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REVIEW

Beyond the Surface: Understanding Demodex and Its Link to Blepharitis and Facial Dermatoses

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Abstract: Demodex represents the most frequent ectoparasite found in humans. Although Demodex mites are considered commensals of human pilosebaceous units, an abnormally high mite density can cause several ocular and cutaneous symptoms and signs, sometimes to a severe degree. Both Demodex spp. (*folliculorum* and *brevis*) play a significant part in eye pathology and facial dermatoses. These mites have been related to blepharitis, ocular rosacea, meibomian gland dysfunction and various skin diseases, including rosacea, demodicosis and seborrheic dermatitis. Understanding the importance of Demodex in both eye and skin conditions is crucial for accurate diagnosis and appropriate management strategies, which may involve targeted treatments to control the mite population and reduce associated symptoms.

Keywords: eyelid inflammation, mite infestation, rosacea, demodicosis

Introduction

Different microorganisms colonize the human body, including bacteria, fungi, and ectoparasites. Among the microscopic parasites found on the human skin, Demodex spp. mites are regarded as one of the most common.[1] Although these microorganisms have been familiar to physicians for nearly 180 years, the degree of their pathogenic significance is still under discussion.[1–3] Within the group of 1600 mite species known as Demodex, two specific ones—Demodex *folliculorum* and Demodex *brevis*—establish colonies on the human body.[4,5] *D. folliculorum* inhabits the follicles of the eyelashes, whereas Demodex *brevis* is found deep into the meibomian and sebaceous glands.[4,6] Found extensively on the human skin, this mite is more prevalent in the facial area, predominantly in the meibomian glands along the margins of the eyelids and in the follicles of eyelashes.[7] The incidence of Demodex infestation rises with age, with detection occurring in 84% of the population at the age of 60 and in 100% of individuals over 70 years old.[1,8] Moreover, the involvement of Demodex spp. is crucial in the development of numerous eye and skin disorders[1,9] such as perioral dermatitis, pustular folliculitis and rosacea or rosacea-like dermatitis.[7,10] The establishment of Demodex infestation on the face may lead to its spread and proliferation in the eyelids, causing blepharitis.[5,8,11] In the field of ophthalmology, Demodex is considered a potential causative factor in chronic blepharitis, conjunctival inflammation, and meibomian gland dysfunction. Additionally, Demodex has been documented to contribute to atypical ocular manifestations, including superficial corneal neovascularization, marginal corneal infiltration, phlyctenule-like lesions, superficial corneal opacity, and nodular corneal scars. This is particularly observed in patients diagnosed with ocular rosacea.[12] Regardless of this phenomenon, the clinical importance of Demodex infestation is somewhat debatable, as it can be present in individuals without apparent symptoms.[8]

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Demodex

Demodex mites represent a genus of parasites that live in or close to hair follicles of mammals. Two species colonize humans: D. *folliculorum* and *D. brevis*. Simon described for the first time *D. folliculorum* in 1842; *D. brevis* was recognized as distinct in 1963 by Akbulatova.[13] Ranging from 0.3 to 0.5 mm in length, *D. folliculorum* primarily resides in the hair follicles of various facial areas, such as the cheeks, forehead, nose, temples, scalp, auricle, and eyes, particularly in the eyebrows and eyelashes.[14,15] With a length of 0.15–0.3 mm, *D. brevis* primarily feeds on sebum and inhabits sebaceous glands on the face, neck, and torso, along with the meibomian glands of the eyelids.[14,16] The parasite has a lifespan of about 3 weeks, with adult mites surviving for approximately one week.[1,17] Their main source of nutrition includes the secretions of sebaceous glands, along with epithelial cells, blood, and blood plasma filtrate.[1] Most of these mites display a worm-like elongation of the body, which is composed of three primary parts: gnathosoma, podosoma, and opisthosoma.[18] Under light microscopy, this mite is visible as a partially transparent organism with two connected segments and eight legs. During nighttime, the mite moves at a velocity of 8–16 mm/h, and exposure to strong light prompts its reentry into the follicle. Scales on its body facilitate self-attachment within the hair follicle, and the mite possesses pin-like mouthparts to consume epidermal cells, sebum, and hormones that accumulate in the hair follicles.[10] In comparison to males, female mites are characterized by a larger and rounder appearance.[19] After fertilization, Demodex females lay eggs inside hair follicles or sebaceous glands located in the follicular orifice.[20]

