

Ann-Caroline Sinisalo

**ASSESSMENT AND MANAGEMENT OF DEMODEX BLEPHARITIS: CASE  
STUDY-BASED DEVELOPMENT PROJECT**

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Ann-Caroline Sinisalo  
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Oulu University of Applied Science

## ABBREVIATIONS LIST

|                 |  |
|-----------------|--|
| BKC:            | Blepharokeratoconjunctivitis               |
| CD:             | Cylindrical Dandruff                       |
| D.Brevis:       | Demodex Brevis                             |
| D.Folliculorum: | Demodex Folliculorum                       |
| IPL:            | Intense Pulsed Light                       |
| IVCM:           | In Vivo Confocal Microscopy                |
| MGD:            | Meibomian Gland Dysfunction                |
| NIK BUT         | Non-Invasive Keratograph Break Up Time     |
| UODS:           | Uludag Ocular Demodicosis Clinical Scoring |
| TTO:            | Tea Tree Oil                               |
| T4O:            | Terpinen 4-ol                              |

BLEPHASOL DUO: Micellar cleansing liquid

BLEPHADEMODEX: Sterile eyelid wipes contain two active ingredients; T4O (2,5%) and Sodium Hyaluronate.

BLEPHEX: This painless in-office procedure removes scurf and debris and exfoliates eyelids carefully.

## **ABSTRACT**

Oulu University of Applied Sciences  
Master of Healthcare Clinical Optometry

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Author: Ann-Caroline Sinisalo

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### **Purpose**

The purpose of this master thesis was to study Demodex via a case study. The aim was to figure out the need for treatment of a symptom-free client with signs of cylindrical dandruff associated with Demodex blepharitis.

### **Methods**

This single case study report involved the clinical assessment and management of a 57-years old Finnish male who went to a privately owned optical shop for an eye examination. The survey was based on different treatment methods and their impact on Demodex, consisting of six return visits. The survey was done from 21.07-14.10.22, and the research method was qualitative. The researcher collected all data on-site while the patient was being seen in the clinic. Therefore, a separate IRB approval was not needed. The primary literature search was conducted in April 2022 from PubMed with the keywords Demodex blepharitis, and nine studies were used.

### **Results**

One week of use of Blephasolduo gave a cleaner edge to the eyelid, but the CD did not disappear and decreased minimally. The first two weeks of using Blephademodex proved to be inefficient. But after four weeks, there was an apparent change. Then again, at six weeks, the result had stagnated with no progress. After eight weeks of total treatment of the eyelids, there was still CD left, which is why Blephex cleaning was chosen as the treatment method. This resulted in CD-free eyelashes. After that, there was a 4-week follow-up period with the use of routine eyelid cleansing morning and evening. After this period, the client had a relapse of CD.

### **Conclusions**

Blephasol duo should be used as a preventive product for cleaning the eyes. It should not be used as a single product once the mites have invaded. It can be used in conjunction with Blephademodex. Using Blephademodex once a day looks like a long-term process, even if the client has no symptoms. Recommend direct use twice daily. For an even faster result, first, BlephEX will remove all CD and any mites in them and then more effectively get Blephademodex into the follicle and meibomian glands. Recommends treatment of symptom-free Demodex clients to avoid sequelae on the conjunctiva, cornea, etc. The optometrist should inform the client about Demodex during a routine eye examination.

Keywords: demodex blepharitis, blepharitis, anterior blepharitis, posterior blepharitis, demodex treatment, demodex management.

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# 1 INTRODUCTION

Demodex came to human knowledge by Henle in 1841. The first mention in PubMed dates from 1914, and Coston associated Demodex with blepharitis in 1967. (Savla et al., 2020,8) Dry and irritated eyes have been talked about for a long time, which has contributed to more thorough investigations of the eye's anterior anatomy and greater interest in Demodex.

There are two types of Demodex on humans, Demodex folliculorum and Demodex brevis. Folliculorum lives in the eyelash follicle, is more associated with anterior blepharitis and Demodex brevis in the meibomian and sebaceous glands and is more related to posterior blepharitis. (Bitton and Aumond, 2021, 285)

Demodex is a normal part of the lid flora, and both symptomatic and asymptomatic people have Demodex. The most common symptoms include lid margin itching, foreign body sensation, burning, and tearing. Infestation increases with age, and it is mentioned that 100 % of people over 70 have been shown to have Demodex mites. (Fromstein et al., 2018, 57-58)

