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REVIEW ARTICLE

Skin microbiome in diabetes mellitus: a literature review

Microbioma cutâneo na diabetes mellitus: uma revisão da literatura

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Abstract

The authors performed a review to investigate if there are alterations in the skin microbiome among individuals with diabetes mellitus (DM) and to assess how these alterations may contribute to specific skin conditions and complications associated with this disease. On December 1st, 2023, searches on the PubMed® and ScienceDirect databases were conducted, using the Mesh Terms "skin microbiome" AND "DM", limiting the results to those published in the last 10 years. The authors identified seven articles, including two reviews and five original research papers. Both type of papers revealed that individuals with DM exhibited significant less diversity in terms of microbial richness, with a notable colonization by *Staphylococcus* spp. In conclusion, the skin microbiome appears to be impaired in individuals with DM. However, more longitudinal studies are necessary to determine whether this impairment is a consequence of DM and to understand how it may interfere with DM complications.

Keywords: Diabetes mellitus. Skin microbiome. *Staphylococcus aureus.*

Resumo

Os autores pretendem esclarecer se existem alterações no microbioma cutâneo em pessoas com Diabetes Mellitus (DM), passíveis de predispor a patologia cutânea e complicações desta doença. As bases de dados PubMed® e ScienceDirect foram pesquisadas a 1 de dezembro de 2023, utilizando os Mesh Terms "skin microbiome" AND "diabetes mellitus", limitando os resultados aos artigos publicados nos últimos 10 anos. Obtiveram-se 7 artigos, incluindo 2 revisões e 5 artigos de investigação original. Ambos os tipos de artigos revelaram que a pele das pessoas com DM apresenta uma diversidade microbiana significativamente menor, com uma forte colonização de *Staphylococcus* spp. Em conclusão, o microbioma da pele parece estar alterado nos indivíduos com DM Contudo, são necessários mais estudos longitudinais para compreender se esse comprometimento é consequência da DM e como pode interferir nas complicações da doença.

Palavras-chave: Diabetes mellitus. Microbioma da pele. *Staphylococcus aureus.*

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Introduction

The skin microbiome refers to a diverse community of microorganisms, including bacteria, fungi, and viruses, that reside on the skin's surface. Most of these microbes are recognized as commensal, playing a vital role in maintaining the overall health and functioning of the skin, although sporadically they may cause skin infections[1].

Bacteria are the most abundant type of microorganisms found on the skin, while fungi are the least abundant. This predominance persists even in cutaneous regions, such as the feet, characterized by a high level of fungal diversity. According to the topography and skin conditions, a unique microenvironment can be created into the skin, which can be categorized into three distinct regions: the sebaceous, moist, and dry areas[1].

The gut microbiota profile in type 2 diabetes mellitus is similar to that observed in other inflammatory pathologies with subclinical inflammation[2]. It is expected that in T2D, the skin microbiome has different characteristics from normoglycemic individuals. This holds particular relevance due to the complications of T2D, especially in the foot, where an impaired microbiome may lead to higher prevalence of infections[3].

In this review, we intend to clarify if alterations occur in the skin microbiome among individuals with diabetes mellitus (DM) and how these alterations may contribute to specific skin conditions and complications associated with the disease.

Methods

A systematic review, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was performed using PubMed® and Web of ScienceTM databases on December 1st, 2023, using the Mesh Terms "skin microbiome" AND " DM" limited to papers written in English and published in the past 10 years. The papers obtained from these searches were combined and duplicates were removed.

All the abstracts from each field were reviewed by two different authors.

The papers retrieved, including reviews and research articles, were considered, while case reports were excluded from the study.

Results

As represented in figure 1, we obtained 50 papers to analyze (22 from PubMed and 28 from ScienceDirect). One duplicate was eliminated, and 20 papers were excluded due to the absence of "skin microbiome" or "diabetes" in the abstract. In addition, one paper was excluded because it was written in German.

After excluding these 22 papers, the authors reviewed the remaining 28 papers. Of these, three did not align with the objective of this review, and three described animal studies.

The remaining papers consisted of two reviews[4,5] and five primary studies or research articles[6-10], all of which were thoroughly analyzed.

The review led to the conclusion that patients with DM have a higher proportion of *Staphylococcus aureus* in the skin microbiome than healthy controls[4,5]. Poor glycemic control was associated with a greater colonization of *Staphylococcus* spp. and *Streptococcus* spp[5].

One review singled out the top ten bacterial, eukaryotic, and viral species commonly found in various anatomical regions, including dry, moist, sebaceous, and foot skin.

