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Review

The role of the microbiome in diabetes mellitus

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ABSTRACT

The microbiome is greatly significant for immune system development and homeostasis. Dysbiosis in gut microbial composition and function is linked to immune responses and the development of metabolic diseases, including diabetes mellitus (DM). However, skin microbiome changes in diabetic patients and their role in DM are poorly elucidated. In this review, we summarize recent findings about the association between the gut and skin microbiota and DM, highlighting their roles in the proinflammatory status of DM. Moreover, although there is evidence that the connection between the gut and skin causes the same activated innate immune response, additional studies are needed to explore the mechanism. These findings might inform future DM prevention, diagnosis and treatment.

Contents

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1. Introduction

Diabetes mellitus (DM) is one of the most important public health challenges of the twenty-first century, producing great social and economic burden [1]. According to the World Health Organization, over 10% of the world's population is estimated to have DM or be at high risk of developing DM [2]. DM is a leading cause of cardiovascular disease (primarily heart disease and stroke), renal failure, and blindness (due to diabetic retinopathy). Due to reduced blood flow in combination with neuropathy in the feet, DM increases the chance of foot ulcers, infection, and even limb amputation, which is associated with an impaired immune response and an high microbial burden.

The microbiota is a complex ecosystem of microorganisms living in different segments of the human body, such as the gastroenteric tract, skin, respiratory system and so on [3]. The microbiota is considered a "second genome" for the human body, as it is responsible for more than 98% of the genetic activity of the organism [4]. Recently, it has been proposed that alterations in the gut microbiome associated with host genetics and diet, as well as with other environmental factors, may contribute to the pathogenesis of DM and its associated complications [5,6]. Additional studies now focus on how the local microbiome influences immunity at distal sites, particularly how the gut microbiome influences other organs, such as the pancreas, brain and skin. These have led to the coining of terms, like the "gut-brain axis" and "gut-skin axis". In this way, it will be possible to genetically modify the microbiota and to obtain a personalized microbiota composition to prevent or treat DM and its complication.

Recent findings also demonstrated the existence of cutaneous microbiome dysbiosis among patients with type 2 diabetes (T2D), which may stem from the same activated innate immune response and could increase the risk of developing skin infections [7]. As the most visible organ of our body, the skin can not only be used as a good predictive marker for evaluating the risk of developing DM but also imply the first warning signals for this metabolic disorder and eventually show the success of treatment. The bacteria residing on the skin produce substances that affect the growth and behavior of neighboring microbes and are considered the first line of defense against pathogens [8]. Skin microbes modulate the release of innate factors and even affect the immune system, which may have wide-ranging systemic sequelae [9]. Therefore, changes in the skin microbiota are ripe for exploring its role in DM.

In this review, we summarize recent findings regarding the association between the gut and skin microbiota and DM, highlighting their roles in modulating local and systemic immunity in DM. Moreover, although there is evidence of the connection between the gut and skin causing the same activated innate immune response, additional studies are needed to explore the mechanism. These findings might inform DM prevention, diagnosis and treatment in the future.

2. Does the gut microbiome have an impact on DM?

2.1. *The gut microbiome and DM*

DM, commonly referred to as diabetes, is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. A growing amount of knowledge has supported the role of the gut microbiota in the pathogenesis of the two main types of diabetes mellitus. Changes in the composition and functionality of the gut microbiota associated with a wide range of health and environmental factors [10] might play a crucial role in the pathogenic process of DM (Table 1).

2.1.1. *The gut microbiome and T2D*

In 2010, the first study demonstrating the strong connection between the human gut microbiota and individuals with T2D was conducted by Larsen et al. [11]. PCR analysis and 16S rRNA gene amplicon sequencing of the gut microbiota of a small cohort of individuals with T2D identified decreased levels of taxa from the phylum Firmicutes and the class Clostridia compared with those of controls. The ratio of Bacteroidetes to Firmicutes significantly and positively correlated with reduced glucose tolerance, which suggests that the gut microbiome may be one of the new biomarkers for predicting DM. Moreover, in a landmark study, Qin et al. [12] provided the first metagenome-wide association study (MGWAS) in T2D, showing that patients with T2D exhibited moderate intestinal dysbiosis characterized especially by a decrease in butyrate-producing Roseburia in their intestines and *Faecalibacterium prausnitzii* and an enrichment of various opportunistic pathogens, as well as an enrichment of other microbial functions conferring sulfate reduction and oxidative stress resistance. This first MGWAS study in T2D was followed by another larger study from Europe [13], in which the authors applied shotgun sequencing to study only postmenopausal female patients with T2D. In both cohorts, *Clostridium clostridioforme* and Lactobacillus species were enriched, whereas Roseburia_272, a major butyrate producer, was depleted. Furthermore, Allin et al. [16] showed that indi-

Table 1 – Summary of the previous studies of the gut microbiome in DM.