Human colonization by Demodex spp. varies depending on age. It is likely that Demodex mites are transmitted to the skin of newborns through direct physical contact after birth. However, due to low sebum production, infants and children under five years old do not harbor a large number of mites.[14] The 20–30 age range has the highest rate of skin area/hair follicle infestation, due to the most abundant sebum secretion.[14,21] With the aging process, there is a decrease in this index, but there is an increase in the number of infected individuals. Multiple studies demonstrate that virtually all adults aged 70 and above are carriers of Demodex spp.[14] Regarding the prevalence of Demodex infestation by gender, studies show various results. Biernat and Kemal observed no correlation between Demodex infection and host's sex, as reported in their study. In contrast, Zhong's findings indicated a higher prevalence of Demodex *folliculorum* among females compared to males, which was attributed to the application of exogenous lipids in cosmetics.[22] In another investigation involving skin biopsies, it was noted that males exhibited a higher degree of infestation than females for both species, with the most significant difference observed in the case of *D. brevis*.[23]

Scientific evidence demonstrates that temperature significantly influences the survival of both *D. folliculorum* and *D. brevis*. The optimal temperature for mite development falls within the range of 16 to 20°C, and for in vitro Demodex studies, the most suitable temperature is 5°C. Additionally, observations indicate a proliferation of Demodex during spring and summer months, as well as during rosacea exacerbation.[16] Demodex transmission occurs through direct or close contact with infested skin (carrying larvae or adult mites) or via dust containing eggs.[24]

Initially considered harmless commensals, numerous current studies highlight the involvement of *D. folliculorum* and *D. brevis*, as pathogens in several clinical syndromes, classified as demodicosis of the eyelid and facial demodicosis.[20] The degree of colonization is influenced by humoral and especially local cellular immune response of the skin which has an essential role in the intensity of Demodex proliferation. It is considered that mites are commensal at a quantity below 5/cm2 so that the diagnosis of cutaneous demodicosis is established when infestation of parasites surpasses this number. Also, diagnosis is suggested by clinical symptoms and/or histological detection of the mites in the dermis.[20,25] The presence of over three to five parasites per hair follicle is regarded as indicative of significant colonization of eyelashes, facial hair, and eyebrows.[15,16,20]

Most individuals serve as carriers of Demodex mites without progressing to clinical symptoms. Therefore, human demodicosis can be regarded as a multifactorial condition influenced by internal and/or external factors.[26] The transition from clinically unnoticed mite colonization to dermatoses can be significantly influenced by primary or secondary immunosuppression.[26] Primary immune suppression is probably linked to hereditary T cell defects, complemented by substances produced by bacteria and mites, while B cell immunity remains unaffected.[26,27] It has been emphasized multiple times that animals and individuals with immunodeficiency are susceptible to infestations by Demodex mites.[26,27] Secondary immune suppression, contributing to a predisposition to demodicosis, can arise from causes such as corticosteroid and cytostatic therapy, as well as diseases like malignant neoplasia, lymphosarcoma, hepatopathies, and HIV infection.[26,28] However, the development of demodicosis may be influenced by factors other than generalized immunosuppression.[26]

There is a suggestion that infestation could be associated with genetic predisposition,[26] including specific types of HLA (Human Leukocyte Antigen), although certain HLA types are deemed resistant to demodicosis.[29]

Demodex and Blepharitis

Demodex infestation can have a notable impact on the anterior part of the eye, leading to conditions such as anterior blepharitis, posterior blepharitis, meibomian gland dysfunction (MGD), keratitis, and ocular rosacea.[17]