The clinical diagnosis of Demodex blepharitis is more commonly made based on the signs that are present rather than the patient's reported symptoms. Clinical signs associated with a Demodex infestation are crusting and redness of the lid margin, misdirected lashes, follicular hypertrophy, debris around the lid margin, and cylindrical dandruff. The most common diagnostic methods in clinics are signs, especially cylindrical dandruff, and lash manipulation. In addition to them, lash sampling, in vivo confocal microscopy, and spontaneous fluorescence also occur. (Fromstein et al., 2018, 59-60)

The surveys show that routine eyelid hygiene does not reduce the Demodex population, and that Tea tree oil is mainly used in clinics and in-home care. Modernized tools such as BlephEX and Intense pulsed light (IPL) exist. On the medical side, there are systematic treatments, Ivermectin and Metronidazole. In addition to Ivermectin and Metronidazole, topical treatments include Permethrin and Pilocarpine. (Fromstein et al., 2018, 60-61) More recent studies have mentioned manuka honey ("Manukahonung," 2020) and the first drug TP-03, which is in the launch stage. ("TP-03," n.d.)

## 2 THEORETICAL BACKGROUND

When you search for the word Demodex in PubMed, you found the first survey in 1914, the following in 1920, and the one in 1923. After that, we must wait until 1946, when two surveys were published; in 2021, we are at 93 surveys. Against this background, we can safely say that interest in Demodex has risen over the years. (Figure 1).

Demodex consists of the words "demos," meaning fat, and "dex," meaning worm, and comes from Greek. (Bitton and Aumond, 2021, 285).

Demodex mites have come to people's knowledge by Henle 1841. Simon identified *D. folliculorum* in 1841 and Albulatova *D. brevis* in 1963. (Zhang et al., 2020, 389) In 1876 Demodex mites were reported as an ocular manifestation when Michel discovered them in the hair follicle. (Shah et al., 2022, 934) In 1900 Raehlmann suggested that Demodex, though asymptomatic at times, could initiate conjunctivitis and angular dermatitis. (Shah et al., 2022a, 934) In 1967 Demodex was associated with blepharitis by Coston. (Savla et al., 2020, 8; Ozcan et al., 2018, 7) All did not accept Coston's study, so Desch 1972, with credit from Albulatova, did further reviews to distinguish between *D. folliculorum* and *D. brevis*. (Shah et al., 2022, 935)

Many variants of Demodex exist, but only two live naturally on human skin until they die. Demodex is a mite that belongs to the genus Demodiciadae family. ("Théa - Let's Open Our Eyes," n.d.)

Demodex overgrowth and diagnostics are perceived as too little. Demodex is a very common type of ectoparasite that can be found on the skin of humans. As the host of the Demodex, the human is the only functioning mammal, and of the general population, it turns out that 100% of over 70-year-olds have Demodex mites. (Fromstein et al., 2018, 57-58)

It is believed that there is no cross-infection of Demodex between animals and humans, but despite this, there are some reports of suspected *D. Canis* from dogs that have infected humans. (Bitton and Aumond, 2021b, 286).



The investigation of the mites presents challenges due to their microscopic size, limited lifespan, delicate handling, and inadequate culture system. In addition, the mite was previously declared dead when its legs or mouth no longer moved. However, a new method has come along that has shown how autofluorescence slowly declines even days after movement has ceased. (Bitton and Aumond, 2021b, 285)

Bitton and Aumond report on Geographical differences regarding Demodex prevalence values. The USA is the lowest with 14%; Poland, Israel, Turkey, and Ireland have over 60% (Bitton and Aumond, 2021b, 290)