Author	Year	Title	Subjects, numbers	Methods	Results
Larsen et al. [11]	2010	Gut Microbiota in Human Adults with Type 2 Diabetes Differs from Non-Diabetic Adults	subjects with T2D (n = 18), nondiabetic controls (n = 18)	PCR analysis and 16S rRNA sequencing	In patients with T2D: ↑ the phylum *Firmicutes* and ↓ the class *Clostridia*, class *Beta-proteobacteria*.
Qin et al. [12]	2012	A metagenome-wide association study of gut microbiota in type 2 diabetes	Chinese individuals (n = 345)	metagenome-wide association study	In individuals with T2D: ↓ butyrate-producing *Roseburia intestinalis* and *F prausnitzii*., ↑ opportunistic pathogens and sulfate reducing species *Desulfovibrio*.
Karlsson et al. [13]	2013	Gut metagenome in European women with normal, impaired and diabetic glucose control	postmenopausal female women (n = 2595)	shotgun sequencing	In women with T2D: ↑ four *Lactobacillus* species, ↓ five other *Clostridium* species. *R intestinalis and F prausnitzii*, both prototypical butyrate producers, were highly discriminant for T2D.
De Goffau et al. [14]	2014	Aberrant gut microbiota composition at the onset of type 1 diabetes in young children	diabetic children (n = 28), control children (n = 27)	HITChip analysis	In diabetic children: ↑ *Bacteroidetes* and *Streptococcus mitis*. In controls: a higher prevalence of *Clostridium cluster IV* and *XIVa* and *Lactobacillus plantarum* which produce butyrate.
Pellegrini et al. [15]	2017	Duodenal Mucosa of Patients with Type 1 Diabetes Shows Distinctive Inflammatory Profile and Microbiota	patients with T1D (n = 19) patients with celiac disease (n = 19) healthy control (n = 16)	16S rRNA sequencing Gene and PCR	In patients with T1D: ↑ *Firmicutes* and *Firmicutes/Bacteroidetes* ratio and ↓ *Proteobacteria* and *Bacteroidetes*. Increased inflammation: ↑ monocyte/macrophage lineage infiltration.
Allin et al. [16]	2018	Aberrant intestinal microbiota in individuals with prediabetes	Individuals with prediabetes (n = 134), individuals with normal glucose regulation (n = 134)	16S rRNA sequencing	In Individuals with prediabetes: ↓ the genus *Clostridium* and *Akkermansia muciniphila*.
Vatanen et al. [17]	2018	The human gut microbiome in early-onset type 1 diabetes from the TEDDY study	mostly white, non-Hispanic children (n = 783)	Metagenomic sequencing	In children with T1D: ↑ *Bifido-bacterium pseudocatenulatum, Roseburia hominis and Alistipes shahii*. In controls: higher levels of *Streptococcus thermophilus* and *Lactococcus lactis* species.

qPCR: quantitative polymerase chain reaction; rRNA: ribosomal RNA; HITChip: Human intestinal tract chip.

viduals with prediabetes have an aberrant intestinal microbiota characterized by a decreased abundance of the genus Clostridium and the mucin-degrading bacterium *Akkermansia muciniphila*. Strengthened glucose tolerance and insulin resistance and reduced adipose tissue inflammation could be promoted by *A. muciniphila* [18]. The composition of the gut microbiome varies to different degrees, and regular analysis of it has significant guiding meaning.