While Coston documented the existence of *D. folliculorum* in eyelashes more than 50 years ago,[5] diagnosing and treating Demodex blepharitis still poses considerable challenges. Both Demodex species contribute to eyelid inflammation,[30,31] potentially accounting for as much as 70% of all blepharitis cases.[32] The arrangement of facial features, including the cheek, brow, and nose, makes it challenging for some individuals to adequately clean the region of the eyelids. This difficulty in cleaning creates a favorable environment for the thriving of Demodex.[33]

Due to the distinct presence of these two mite species in the eyelids, the pathological development of Demodex blepharitis has been divided into two essential areas within the eyelids. *D. folliculorum* generally inhabits the eyelash follicles and roots, leading to anterior blepharitis. Demodex mites consume glandular and follicular epithelial cells, and they lay their eggs at the roots of the eyelashes, which results in follicular distension and improperly oriented eyelashes. The claws of the mites induce reactive hyperkeratinization and epithelial hyperplasia around the base of the eyelash, leading to direct mechanical injury.[33] Since these parasites do not possess excretory organs, undigested material is regurgitated, combining with epithelial cells, eggs, and keratin to form the distinctive cylindrical lash accumulations characteristic of Demodex infestation (Figure 1). These accumulations, in consequence, contain lipases and proteases, leading to symptoms of irritation.[17]

Instead, *D. brevis* is located deep in the meibomian and sebaceous glands, causing posterior blepharitis through mechanical blockage of the meibomian gland openings, resulting in dysfunction of the meibomian glands and lipid tear insufficiency. Upon penetrating deep into the meibomian glands, the chitinous exoskeletons of these mites function as foreign objects, initiating a granulomatous response.[33] Also, *Demodex* spp. represents a carrier for bacteria like *Staphylococci* (on their surface), *Streptococci* and *Bacillus oleronius* (inside the abdomen) which as well cause anterior and posterior blepharitis.[1] In addition, it has been identified that Bacillus oleronius isolated from Demodex *folliculorum* functions as a stimulant for inflammation in rosacea.[34] Other endosymbionts identified as linked to Demodex are: *Bacillus pumilus*, *Bacillus simplex* and *Bacillus cereus*.[35,73] *B. pumilus* is frequently isolated from multiple environmental sources, especially animal excrements. *B. pumilus* has cytotoxic properties and hemolytic activity, which could explain the development of the inflammatory clinical features of rosacea.[36]

Furthermore, inflammation may be triggered by dying mites as they release bacterial antigens, initiating the host inflammatory cascade. Subsequently, the waste products discharged by the mites prompt a delayed hypersensitivity immune response. This is supported by the observation that an elevation in the count of CD4+ T cells, Langerhans cells, and macrophages was evident solely in patients with positive *D. folliculorum* findings.[17] Additionally, both anterior and posterior blepharitis can impact the cornea, leading to conditions such as superficial punctate keratopathy, stromal and marginal infiltration, corneal neovascularization, phlyctenular lesions, nodular scars, superficial opacities, limbitis, and potentially

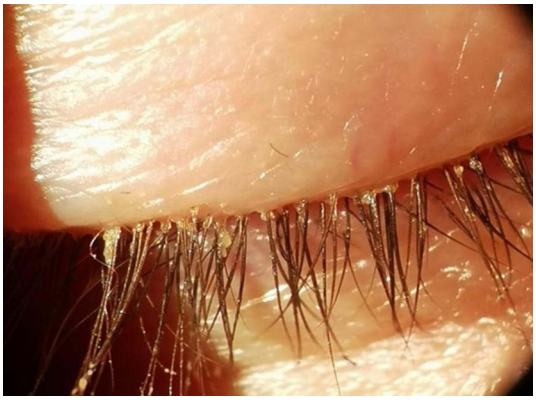

Figure 1 Patient with Demodex blepharitis and cylindrical dandruff at the base of the eyelashes.

perforation.[17,37] According to recent findings, Demodex blepharitis was observed in 60% to 70% of patients diagnosed with dry eye. The symptoms of Demodex blepharitis often overlap significantly with those of dry eye disease. The compromise of the tear film in dry eye disease (DED) could create a more favorable environment for Demodex mites.[38]