Dry skin in non-diabetic individuals tends to be colonized more frequently by *Cutibacterium acnes*, *Corynebacterium tuberculostearicum*, and *Streptococcus mitis*. Among eukaryotic species, *Malassezia restricta*, *Malassezia globosa*, and *Aspergillus tubingensis* are the most commonly encountered. Moist skin harbors a higher proportion of *C. tuberculostearicum*, *Staphylococcus hominis*, *C. acnes*, as well as fungi like *M. globosa*, *M. restricta*, and *Tilletia walkeri*.

Sebaceous skin is enriched with *C. acnes*, *Staphylococcus epidermidis*, and *C. tuberculostearicum*, along with fungi such as *M. restricta*, *M. globosa*, and *Malassezia sympodialis*.

Notably, *S. aureus* does not appear among the ten most prevalent bacterial species in any anatomical region representative of dry, moist, or sebaceous skin.

Several primary studies included the analysis of foot samples collected from various sites, including the plantar surface of the foot (both from wound and intact skin, either dry or moist)[6], intact skin from the plantar arch of the feet (dry skin)[8], the fourth interdigital area of the feet (moist skin)[9], chronic skin lesions of the lower limbs (moist and dry skin)[7], and both the plantar forefoot (dry skin) and the interdigital space (moist skin)[10]. However, many of these studies lacked comprehensive descriptions of the features and findings across these different foot areas, hindering proper comparisons. In addition, these studies exclusively focused on patients with type 2 diabetes among individuals with diabetes[6-10].

Concerning diabetic foot ulcers (DFUs), the superficial ones, namely, those of short duration, were associated with a predominance of *Staphylococcus* spp., particularly *S. aureus*. In contrast, deeper ulcers and those of longer duration exhibited greater microbial diversity, with a higher relative abundance of anaerobic

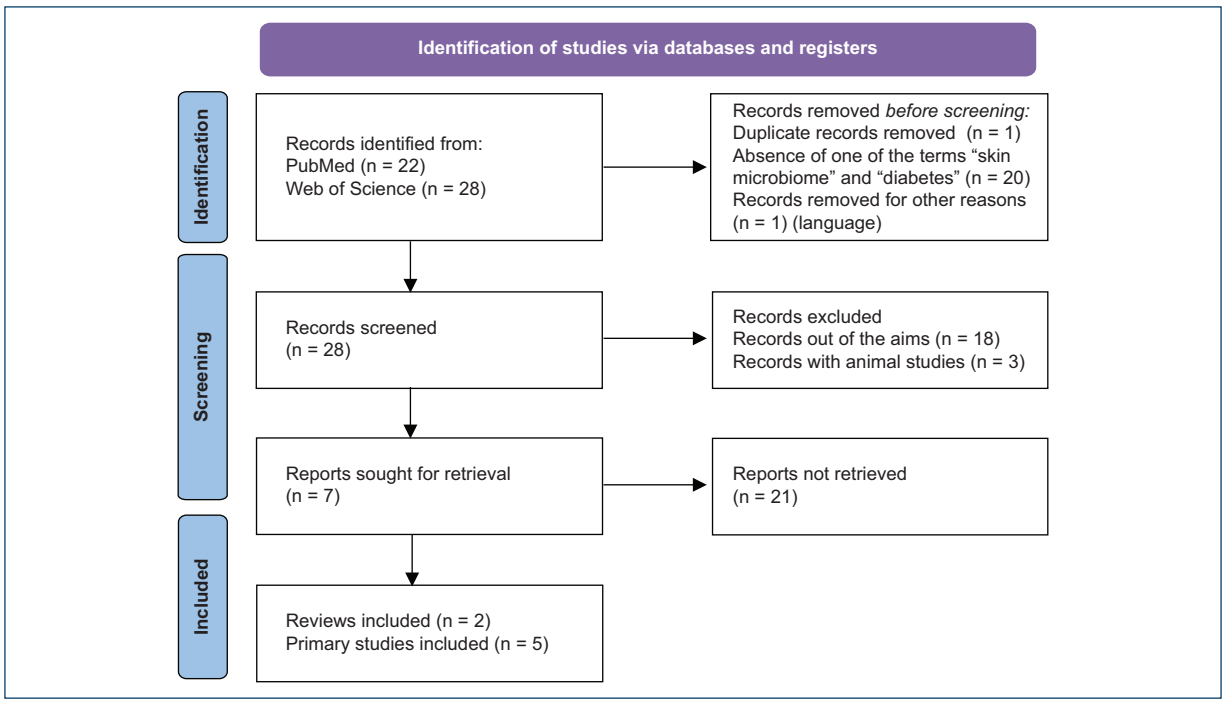

Figure 1. Flow diagram of the literature review using MESH terms "skin microbiome" and "diabetes mellitus".

bacteria and Gram-negative *Proteobacteria* spp. However, the specific period of evolution of these ulcers was not clarified[5]. *Cladosporium herbarum* and *Candida albicans* were identified as the most abundant fungal species found on DFUs. The presence of increased fungal diversity, along with the formation of polymicrobial biofilms consisting of fungi and bacteria, was associated with poor clinical outcomes in chronic wounds[5].

