatitis demonstrated that oral administration of probiotic *Lactobacillus fermentum* was protective and reduced skin barrier disruption and increased diversity of the intestinal microbiome [137]. Additionally, oral probiotics showed reduction in symptoms as measured by SCORAD (scoring atopic dermatitis) in patients with atopic dermatitis [138, 139]. Conversely, in a clinical study of IBD patients with skin lesions, addition of probiotics led to reduced incidence of skin manifestations, again providing evidence for the gut–skin axis [140]. While probiotics has been proposed as a possible therapeutic strategy in HS, there are no studies to date exploring this topic [141].

5 Conclusions

HS is a chronic inflammatory disease of the skin with frequent bacterial colonization of abscesses and tunnels in affected areas. While lifestyle, genetic factors, and disrupted immune regulation could all potentially contribute to disease progression, increasing evidence suggests that dysbiosis may be an important component. While we cannot definitively identify microbial dysbiosis in the skin or gut as a causal factor for HS, the studies discussed in this review demonstrate the importance of further investigation and a proposed model in Fig. 1. Current studies demonstrate significant shifts in skin microbial populations to an increased abundance of anaerobes in HS lesions and a decrease in *Staphylococcus* species. In addition, HS patients display reduced diversity in their intestinal microbiome, which may contribute to extra-intestinal disease. Larger studies of the intestinal microbiome in HS patients are needed to further elucidate patterns of microbial dysbiosis and potential for intervention to decrease inflammation and disease.

It is unclear whether dysbiosis predisposes patients to develop HS or whether other factors, such as metabolic syndrome or other patient characteristics, precede microbial dysbiosis in HS. Similarly, it is difficult to elucidate whether dysbiosis precedes inflammation, or whether pro-inflammatory conditions accelerate skin and intestinal dysbiosis in HS patients. This presents a challenge to translating current findings to translational interventions in HS patients. However, there are several promising avenues to further our understanding on how the skin and gut microbiome contribute to development or exacerbation of HS. While current literature focuses on shifts in microbial communities or dysbiosis, further work should expand to consider bacterial

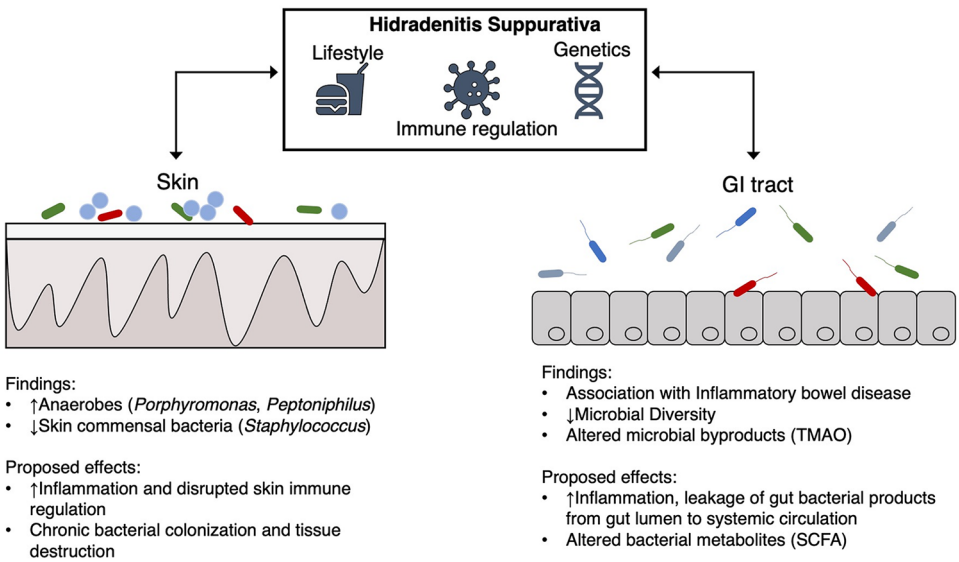

Fig. 1 Findings of skin and gut microbiome dysbiosis in hidradenitis suppurativa (HS) and proposed effects of dysbiosis. Development of HS has many contributing influences including genetics, immune dysregulation, and lifestyle components. Dysbiosis of the skin and gut has also been established in HS, with both organ systems demonstrating loss of commensal bacteria. Proposed effects of microbial dysbiosis in these two organ systems are demonstrated. *HS* hidradenitis suppurativa, *TMAO* trimethylamine N-oxide, *SCFA* short chain fatty acid

metabolites like SCFAs, other microbial byproducts including toxins, and the contribution of diet and probiotics.

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