Demodex and Facial Dermatoses

Typically, both species of Demodex are present on the regular skin of adult humans, particularly within the pilosebaceous units of the face (Figure 2). [39] The keratinocytes lining the pilosebaceous follicles are infiltrated by Demodex mites, where they consume the cellular contents. The mites acquire cellular proteins and sebum through protease activity, facilitated by the salivary enzymes of the mites.[39] Moreover, the role of Demodex lipase enzymes extends to the digestion of bacteria or other microorganisms, along with the digestion of lipid material.[39] Degradation of the follicular epithelium is induced by the enzymatic process, and this may lead to inflammation in the perifollicular region.[39] The release of internal contents and chitinous exoskeletons from deteriorating mites upon their death may prompt an immune response in the host, resulting in subsequent inflammatory alterations.[39] The viability of Demodex mites is sustained by their ability to suppress the natural immune response of the host. Research has revealed that Demodex mites express the Tn antigen, a carbohydrate coating that offers protection for cancer cells and parasites against immunity.[39,40] Additionally, it has been demonstrated that Demodex mites influence the production of inflammatory cytokines such as TNF-alpha and IL-8, as well as TLR, by interacting with cells within the pilosebaceous unit.[39]

Recently, the number of studies evaluating Demodex infestations has increased.[39] Many case reports and epidemiological studies have demonstrated that Demodex is linked to facial skin lesions and is an important cause of skin diseases. An increased prevalence of Demodex has been identified in patients with skin disorders including pityriasis *folliculorum*, perioral dermatitis, acne, seborrheic dermatitis, Grover's disease, blepharoconjunctivitis, eosinophilic folliculitis, papulovesicular facial, scalp eruptions, scabies-like eruptions, pustular folliculitis, demodicosis gravis, Demodex abscess and basal cell carcinoma.[41,42] Furthermore, higher Demodex colonization has been observed in nevi, indicating a preference of the mite for melanin pigment.[41] The highest prevalence of infestation was found in the rosacea patients, followed by seborrheic dermatitis and acne vulgaris.[39]

Rosacea is a persistent inflammatory condition affecting the central facial skin. It is typically categorized into various subtypes, including erythemato-telangiectatic (characterized by facial redness and flushing), papulopustular (associated with acne, featuring papules and pustules), phymatous (involving conditions like rhinophyma and skin thickening), and ocular (manifesting as periocular symptoms). It is also possible for individuals to exhibit a combination of one or more of these subtypes.[40]

Rosacea demodicosis is a drier form of rosacea, displaying superficial vesicles, pustules, and follicular scaling, in contrast to typical rosacea, which is characterized by oily skin, the absence of follicular scaling, and deeper tissue involvement.[26] The onset of blepharitis is primarily influenced by rosacea, as it creates a skin environment that obstructs the functioning of oil-producing glands essential for maintaining a healthy dermis and epidermis.[8] There is a significant correlation between Demodex infestation and the onset of rosacea.[43] It has been shown in skin biopsies that individuals affected by rosacea exhibit a greater density of Demodex compared to those without the condition.[43] According to El-Shazly et al, 44% of individuals aged 11–50 with rosacea are excessively populated with *D. folliculorum*, in contrast to the 23.0% found in normal

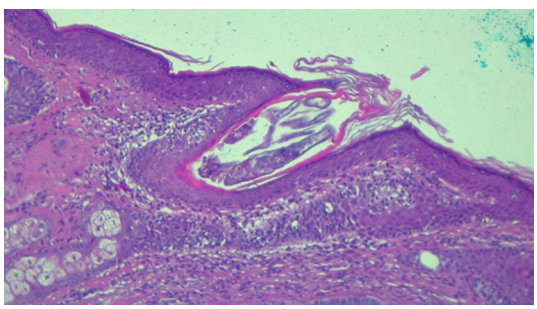

Figure 2 Histologic aspect of Demodex mite in pilosebaceous unit.