2.1.2. *The gut microbiome and T1D*

In contrast to T2D, type 1 diabetes (T1D) is characterized by damage to insulin-producing beta cells in the pancreas. Although the pathogenesis of T1D differs from that of T2D, some studies have also observed an altered microbiota in T1D [14,15,17] (Table 1). Notably, dysbiosis of the gut microbiota is suggested to occur early in life and aggravate gut inflammation, even influencing the immune system, before the onset of T1D. In humans developing T1D, it has been reported that regardless of geographical location, the proinflammatory environment in the gut is associated with the combination of an increased relative abundance of Bacteroidetes and a decreased level of Firmicutes [19]. Recently, in a longitudinal study of stool samples from children followed from three months to up to five years of age, Vatanen et al. [17] indicated that children ultimately diagnosed with T1D contained higher levels of *Bifidobacterium pseudocatenulatum*, *Roseburia hominis* and *Alistipes shahii*, whereas controls without T1D had higher levels of *Streptococcus thermophilus* and *Lactococcus lactis*, both common species in dairy products. Moreover, the microbiomes of control children contained more genes that were related to fermentation and the biosynthesis of short-chain fatty acids (SCFAs), supporting the protective effects of SCFAs in early-onset human T1D [17]. Because the process of T1D usually begins very early in life, the gut microbiota may play a crucial role in preventing the initiation and progression of the T1D process by establishing a healthy microbiota as soon as birth.

Overall, the results from all studies presented here suggest that patients with DM show evidence of gut dysbiosis. Alterations in the gut microbiome affect immune system balance via the production of metabolites, such as reduced SCFAs, which can cause an inflamed microenvironment in the presence of a specific microbiome in the gut. Further studies need to identify whether the observed dysbiosis in DM is a consequence of the disease phenotype or is involved causally in its pathophysiology.

3. How does the gut microbiome impact DM?

3.1. *Metabolite pathway*

SCFAs, such as butyrate, propionate and acetate, are among the most widely known metabolites produced by the gut microbiota [20], which have been documented to interact with host metabolism. It has been shown that the gut microbiome in DM exhibits a low level of SCFA production as well as in other metabolic disorders, inducing or exacerbating the host's autoimmune response, which is not only related to T2D but also important in the process of T1D autoimmune islet inflammation. A very recent study based on genome-wide genetic data, gut metagenomics, and determinations of fecal SCFAs in 952 normoglycemic subjects showed that the host genetics-driven increased production of the SCFA butyrate provides a beneficial role in β-pancreatic cell function, particularly after food ingestion, whereas the production or absorption of the SCFA propionate has a detrimental effect related to T2D risk [21]. Perry et al. [22] demonstrated that SCFAs act on parasympathetic activity to increase food intake and support glucose-stimulated insulin secretion in a rodent model. Moreover, SCFAs strengthen epithelial barrier function by promoting epithelial growth and innate responses to damage, as well as invading microbes. SCFAs not only make macrophages and dendritic cells more tolerogenic and efficient in inducing regulatory T cells [23,24] but also boost antibody production by promoting B cell activation and differentiation into plasma B cells [25], which prepare tissue and immune cells to better eliminate pathogens. Oral administration of metabolites can influence the skin anti-inflammatory effects [26]. These findings suggest that analysis of the gut microbiota could be used to gain an understanding of individual responses to dietary interventions.

Based on long years of follow-up, a series of alterations involving changes in the reduced branched-chain amino acid (BCAA) catabolism and bile acid pool occur during the development of T2D [27]. Another recent study integrated data on insulin resistance, the gut microbiome and the fasting serum metabolome of 277 Danish individuals without DM to investigate whether the gut microbiome impacts insulin resistance-associated metabolic signatures. The serum metabolome of individuals with insulin resistance was characterized by an increased potential for BCAA biosynthesis, which correlates with the gut microbiome constituents *Prevotella copri* and *Bacteroides vulgatus* that have an enriched biosynthetic potential for BCAAs and lack genes encoding bacterial importers for these amino acids [28]. This finding suggested that dysbiosis of the human gut microbiota impacts the serum metabolome, thus influencing systemic immunity, and contributes to insulin resistance.

Conversely, bile acids can modulate gut microbial composition both directly and indirectly through activation of innate immune genes in the small intestine [29]. Secondary bile acids bind to cellular receptors such as the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5), thereby triggering various processes, including energy expenditure, insulin sensitivity, and cholesterol synthesis [30]. Kuno et al. [31] indicated that secondary bile acid-producing bacteria contribute to the homeostasis of glucose and triglyceride levels and have potential as therapeutic targets for treating metabolic disease. Thus, microbial modifications of metabolites can affect host metabolism, which could lead to insulin resistance and DM. However, additional studies are required to clarify the role of the gut microbiome in regulating metabolites as a potential mechanism in DM.