#### RESULTS BY YEAR

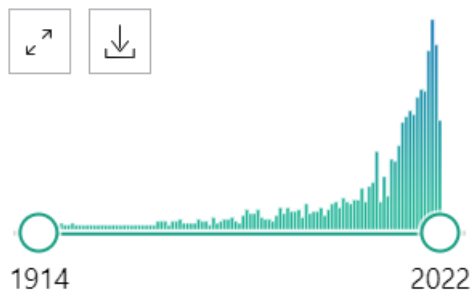
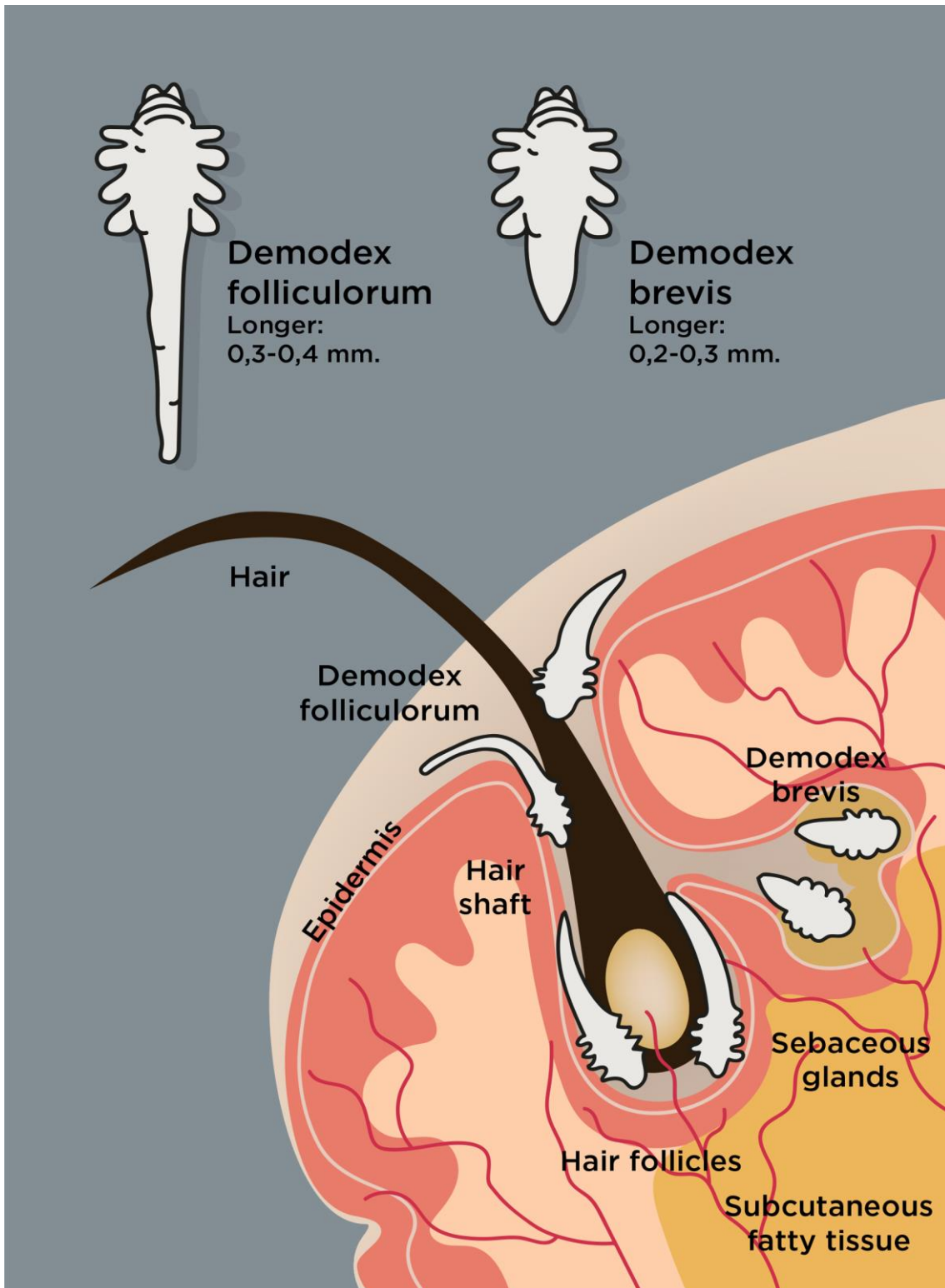


Figure 1. PubMed Publications count from 1914 to 2022 with the search term Demodex. (PubMed 2022)