controls. The prevalence of Demodex was 66.7% and 83.3% in the erythemato-telangiectatic and papulopustular subtypes, respectively. The cheek was the most heavily infested area, followed by the periocular region, nose, chin, and mouth.[41] Demodex might contribute to the granulomas observed in papulopustular rosacea, but it is also found in the erythemato-telangiectatic subtype.[41] Interestingly, Demodex infestation tends to increase during the warmer seasons, such as spring and summer, overlapping with the period when rosacea exacerbates.[44]

The pathogenesis of rosacea has long been debated amongst researchers. Some authors indicated that Demodex mites may have a role in the pathology of rosacea, although it is not clearly understood if mites induce pathological changes or if rosacea simply provides a favorable environment for mite growth.[45] Other researchers showed various factors including vascularity (vascular growth factors, vasodilatation), immune dysregulation, genetic predisposition, inflammation, neurovascular dysregulation (neuropathic pain, hypersensitivity), microorganisms (like Demodex), infections and environmental factors.[46–48] Demodex can be involved in the pathological process of rosacea by triggering inflammation or stimulating certain immune responses, mechanical obstruction of the follicles, or acting as a carrier for microorganisms.[44,49] It was found that bacteria isolated from a Demodex mite have the potential to initiate an immune reaction in patients with papulopustular rosacea (PPR) or ocular rosacea. This finding may be linked to the inflammatory erythema seen in rosacea.[50] In addition, increased skin temperature in individuals with rosacea has influence on growth and protein production pattern of B. oleronius, which can lead to an increased production of immunostimulatory proteins.[51] It has been suggested that the sensitivity to B. oleronius is crucial in the etiology of rosacea.[46]

One study found that students affected by skin diseases have higher rates of Demodex infestation compared to normal individuals and suggested that mite infestation is associated with the occurrence of not less than five skin conditions (rosacea, blepharitis, acne vulgaris, seborrheic alopecia and pityriasis).[52] Another research investigated a possible link between alopecia and Demodex. It was observed that under the influence of dihydrotestosterone, the sebaceous glands of hair follicles damaged by alopecia undergo distension and heightened activity. This leads to an increased production of oils, establishing a more conducive habitat for mite growth. They concluded that Demodex is the result of alopecia and not its cause,[26] although some research studies have suggested Demodex plays an essential role.[53] In 2016, a study reached a different conclusion, showing that Demodex is occasionally detected in scalp biopsies in cases of alopecia and hair loss.[41,54]

The present nomenclature in regard to demodicosis is not specific and includes numerous dermatological conditions such as rosacea-like (rosaceiform) dermatitis, pityriasis *folliculorum*, demodectic rosacea, granulomatous rosacea-like dermatitis, Demodex facial dermatitis, perioral/periorbital dermatitis-like demodicosis, pityriasis folliculitis, facial demodicosis, scalp folliculitis, Demodex abscess, favus-like scalp demodicidosis and facial abscess-like conglomerates.[9] To eliminate potentially confusing information in publications, Chen and Plewig (2014) categorized demodicosis into primary and secondary forms. Primary demodicosis includes pityriasis *folliculorum*, papulopustular/nodulocystic or conglobate demodicosis, auricular demodicosis and ocular demodicosis. Immunocompromised states are commonly associated with the secondary form of the disease.[41]

Diagnosis and Treatment

The identification of Demodex spp. primarily relies on microscopic analysis of samples taken from the patient's skin, hair, eyelashes, or eyebrows. Techniques for acquiring skin or epidermis samples encompass surface biopsy using cyanoacrylate adhesive glue, skin biopsy, skin scrapings, or the application of adhesive tape.[1] Other diagnostic procedures can also be used, such as PCR (polymerase chain reaction) and dermoscopy,[1,25] as well as confocal laser scanning microscopy in vivo. In vivo confocal scanning offers the advantage of requiring no prior preparation for analysis and the potential for species identification and recognition based on the size of Demodex spp.: *D. brevis* measuring between 100 and 200 μm and *D. folliculorum* measuring between 200 and 400 μm, located in the spinous layer of the epidermis.[1]