3.2. *Immunologic pathway*

DM is associated with chronic low-grade inflammation, and gut microbes contribute to this state. Several recent studies have suggested that lipopolysaccharides (LPSs), which are

components of the cell walls of gram-negative bacteria, play a key role in the development of inflammation and insulin resistance [32]. Shi et al. [33] demonstrated that LPS may initiate inflammation by binding to the CD14 Toll-like receptor 4 (TLR-4) complex at the surface of innate immune cells. In this context, CD14 controls insulin sensitivity and metabolic diseases, such as obesity and T2D. Growing evidence supports that the stimulation of TLR-4 by bacterial LPS results in an inflammatory response, cytokine production and chemokine-mediated recruitment of inflammatory cells [34–36]. Importantly, the T2D microbiota exhibited an increase in the oxidative stress response, which could represent a direct link to the proinflammatory state of patients with T2D [12]. Moreover, diabetic subjects presented higher fasting and postprandial LPS concentrations than lean nondiabetic subjects and/or obese subjects due to increased intestinal permeability and elevated LPS absorption contributing to the development of macrovascular and microvascular complications, so the LPS concentration is a potential tool to assess the metabolic risk profile in diabetic patients [37]. This approach is in accordance with the recently proposed concept of 'metabolic infection', where parts of the intestinal microbiota might affect systemic inflammation [38]. In support of this concept, it has been demonstrated that antibiotic and prebiotic therapy could change the gut microbiota and improve metabolic inflammatory parameters in rodent models, which is useful to develop strategies for reversing the process of DM [39].

3.3. *Neuroendocrine pathway*

Increased intestinal permeability in diabetic patients and the consequential spread of bacteria to other parts of the body are a rapidly emerging area of study in DM [40,41]. Acting indirectly, the normal microbiota of the gut will dampen the stress response of the nervous system, whereas dysbiosis will result in an exaggerated hypothalamic–pituitary–adrenal (HPA) reaction to stress [42,43]. The exaggerated HPA response can then lead to increased cortisol release [42], causing exacerbated barrier dysfunction by the subsequent breakdown of the gut's extracellular matrix (ECM), as well as the ECM of other organs, including that of the skin. Prolonged glucocorticoid elevation can present serious health risks, including DM. Moreover, it is hypothesized that endotoxin and/or peptido-