## 2.1 Two Types of Demodex in Humans

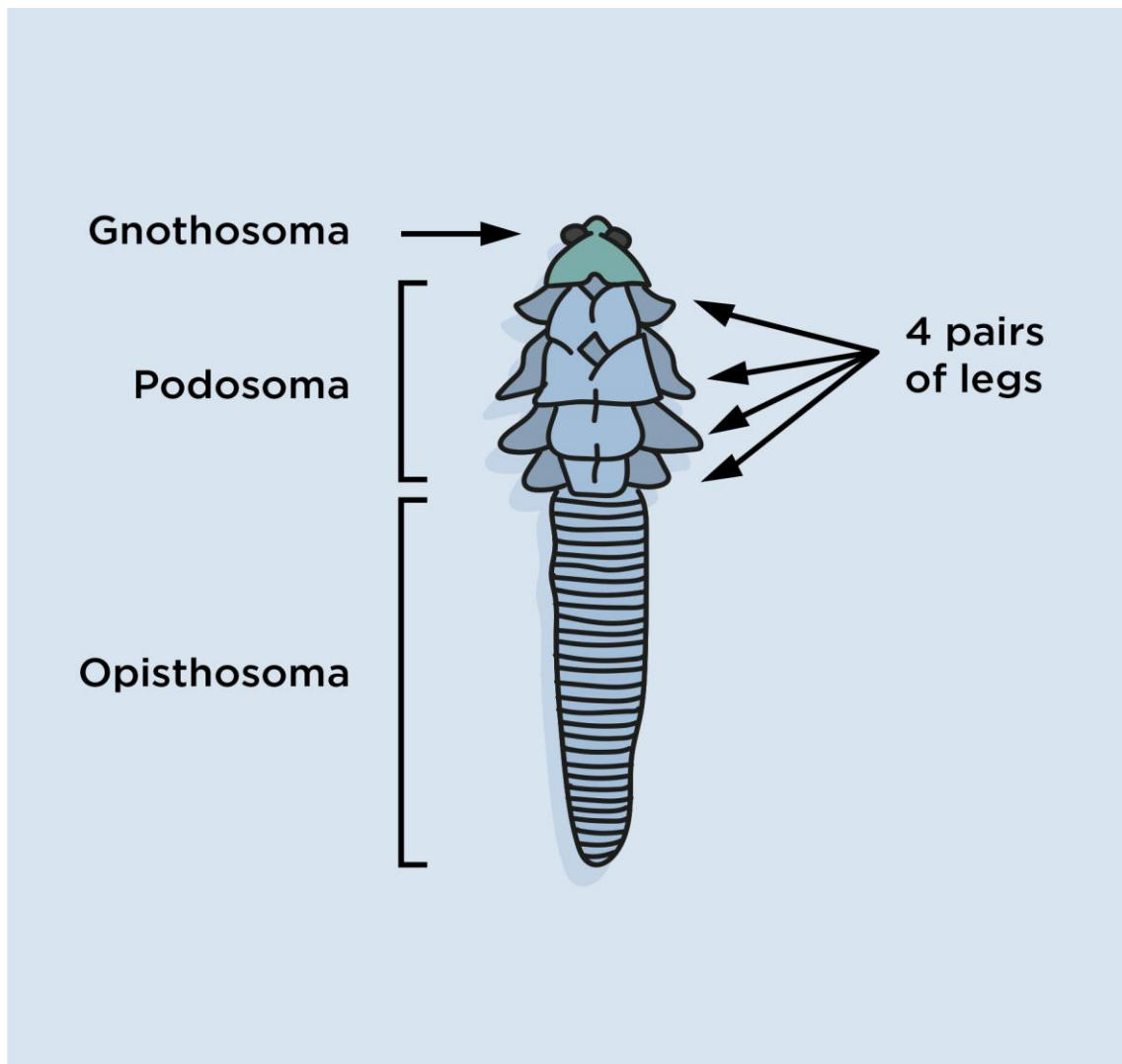
Demodex folliculorum lives around lash follicles in clusters and is 0,3-0,4mm long, and Demodex brevis is found solely in the Meibomian glands, and the sebaceous units live individually. D. brevis is shorter and measures 0,2-0,3 mm long. (Figure 2) ("Demodex Infestation - EyeWiki," n.d.) Female organs tend to be slightly rounder and shorter than males. (Ozcan et al., 2018, 16).



Adopted from Murube, J. (2015). Demodex hominis. *The ocular surface*, 13 3, 181-6.

Figure 2. Demodex folliculorum & Demodex brevis. Picture: Ann-Caroline Sinisalo.

D. folliculorum is more commonly found on the face, and D. Brevis occurs more on the neck and chest. The color of the mite is white or yellow. (Fatemeh, 2021). Bitton mentioned that the mite is colorless and hairless. The body is divided into three parts. (Figure 3) Two-thirds consists of the opisthosoma, the middle part of the podosoma, and the front part the gnothosoma. Opisthosoma tapers in the end and is longer in folliculorum than in brevis. (Bitton and Aumond, 2021, 285.)



Adopted from Bitton and Aumond, 2021b.

Figure 3. Demodex body. Picture Ann-Caroline Sinisalo.

Both have a cigar-shaped form, an exoskeleton covering their body, and four pairs of legs. (Figure 3) In adulthood, the mites can only move 8-16 cm per hour due to their short legs. (Bitton and Aumond, 2021b, 285) They have a mouth digestive pouch. (Fromstein et al., 2018, 57-58).

Demodex mites have no anus. When they die, they explode and spread the accumulated bacteria waste. The trash has no smell. (Fatemeh, 2021). Their genital opening is on the dorsal side. (Bitton and Aumond, 2021b, 285.)