Primary cross sectional studies included 8-41 participants in each group (individuals with DM and controls), and studies performed cultural examination, 16S ribosomal RNA sequencing or PCR of the fungal internal transcribed spacer (ITS2) region. These studies revealed that the skin microbiome in individis uals with diabetes, both for bacteria and fungi, was significantly less diverse than in control subjects[6-8]. Chronic wounds tended to be dominated by the most abundant skin *Staphylococcus*[6,9]. A significant association between T2D status and heavy colonization by *S. epidermidis* (OR-5.40, p = 0.02) was found[9].

The bacteriological colony test revealed a higher proportion of both positive bacteriological colony tests and respective polymicrobial result among the individuals with T2D[10]. This phenomenon confirms an alteration in the skin microbiome of diabetic subjects, indicating a modification in the "opportunistic role" of some species of the skin bacterial flora[10].

The 16S rRNA gene sequencing demonstrated dynamic changes in the skin microbiome of the foot during the progression of DM. In patients with DM, the dominant skin microbial phyla were *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Bacteroidetes*[7,8].

A single study conducted in China[8] investigated the variations in the microbiome among individuals with type 2 DM, without associated complications, across different durations of the disease.

In summary, individuals classified into short-term DM (< 2 years), middle-term DM (5-8 years), and long-term DM (more than 10 years) categories exhibited notable alterations in the microbial community structures of their foot skin compared to the control group (without DM). Moreover, these changes were found to be positively correlated with the duration of the illness[8].

At the onset of the disease (short-term DM group), there was a slight reduction in the abundance of Proteobacteria, which steadily increased as the disease progressed (long-term DM group). Conversely, the abundance evolution of actinobacteria displayed an opposite pattern. In addition, the diversity of low-abundance microbes increased with disease progression. All three DM groups demonstrated higher microbial diversity compared to the control group, with the long-term diabetes group exhibiting the highest diversity among the short- and middle-term groups[8]. Regarding fungi, *Trichophyton rubrum* was more abundant in DM samples in, exhibiting a lower Shannon diversity index for fungi[8].

Discussion

Reviews have underscored the direct involvement of microorganisms in regulating the skin's immune response.

It is speculated that *S. aureus* colonization in individuals with DM predisposes them to minor-to-moderate foot infections and even life-threatening bloodstream *S. aureus* infections, throughout the skin inflammation and an immune response. The role of *S. aureus* juxtaposes to that in a model of atopic dermatitis, in which *S. aureus* cutaneous colonization could elicit skin inflammation and induce an immune response[4]. The proposed mechanisms involves the activation of an inflammatory cascade, intensified by the exposure to *S. aureus* on the skin surface, which promotes IL-36a production by keratinocytes (partly through the activity of PSMa), which triggers IL-36R/MyD88 signaling on T cells to produce IL-17A/F. In addition, it is suggested that colonization with *S. aureus* could impair the suppressive activity of Treg cells and staphylococci have the ability to produce lipoprotein acids that can inhibit skin inflammation through a TLR-dependent pathway. The inhibition of complement component C5a receptors reduces the diversity of the skin microbiota, while symbiotic flora can regulate the expression of certain complement genes in the skin, thereby modulating immunity[4].

A shared observation across these primary studies is the loss of microbiologic diversity in DM and the increased risk of developing skin infections associated with microbiome dysbiosis.

It was suggested that microbiome dybiosis in T2D could stem from the same activated innate immune response thought to be central to the development of T2D. The extent to which alterations in the microbiome at one organ site influence distal organs or different organ sites remains unclear. In addition, it is uncertain whether these systemic effects are specific to particular tissues or organs, along with the underlying mechanisms involved[9].

For the reasons mentioned so far, targeted microbiome modulation reveals such a promising candidate that was recently discovered to exert anti-inflammatory and beneficial metabolic functions, that can mitigate dysbiosis and combat pathogens[4,5].

The majority of the previously cited studies adopted a cross-sectional design, incorporating a relatively small number of patients. Yet, more longitudinal studies are needed to understand if this impairment is a cause or a consequence of DM and to elucidate how it might interfere with DM complications.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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