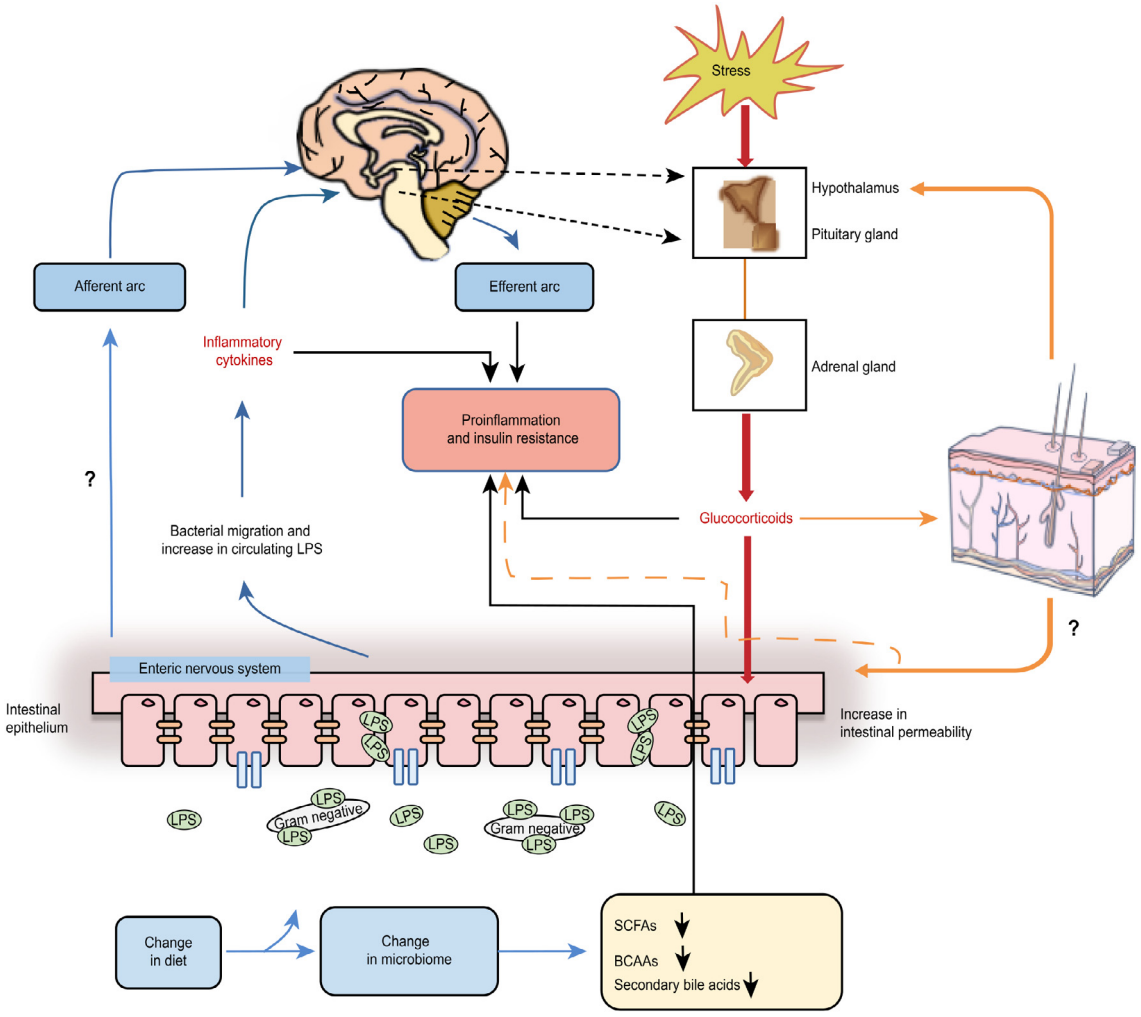

Fig. 1 – Mechanisms of the interaction between gut microbiome with skin and brain in DM. DM: diabetes mellitus; SCFA: short-chain fatty acid; BCAA: branched-chain amino acid; LPS: lipopolysaccharide.

Table 2 – Summary of the previous studies on the skin microbiome in DM.

Author	Year	Title	Subjects, numbers	Methods	Results
Gontcha-rova et al. [55]	2010	A Comparison of Bacterial Composition in Diabetic Ulcers and Contralateral Intact Skin	Patients with DFW: samples were collected from wounds (n = 23) and from contralateral intact skin (n = 28)	bTEFAP	In DF: ↑ anaerobic bacteria, like *Peptoniphilus, Finegoldia, and Anaerococcus*, and other detrimental genera such as *Corynebacterium and Staphylococcus*. The diversity is higher compared with intact skin.
Oates et al. [56]	2012	Molecular and Culture-Based Assessment of the Microbial Diversity of DFWs and Contralateral Skin Sites	Patients with DFW (n = 26): specimens were collected from DFW tissue and contralateral skin swabs of each subject.	culture and DGGE	In DFW: Four genera (*Klebsiella* sp., *Abiotrophia* sp., *Escherichia coli, and Peptoniphilus* sp.) were unique. The most abundant genera (*Staphylococcus and Bacillus*) were similar between groups.
Redel et al. [49]	2012	Quantitation and composition of cutaneous micro-biota in diabetic and nondiabetic men	Diabetic subjects (n = 30), nondiabetic subjects (n = 30)	qPCR and 16S rRNA sequencing	In feet of diabetic men: ↑ *S. aureus*, and the genus *Corynebacterium*.
Gardiner et al. [50]	2017	A longitudinal study of the diabetic skin and wound microbiome	Type II diabetic subjects with chronic foot ulcers (n = 8), control group (n = 8)	high-throughput sequencing	The diabetic skin microbiome: ↓ diversity of total microbiota, dominated by the genera *Staphylococcus*, followed by *Acinetobacter* and *Corynebacterium*, then unclassified *Enterobacteriaceae*.
Thimma-ppaiah et al. [7]	2017	Culture characterization of the skin microbiome in Type 2 DM	DM patients (n = 41), controls without DM (n = 41)	Culture and isolation	In patients with T2DM: ↑ *Staphylococcus epidermidis* and highly pathogenic bacteria such as *S. aureus*.
Park et al. [57]	2019	Influence of Microbiota on DFW in Comparison with Adjacent Normal Skin	Patients with DFW: specimens were collected from normal skin and DFW tissue of each subject (n = 20)	high-throughput sequencing	The diversity of skin microbiota was higher than that of DFW tissues. *Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria* were dominant phyla in both tissue and skin samples.
Pang et al. [51]	2020	Changes in Foot Skin Microbiome of Patients with DM Using High-Throughput 16S rRNA Gene Sequencing: A Case Control Study from a Single Center	short-term group (diagnosed with DM for ≤2 years); middle-term group (5–8 years); long-term group (≥10 years ago); control group (n = 13 in each group)	16S rRNA Gene Sequencing	Species abundance and diversity in the skin microbiome increase as the duration of diabetes increases. In patients with DM, the dominant skin microbial phyla were *Firmicutes, Proteobacteria, Actinobacteria, and Bacteroidetes*.