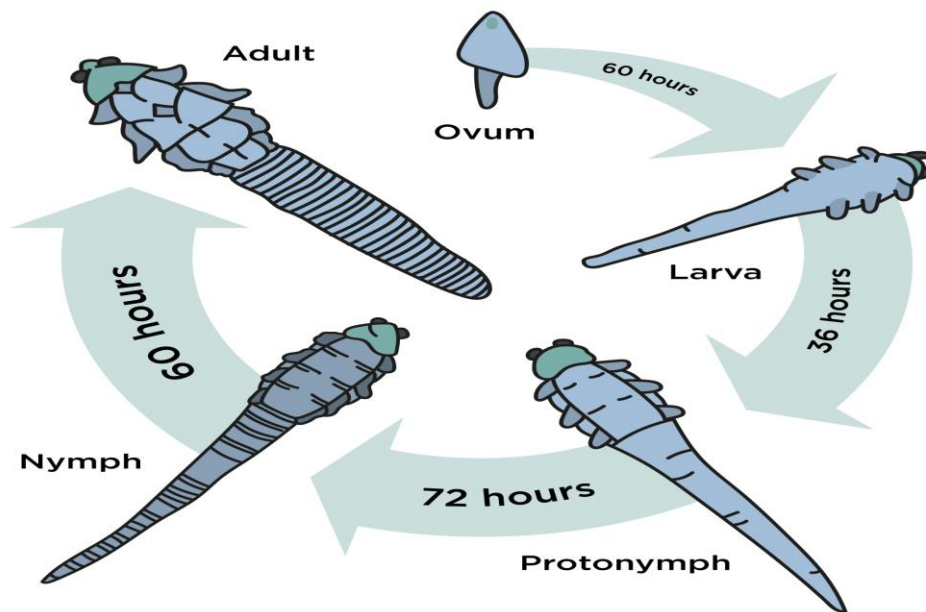
Demodex mites are sensitive to light in all stages and usually have their head inside the follicle and only come out in the dark (nighttime). Demodex mites' in vivo survival are mostly a few days because they are host-dependent. (Bitton and Aumond, 2021, 285.)

The genes demonstrate that *D. folliculorum* is more active and may be involved in type 1 allergic reactions such as erythema and itching. Its genes are related to metabolism, movement, allergen coding, detoxification, and stress response. *D. Brevis* genes are associated with protein metabolism enzymes. The enzyme asparagine protease can digest host skin and serum molecules, which makes it easier for *D. Brevis* to penetrate the skin. (Bitton and Aumond, 2021, 286)

## **2.2 Demodex Lifecycle**

The full-grown mites mate near the follicle openings. Adult female Demodex mites lay 10-12 eggs in the follicles or sebaceous glands. The stages in the lifecycle are ovum, larva (appear after 3-4 days), protonymph, and nymph to adult. (Figure 4) (Ozcan et al., 2018, 18) The life cycle lasts 14-18 days, followed by five days as an adult. Adult females can live another five days after laying their eggs. (Luo et al., 2017, 2)

The fully grown female mites re-enter a hair follicle, but the male Demodex mite will leave the follicle searching for a mate. They are more active during nighttime and can walk approximately 10 mm/h. ("Demodex infestation requires immediate, aggressive treatment by doctor, patient," n.d.) It is mentioned in Savlas research that you should kill two lifecycles which means about six weeks of treatment. (Savla et al., 2020, 9)



Adopted from Fatemeh. sh, 2021b

Figure 4. Demodex Life cycle. Picture Ann-Caroline Sinisalo.

### 2.3 Demodex Method of Infection

Demodex is transmitted by direct contact with humans, usually by contact with hair, eyebrows, and sebaceous glands on the nose. (Ozcan et al., 2018), 16). The two species have geographical differences, and *D. folliculorum* does not show a clear geographical difference, whereas *D. brevis* does. Because of the clear geographical difference, *D. folliculorum* is thought to be more contagious. After all, *D. folliculorum* is located anteriorly. (Shah et al., 2022, 935)

Demodex is found in people with and without symptoms, and the correlation between infection and symptoms is poor. It has been suggested that population density and overpopulation can cause homeostasis and become a disease. (Fromstein et al., 2018, 57)

Zhang mentioned that Demodex divides overpopulation into primary demodicosis and secondary. Primary rules D .folliculorum and secondary D. brevis and that primary demodicosis consists of certain conditions such as blepharitis and chalazia, and secondary is more associated with systemic or local immunosuppression. (Zhang et al., 2020, 390)