Analysis of the patient's sample involves placing it on a glass slide treated with a 10% KOH solution, and examining it under a light microscope at either 40× or 100× magnification.[1,13] Adhesive tape is used for skin surface biopsy, helping to pull the superficial layers of the epidermis and hairs (with roots) to identify Demodex spp. Additional diagnostic methods include superficial skin scraping (SSS) and tape imprint (TI), which are also utilized for the detection of other parasites.[1,55] Additionally, the skin surface standardization biopsy method (SSSB) assesses the density of parasites per 1 cm^2, allowing for the identification of living, mobile Demodex spp. parasites. This method involves using a microscope slide with a specified 1 cm^2 spot containing a drop of cyanoacrylate glue applied to the affected skin area. Subsequently, the material is covered with

immersion oil and a coverslip, and the analysis is conducted using an immersion microscope.[1,55] Also, biological material from scrapings can be analyzed with molecular biology methods like PCR, but they are not realized by routine.[1] The standardized superficial skin biopsy (SSB) is the most prevalent method employed to compare mite densities between patients with dermatoses and healthy controls.[21] Furthermore, Liu et al noted that infrared photography can be beneficial in establishing a proportional correlation between the severity of inflammation caused by Demodex infestation and skin temperature, revealing a "fire-red" Demodex facies.[41]

Lately, high-definition optical coherence tomography (HD-OCT) allows rapid and noninvasive in vivo identification of Demodex mites.[35] OCT images with high lateral and axial resolution with horizontal (en-face) and vertical (slice) imaging modes identify mites; in the en-face mode, they appear as shiny round spots in groups of 3–5 mites per hair follicle. This method can be a practical tool for diagnosis and monitoring the treatment in cases of demodex-linked skin diseases.[56]

Diagnosis of eyelid demodicosis relies primarily on clinical assessment, and confirmation is established through microscopic identification of Demodex mites on epilated eyelashes. While the clinical diagnosis lacks specificity, the presence of cylindrical dandruff consistently serves as a diagnostic indicator.[57] Under biomicroscopy examination, cylindrical dandruff has the aspect of dried exudative excretions surrounding the base of the eyelashes.[37] After removing the eyelashes, Demodex eggs, larvae, and adult mites are detected and counted under a microscope.[8] It is recommended to epilate at least four nonadjacent lashes from each eyelid, and there is a higher likelihood of obtaining results when eyelashes exhibit cylindrical dandruff.[17,41] Enhancing the technique by using an alcohol or fluorescein solution during the microscopic examination of samples appears to prevent miscounting.[17,37] Kheirkhah et al observed that fluorescein solution added after epilation allows dense cylindrical dandruff to enlarge and expose embedded Demodex mites in a yellowish and semitransparent habitat. Therefore, this effective method may increase the Demodex count per eyelash. Muntz et al introduced a clinical diagnostic method that allows for the efficient evaluation and grading of Demodex in situ without the need for lash removal. This approach includes the removal of cylindrical dandruff and the application of lateral, constant tension to the eyelash using forceps, revealing a significant number of mites in the eyelash follicle. This method requires 25–40x biomicroscope magnification.[41]

In vivo confocal microscopy (IVCM) appears to be an effective tool which improve diagnosis.[58] A comparative study between IVCM and conventional epilation methods revealed that IVCM identified 100% mite infestations in patients with anterior blepharitis, 60% in dry eye patients without blepharitis, and 12% in healthy subjects. The findings from the eyelash epilation method were 100% for anterior blepharitis, 50% for dry eye patients, and 0% in healthy subjects, respectively.[58] Additionally, IVCM provided more precise identification of *D. brevis* and Demodex larvae within lash follicles and meibomian glands.[41]

The essential goal in treating Demodex is to decrease mites' overpopulation and to reduce inflammation. However, this therapy is complex and difficult to administer. It is a long process that lasts for a few months, and drug selection is an individual option. An essential factor involves averting infestation by adopting proper hygiene practices, utilizing cleaning and washing products such as soaps, shampoos, and wipes for the daily care of the eye and facial area.[1] Regular washing of bedding, especially at elevated temperatures, further aids in the elimination of the parasite.[59] Demodex mites possess inherent resistance to various antiseptic products, including 75% alcohol, erythromycin, and 10% povidone-iodine.[17]