DFW: diabetic foot wound; bTEFAP: bacterial Tag-encoded FLX amplicon pyrosequencing; DGGE: denaturing gradient gel electrophoresis.

glycan, components of the bacterial cell wall, can stimulate immune cells within the gut or elsewhere to release these cytokines, which consequently influence the parts of the central nervous system involved in the regulation of the HPA axis response [44]. Parekh et al. [45] showed that one of the earliest changes detectable in the evolution of DM is abnormalities in autonomic balance, which could be influenced by the gut microbiome. Acetylcholine binding to its receptor could restrain the activation of NF-κB-mediated inflammation. The neuroendocrine pathway may be key for the gut microbiome link to other organs, such as the brain and skin, but the mechanisms remain poorly understood (Fig. 1).

4. Does the skin microbiome have an impact on DM?

4.1. *The skin microbiome and DM*

The skin, the largest organ of human body, is one of the major microbiota sites, with every square centimeter containing approximately one billion bacteria [46]. *Actinobacteria*, *Proteobacteria*, *Firmicutes* and *Bacteroidetes* are the four main bacterial phyla found on human skin [47]. It has been shown that multiple factors, including local skin anatomy, lipid content, pH, sweat, and sebum secretion, correlate with the predominant microbiota [48]. However, the composition of the skin microbiome may ultimately determine whether this interaction has beneficial or detrimental effects on the host. Especially in diabetic patients, if the immune response is impaired, they are at an increased risk for diabetic foot ulcers (DFUs) when the skin is breached. Previous studies have compared the difference in the composition and diversity of the foot skin microbiota between diabetic patients and nondiabetic patients [7,49,50], all showing statistically significant differences in the microbiota composition and diversity of the foot skin; DM patients have a higher proportion of *S. aureus* in their skin microbiome than healthy controls (Table 2). Redel et al. [49] showed that the phylum Firmicutes is more prevalent in nondiabetic foot skin, while the phylum Actinobacteria, more specifically the genus Corynebacterium, is more prevalent in diabetic foot skin, along with higher carriage rates of *Staphylococcus aureus* and higher microbial diversity in the latter. Recently, it has been found that the species abundance and diversity in the skin microbiome of diabetic people show an increasing trend as the duration of DM increases without complications [51]. However, Gardiner et al. [50] also suggested that the microbiome of diabetic skin is less diverse than that of control skin and that the foot skin microbiome may predict diabetic status by a random forest classifier. Changes in the skin microenvironment in diabetic people, such as dysfunction of sweat glands, altered cutaneous thermoregulatory function, and elevated skin surface pH [52,53], are thought to promote skin microbial dysbiosis in T2D. As AMPs, such as dermcidin [54], secreted from eccrine sweat glands have activity against *S. aureus* and other cutaneous microbes, characteristic low levels of eccrine sweat glands on diabetic feet associated with low levels of AMPs are hypothesized to partly explain these observations [49]. Further investigation of the pathogenesis of the cutaneous microbial composition may provide a link between the functions of resident microbiota during dysbiosis and DM.