The literature suggests a correlation between different anterior segment conditions, such as eyelash changes (loss and misalignment), basal cell carcinoma (BCC) of the lid, blepharitis, meibomian gland dysfunction, and ocular rosacea, conjunctivitis, keratitis, among others. (Zhang et al., 2020, 409) D. brevis creates a strong connection with acne rosacea and MGD as it is found on the face, especially cheek and nasolabial folds, and in the meibomian glands, whereas D.folliculorum eyelash infestation and adult demodicosis are detected in non-rosacea patients. (Bitton and Aumond, 2021b, 288)

Zhang et al. mentioned a connection between ocular Demodex infestation and pterygium. Pterygium contributes a favorable microenvironment to Demodex and should be considered, especially in recurring cases. They found that individuals with type 2 diabetes have a higher prevalence of ocular Demodex than age-matched and a relationship between ocular Demodex and allergic rhinitis. (Zhang et al., 2020, 409)

Clinical signs associated with a Demodex infestation are crusting and redness of the lid margin, follicular hypertrophy, debris around the lid margin, cylindrical dandruff, and tails pointing from follicles when collarettes are removed. (Fromstein et al., 2018, 59)

One source mentioned that as long as the number of mites does not exceed five per square centimeter of skin, they are not considered a problem. Our immune system mostly keeps them under control. But people with, for example, a weakened immune system may be more vulnerable and suffer from depression. (Fatemeh. 2021a). Immunodeficiency factors include emotional stress, poor nutrition, poor sleep, ultraviolet light treatment, skin tumors, and concomitant diseases (Bitton and Aumond, 2021, 288). Demodicosis is used as a term for infestation by these mites. (Fromstein et al., 2018, 57)

The Navel investigation found that people with oily or mixed skin in humid tropical climates, immunocompromised patients, or malnourished children have a higher incidence of attacks.

In most studies, age is mentioned as a cure for mites, which the reduced activity of the zeiss and meibomian glands with age can perhaps explain. But in Navel's results, no significant influences of gender or age emerged. It is also noted that Demodex may play a role in recurrent chalazia, itching, and redness of the eyelid in pediatric and adolescent patients. (Navel et al., 2019, 661) Zhang also cites poor hygiene and excessive fat production as a cause. (Zhang et al., 2020, 393)

There is a 7-8 times greater risk of having Demodex in patients with acne rosacea, which proves a strong correlation between acne rosacea and Demodex. *D. brevis* creates this correlation between acne rosacea and MGD because it is found in sebaceous glands and resides in many places of the body, such as cheek and nasal labial folds, as well as in the meibomian glands. It has also been mentioned a connection between eyelashes and facial demodicosis. The eyelash infestation of *D. folliculorum* and facial demodicosis were demonstrated in non-rosacea patients. (Bitton and Aumond, 2021, 288)

Demodex is most effective during the spring and summer, coinciding with rosacea's exacerbation. Bitton and Aumond mention that 5 degrees Celsius are the most suitable maintenance temperature for in vitro Demodex studies; 16-20 degrees is the ideal temperature for development. (Bitton and Aumond, 2021, 291)

## **2.4 Blepharitis**

In blepharitis, the eyelids are inflamed, an inflammatory ocular disorder. The symptoms are usually red and swollen eyelids. Experience a burning or painful sensation. Signs of blepharitis are flakes and oily particles (crusts) also wrapped around the eyelashes. ("What Is Blepharitis?" 2021)

Bacteria such as staphylococci, streptococci, or *Moraxella* found at the lash line and the edge of the eyelids can cause blepharitis. Also, viral infections such as herpes simplex or zoster. (Figure 5) (Ophthalmologists & Retina Specialists of Vitreous Retina Macula Consultants of New York, n.d.)

Blepharitis is divided into anterior and posterior. Anterior affects the front of the eyelid margin, centered on the eyelashes, eyelash follicles, and eyelid skin. It is usually caused by seborrhea or staphylococci involving the cilia's hair roots. At posterior blepharitis, the inside of the eyelid is affected by inflammation and blockage of the meibomian glands. (Figure 5)

It can also cause inflammatory changes to the tarsal plate. Posterior blepharitis is often associated with seborrheic dermatitis and rosacea. ("Blefarit (ögonlocksinflammation)," n.d.)

Blepharitis is a chronic condition and tends to recur. "The treatment is mainly based on eyelid hygiene, cleaning, and eye lubrication. Self-care reduces the risk of bacterial complications and the amount of cylindrical dandruff. ("Blefarit (ögonlocksinflammation)," n.d.)