The treatment of demodicosis involves the administration of systemic antibiotics such as tetracycline, doxycycline, ivermectin, and metronidazole.[60,61] Additionally, other agents like permethrin, benzoyl benzoate, lindane, crotamiton, and sulfur are utilized.[60] Systemic metronidazole therapy, even in a short cycle, is recommended for its effectiveness in reducing mite density. Furthermore, local treatment with permethrin, crotamiton, and benzyl benzoate has demonstrated efficacy, although the use of these agents may lead to skin irritation in patients. It is noteworthy that there is a lack of conclusive results from studies establishing standardized treatment procedures and indicating the long-term efficacy of the treatment.[62]

In addition, the treatment approach includes the use of various medicinal oils like camphor oil, tea tree oil, bergamot oil, salvia oil, and peppermint oil. Alongside these, sulfur ointment, yellow or white mercury ointment, and choline esterase inhibitors are employed.[1] Also, special heating glasses and infrared irradiation can be used.[1] Plant and herbal extracts with antiparasitic properties, such as extracts from celandine, calamus, or mugwort, can be used to cleanse the periocular area.[1]

Tea tree oil (TTO) has received particular attention, as it seems to draw Demodex mites out of the lash follicle in a dose-dependent mode.[16] TTO is extracted from the leaves of the Australian native Melaleuca alternifolia tree[63] and includes 15 known substances, with terpinen-4-ol (T4O) being the most prevalent and exhibiting a robust affinity for demodectic infestations[64] with antifungal, antimicrobial, antiviral, acaricidal and antiseptic properties. A growing number of eyelid hygiene products are available to control Demodex infestation[16] comprising either TTO or T4O with different concentrations which is the most effective treatment agent.[17] Tea tree oil (TTO) and its derivatives, particularly terpinene 4-ol (T4O), can be found in both over-The-counter and prescription formulations, ranging from 3% to 100%. These are available in various forms such as gel, shampoo, ointment, lid wipes, or scrubs. However, it is important to note their limitations, which may encompass issues such as contact dermatitis, ocular irritation, allergic reactions, and potential epithelial cell toxicity.[38] Also, linalool, an alcohol found in oils from rosewood (Aniba rosaeodora) and Camphor tree (Cinnamomum camphora), has been shown to possess strong antimicrobial properties, including efficacy against leishmanicidal activity.[65] Eyelid hygiene products containing T4O, TTO, linalool, or a combination of these ingredients effectively decrease Demodex survival time.[16]

In 2023, a group of twelve experts in ocular surface diseases collaborated to establish consensus on Demodex blepharitis through a modified Delphi panel process. Managing Demodex infestation revolves around restoring balance to the ocular ecology, with mechanical interventions such as lid scrubs and blepharoexfoliation playing a crucial role in treatment. The effectiveness of heat, whether from warm compresses, steam-based devices, or radiant heat devices, was deemed to be minimal, marginal, or not useful. The unanimous agreement among these experts was that a decision tree considering clinical signs and patient symptoms might be the most effective approach to treating blepharitis. Additionally, the panel concurred that patients exhibiting minimal symptoms but a moderate number of collarettes should undergo a treatment trial for Demodex blepharitis.[4] Management involves a combination of lid cleaning and elimination of eyelash cylindrical dandruff with the use of a blepharitis brush or lid foam and a cotton-tipped applicator.[17] Research findings demonstrate the efficacy of tea tree oil in decreasing Demodex infestation when applied to the eyelids twice daily, with concentrations ranging from as low as 5% to as high as 50% when used once a week.[17,64] Patients diagnosed with mites are commonly given an eyelid scrub incorporating tea tree oil for twice-daily use to eliminate Demodex. It is advised that individuals use the wipes on their eyelashes, eyebrows, forehead, and cheeks, as mites are present in all these regions.[17] Recently, XDEMVY™ (lotilaner ophthalmic solution) 0.25% has received approval from the US Food and Drug Administration (FDA) for the treatment of Demodex blepharitis. Formerly referred to as TP-03, XDEMVY stands as the initial and sole FDA-approved treatment specifically designed to address Demodex mites directly. The FDA's endorsement is rooted in the outcomes of two randomized, multicenter, double-masked, vehicle-controlled studies, namely Saturn-1 and Saturn-2. The efficacy of XDEMVY was demonstrated by a noteworthy enhancement in eyelids, characterized by a reduction of collarettes to no more than 2 collarettes per upper lid in each study by Day 43. Some patients experienced improvement as early as the second week.[66] Additionally, microblepharoexfoliation can be utilized every 3–6 months to eliminate the biofilm on the surface of the lids and lashes. This technique involves the use of a high-speed rotary sponge soaked in a lid cleaner, effectively removing the eggs of the mites located at the base of the eyelash follicle.[17] Patients with different levels of impairment are also advised to discard their make-up, wash their clothes using hot water, and dry clothes on the high-dryer programme.[17]