The imbalance in the composition of the skin microbiota and the large amount of *S. aureus* colonization can cause inflammatory changes in the skin, increasing the risk of skin infections. Other studies compared DFUs with contralateral intact skin and adjacent normal skin [55–57]. Diabetic foot wounds (DFWs) contained lower bacterial diversity than contralateral skin, and the most abundant taxa were similar between groups. For both tissue and skin samples, the most prevalent genera were Staphylococcus and Bacillus, and four species were unique to the wounds (*Klebsiella* sp., *Abiotrophia* sp., *Escherichia coli*, and *Peptoniphilus* sp.) [56]. Contralateral intact skin samples may provide insight into the normal microbiota of the site and thus the microbial composition of skin prior to wounding. Park et al. [57] indicated that the microbiota in adjacent normal skin is related to the colonizing microbes in DFW tissue according to clinical features, meaning that the skin microbiota may transfer to the wound and exacerbate the infection. Firmicutes, Actinobacteria, Proteobacteria, Bacteroidetes, and Fusobacteria were dominant phyla (>99% in all microbiota) in both tissue and skin samples [57]. This altered cutaneous microbiome could be a parameter that contributes to the high susceptibility to skin and soft tissue infections (SSTIs) seen in DM patients [58]. Therefore, the identification of the normal skin microbiota can be used for the early prediction of DFW prognosis, and modulation of the skin microbiome can be applied to prevent or manage DFWs. However, there has been no special and longitudinal study on the skin microecology of diabetic feet before the emergence of DFUs, especially comparing the clinical prognosis of diabetic patients with or without DFUs, which is helpful to discover the microbial characteristics that can reveal the prognosis of DFUs.

5. How does the skin microbiome influence systemic immunity and DM?

5.1. *Cutaneous microbiota and skin immunity*

The skin is a key component of the innate immune response even before injury occurs. Regulating the immune response upon physical, chemical, or microbial insult is key to maintaining skin barrier integrity. The response to the barrier breach must be carefully balanced between tolerance and activation to rapidly control microbial invasion and infection without eliciting a potentially harmful, excessive inflammatory response [59]. Dysbiosis of the skin commensal microbiome in diabetic people may contribute to the disruption of immune homeostasis in the skin and promote the development of skin disease [60]. Inflammation at the skin level is increased in patients with DM, and the number of inflammatory cells increased significantly in diabetic animal models [61]. Inflammatory cells in diabetic patients have high dermal infiltration, and the expression of matrix metallopeptidase 9 (MMP-9) and protein tyrosine phosphatase-1B (PTP1B) is increased in skin biopsies, which can lead to resistance to growth factor action and may be responsible for the difficulty in skin wound healing of diabetic patients [62]. Chronic

inflammation in the skin could exacerbate skin barrier impairment and is associated with abnormalities in the functions of skin barrier-associated genes [63]. When a lesion occurs, skin microorganisms can enter the affected tissue, which can help trigger local immune responses by providing the necessary pathogen-associated molecular pattern (PAMP) signals to stimulate the inflammatory cascade [59]. Thus, the skin microbiota could increase the risk of diabetic skin signs and even the occurrence of DFWs. How the skin microbiome locally impacts diabetic people needs additional study.

The analyses above have shown that DM patients have a higher proportion of *S. aureus* in the skin microbiome than healthy controls. *S. aureus* colonization predisposes patients with DM to minor-to-moderate foot [64] and even life-threatening blood [65] *S. aureus* infections. It was demonstrated that *S. aureus* cutaneous colonization could elicit skin inflammation and induce an immune response in a model of atopic dermatitis [66]. Epicutaneous *S. aureus* exposure could promote IL-36α production by keratinocytes (in part via the activity of PSMα), which triggered IL-36R/MyD88 signaling on T cells to produce IL-17A/F that mediated skin inflammation [67]. In addition, colonization with *S. aureus* could impair the suppressive activity of Treg cells [68]. To date, no broad study on *S. aureus* and its role in the skin of diabetic people has been performed.