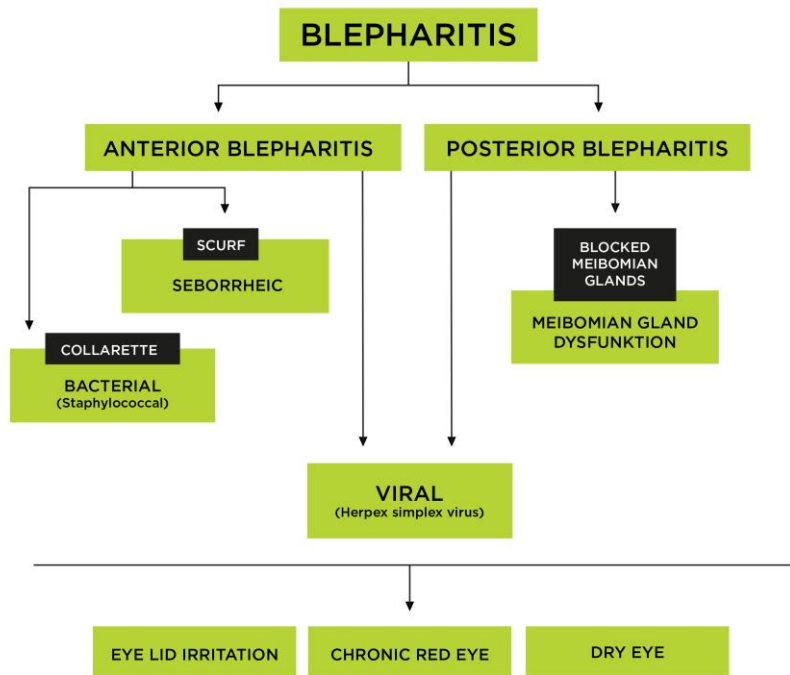
Anterior blepharitis can be presented depending on the cause of blepharitis. Collarette is used for staphylococcal origin, scurf for seborrheic, and cylindrical dandruff for Demodex. (Figure5) (Bitton and Aumond, 2021, 290)

In the case of moderate and severe blepharitis, pharmacological treatment such as terracortril is also used, and in case of infection, fucithalamic as oral antibiotic tetralysal. Ketoconazole shampoo relieves blepharitis caused by seborrheic eczema. In case of chronic complaints and difficult diagnosis, bacterial culture of secretions can be considered; don't forget chlamydia. ("Blefarit (ögonlocksinflammation)," n.d.)

One survey also mentioned that blepharitis had been treated with sulfuric acid ointment, mercury ointment, Pilocarpine, and antibiotics. Sulfuric acid and mercury treatment received poor support and thus are no longer used. (Navel et al., 2019, 659)

Luigi mentions that it is recommended to treat blepharitis before cataracts- or refractive surgery to reduce the risk of endophthalmitis. (Capasso et al., n.d. p.1) ()





Adopted from ("Blepharitis," n.d.)

Figure 5. Blepharitis division. Picture Ann-Caroline Sinisalo

### 2.4.1 Demodex Blepharitis

Zang et al. wrote that the first association between Demodex and blepharitis would be as early as 1878, but the reference is controversial. (Zhang et al., 2020, 393) Xiaohui Luo writes that the first association with Demodicosis is blepharitis as early as 1899. (Luo et al., 2017, 3) Whereas Coston described that Demodex had been associated with blepharitis since 1967. (Ozcan et al., 2018, 7)

Demodex blepharitis is divided into anterior and posterior, and *D. folliculorum* is associated with the anterior and *D. brevis* with the posterior. (Fromstein et al., 2018, 58) Shah mentions that anterior blepharitis is a type of eyelid inflammation that is less common than posterior blepharitis. Anterior blepharitis is usually associated with younger women. (Shah et al., 2022, 935)

Demodex has a significant connection with blepharitis, depending on the research ranging from 29 -100%. (Savla et al., 2020, 8) According to Elisabeth Yeus's presentation;(2021), 2/3 of blepharitis cases in the USA are associated with Demodex. (Yeu, 2021)

In a study of 500 people with diagnosed blepharitis, Demodex was detected in 79,2%; however, in a dry eye study of 229 patients, 40,2% had Demodex. (Shah et al., 2022, 935) Martínez-Pulgarín mentions that 41.6-81,25 % of patients with blepharitis are positive for Demodex infestation. (Martínez-Pulgarín et al., 2021, 1)

Risk factors for Demodex blepharitis are age, sex (Demodex blepharitis is more common in men in some studies), contact lens wearer, keratitis, chalazia, rosacea, poor hygiene, and immunodeficiency (Ozcan et al., 2018, 32-33). In addition to the risk factors mentioned above, Martínez-Pulgarín adds alcohol intake, sun exposure, smoking, and stress as the most critical risk factors. (Martínez-Pulgarín et al., 2021, 1)