New agents for the treatment of Demodex involve New Zealand native Manuka honey (Leptospermum scoparium), which contains a non-peroxide constituent, cyclodextrin-complexed methylglyoxal (MGO), that shows increased resistance to enzymatic inactivation.[16,67] While Manuka honey demonstrated effects comparable to 50% tea tree oil (TTO) in reducing Demodex viability in vitro, it exhibited a favorable tolerability and safety profile when formulated as an eye cream preparation,[16] it has not yet been commercialized. Another emerging category of substances with antimicrobial properties includes hypochlorous acid[68] as well as a polysaccharide derived from okra (Abelmoschus esculentus),[69] although their anti-demodectic effects have yet to be revealed.[16] In the majority of studies, the effectiveness of the treatment is assessed solely on *D. folliculorum*, as these mites are more accessible than *D. brevis*. The evaluation of therapy success involves a reduction in mite counts and minimizing symptoms. For unresponsive cases of ocular demodicosis, oral therapies have been explored. The broad-spectrum antiparasitic agent oral ivermectin efficiently diminishes Demodex infestation. The combined therapy of ivermectin and metronidazole has demonstrated greater success compared to ivermectin alone in reducing mite numbers

associated with *D. folliculorum* infestation.[70] Additional therapeutic recommendations include washing the face twice daily, avoidance of greasy makeup and oil-based cleansers and peeling the skin frequently to remove dead cells.[16,26] A study on facial demodicosis highlighted the potential protective role of makeup use, suggesting that it might block skin follicles and hinder the transmission of mites. Additionally, it is speculated that individuals using makeup may engage in more frequent face cleansing. However, caution is advised against the excessive use of creams or moisturizers, as it could serve as additional lipid nourishment for Demodex.[16]

Intense pulsed light (IPL) is a technique employed in various medical and aesthetic skin conditions, and it has shown promising outcomes in the treatment of demodicosis, including individuals with rosacea[71] and for patients with ocular infestation.[72] The precise mechanism behind the effect of IPL on Demodex is not completely understood; nevertheless, it is suggested that Demodex mites may respond to the energy delivered by IPL and/or the generated heat, potentially raising the temperature to critical levels for their eradication.[16] While treatment approaches such as tea tree oil and microblepharoexfoliation effectively reduce Demodex colonization, research has shown that no single treatment option completely eliminates Demodex after one month of therapy. This underscores the chronic nature of the disease and the need for long-term treatment.[17]

Conclusions

Although Demodex was discovered many decades ago, it is only lately that its implication in eye and skin diseases has been extensively debated. These mites are commensal organisms found in folliculosebaceous units, the incidence of which increases with age, but which can become pathogenic with overgrowth or immune reaction causing rosacea or different facial skin diseases. In conclusion, the emerging understanding of the connection between Demodex blepharitis and facial dermatoses represents a significant advancement in both ophthalmology and dermatology. This relationship offers new avenues for research, potential therapeutic interventions and enhanced patient care, ultimately aiming to improve the quality of life for individuals affected by these skin conditions.

Ethics Statement

Written informed consent was obtained from our patient as per our current legislation, which includes medical data sharing and photographic content.

Disclosure

The authors declare no conflicts of interest in this work.

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