Analysis of the diabetic skin microbiota not only is a potentially good diagnostic marker for targeted antibiotic therapies but also can be used to develop new therapeutic strategies, such as probiotic or commensal formulations, which can potentially modulate pathogenic skin flora into new bacterial groups. The use of specific antibiotics can almost completely eradicate the flora and eliminate skin inflammation [66]. Lipoprotein acids produced by staphylococci can inhibit skin inflammation through a TLR-dependent pathway [69]. Another study showed that inhibition of complement component C5a receptors reduces the diversity of the skin microbiota, while the symbiotic flora can regulate the expression of certain complement genes in the skin, thereby regulating immunity [70]. Both studies emphasized the direct involvement of microorganisms in the regulation of the skin's immune response. It is now recognized that this interaction between our immune system and the microbiome is important for skin health-disease balance.

5.2. *The role of skin immunity in systemic immunity*

Whether skin dysbiosis is the cause or consequence of DM is not yet clarified, but it has been proposed that locally amplified immune responses to particular skin microbes or increased microbial load in the setting of impaired skin barrier and genetic predisposition might contribute to pathology [9]. Lyte [71] recently put forward the terminology "microbial endocrinology", which is defined as the study of the ability of microorganisms to produce and recognize neurochemicals that originate either within the microorganisms themselves or within the host they inhabit. An extensive list of neurochemicals and hormones have been isolated from microorganisms and shown to have biological activity in mammalian cells [72]. The cutaneous neuroendocrine system mediates the coordination between these local and systemic responses via the local equivalents of the HPA axis, hypothalamic-pituitary-thyroid (HPT) axis [73]. Recent studies have shown that skin stressors, including dryness and barrier disruption, could stimulate cutaneous cortisol production and that this action may be mediated through activation of inflammatory cytokines, such as IL-1β, with systemic implications [74]. The skin microbiome is also involved in the production/metabolism of these molecules and influences the immune system, giving rise to the "skin–brain axis".

Cutaneous microbial dysbiosis could trigger skin inflammation and lead to massive immune cell infiltration, resulting in a disrupted barrier and local skin rupture. Moreover, the pathogens can penetrate into any organ in the body and lead to potentially fatal conditions, such as sepsis and osteomyelitis. Amar et al. [75] conducted a follow-up of 3280 healthy subjects without DM at baseline for 9 years and found that the blood level of 16S rDNA (a broadly specific bacterial marker) of patients with T2D increased significantly after the follow-up. The cutaneous inflammatory mediators migrate into the systemic circulation and the release of these proinflammatory cytokines results in the chronic systemic inflammation and metabolic syndrome. The "inflammatory skin march" might be another mechanism underlying the connection of cutaneous microbiome and DM.

Remarkably, *S. aureus* has been found to produce variety of factors to exploit a weakened skin barrier and activate deleterious host immune reactions [76]. Chronic exposure to *S. aureus* may disrupt the immune system, subsequently causing impaired glucose tolerance and even DM [77]. Insulin resistance results from defects in insulin signaling, which can be inhibited by diacylglycerol, tumor necrosis factor alpha (TNF-α) and LPS, and chronic inflammation caused by an imbalance in pro- and anti-inflammatory immune cells could also contribute to insulin resistance [78]. Previous studies have shown that endotoxin is able to induce proinflammatory cytokine production in adipocytes, which contributes to insulin resistance [79]. Liu et al. [80] provided direct evidence that *S. aureus* infection impairs glucose tolerance via the secretion of the extracellular domain of LtaS (eLtaS), a functional extracellular *S. aureus* protein, by binding to insulin and blocking its activity; thus, targeting eLtaS may be an effective treatment strategy for insulin resistance. Overall, these findings reveal that *S. aureus* infection is a risk factor for DM and provide a potential mechanism underlying insulin resistance.

6. Summary

This article reviews the current evidence for the relationship between the microbiome and DM. The roles played by the gut and skin microbiomes have recently been revisited, and abundant evidence suggests that microbial dysbiosis can actually influence the immune response and pathophysiology of DM. It is unclear whether changes in the microbiome at one organ site affect distal organs or different organ sites and whether these systemic effects might be specific for certain tissues or organs and the mechanisms involved. Extensive research is required to explore the systemic effects of the microbiome in DM. Targeted microbiome modulation reveals such a promising candidate that was recently discov-

ered to exert anti-inflammatory and beneficial metabolic functions [81].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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