Demodex blepharitis's most pre-eminent symptoms are itching and a foreign body sensation. Burning and tearing are also associated. (Ozcan et al., 2018, 33)

The pathogenesis of Demodex blepharitis is divided into three subareas. Direct damage (micro-abrasions caused by the mite's claws) blocking the opening of meibomian glands and consuming epithelial cells. (which is a vector for bacteria). (Martínez-Pulgarín et al., 2021, 1)

If you do not treat D. blepharitis, it can lead to severe complications. Untreated D. blepharitis can give further complications such as blepharoconjunctivitis and blepharokeratoconjunctivitis. (Ozcan et al., 2018, 35) Madarosis / Milphosis (lash loss) and trichiasis (misdirected lashes) can occur when you are affected by Demodex. Demodicosis can also block the openings of follicles and sebaceous ducts and contribute to epithelial hyperplasia and hyperkeratinization. (Bitton and Aumond, 2021b, 287)

Aumond et al. (2021) suggest that the severity of Demodex blepharitis should be assessed according to how many CD:s are present in the eyelashes. Because they found out that 100% of patients with Demodex blepharitis had at least one eyelash with CD on each upper eyelid compared to 64,2% who had a CD on the lower eyelid. (Zhang et al., 2020, 414)

#### **2.4.2 Demodex and Anterior Blepharitis**

*D. folliculorum* is located at the eyelash follicle. It feeds on follicular and glandular epithelial cells and causes mechanical damage. Mechanical damage causes epithelial abrasions, which can cause epithelial hyperplasia and reactive hyperkeratinization. (Fromstein et al., 2018, 58)

The mites lay their eggs in dark at the lash line causing follicular distension and misdirected lashes. Demodex mites have no anus resulting in undigested material that combines with epithelial keratin and eggs to form the bulk of the cylindrical ciliated deposits typical of Demodex infestations. CD causes irritation symptoms and is the only symptom directly correlated with Demodex. Proteases and lipases cause deposits. (Fromstein et al., 2018, 58) Specific to *D. folliculorum* is gelatinous debris, Cylindrical dandruff surrounding the lash base. This should be distinguished from collarettes-caused bacterial overgrowth that is displaced along the lash shaft with lash growth. (Bitton and Aumond, 2021b, 287)

The mites also irritate because they bite. Lipolytic enzymes are used to digest sebum, which is their primary food source. On the surface of the mites, streptococci and staphylococci are involved in microbial blepharitis. Inside the mites is the bacterium *Bacillus oleronius*, which has activated the host's immune response. (Fromstein et al., 2018, 58)

When the mites die, they can induce an inflammatory response and release several bacterial antigens. Debris removed from the mites causes a delayed hypersensitivity immune response, which increased CD4 T cell macrophages can determine. Langerhans cells were observed only in people with *D. folliculorum*. (Fromstein et al., 2018, 58)

#### **2.4.3 Demodex and Posterior Blepharitis**

*D. brevis* is found mainly in the meibomian glands. It is associated with keratitis, chalazia, superficial corneal vascularisation, marginal infiltration, and BKC. (Ozcan et al., 2018, 35) *D. brevis* is linked to MGD symptoms because it is mainly located in the meibomian glands and blocks the gland's opening. Blockage of meibomian glands contributes to congestion, swelling, and gland enlargement. The mite's secretion contributes to the blockage of meibomian glands, which can induce a mediated reaction. (Fromstein et al., 2018, 58)

A granulomatous response occurs from the mite's exoskeleton, and it can develop a hordeolum or chalazion. Recurrence of chalazion after surgery is more likely if *D. brevis* is involved. Suppose the inflammation continues from the edge of the eyelid to the conjunctiva. In that case, it results in blepharoconjunctivitis, and if Demodex causes it: antibiotics, antivirals, or lubricants do not help. (Fromstein et al., 2018, 58)

Demodex mites can act as a vector for staphylococcus- epidermis and aureus, the primary pathogens in pediatric blepharoconjunctivitis. When we move on from the conjunctiva to the cornea, Demodex can also destroy and cause changes in the cornea. Both anterior and posterior blepharitis can cause unexplained superficial punctate keratopathy, corneal neovascularization, stromal and marginal infiltration, phlyctenular lesions, superficial opacities, nodular scars, limbitis, and even perforation. *D. brevis* is the cause of keratitis because it resides closer to the cornea. (Fromstein et al., 2018, 58-59)

It is mentioned in some studies that Demodex keratitis has been misdiagnosed as herpetic keratitis. (not responding to antiviral medications). The slit-lamp appearance of demodicosis-related keratitis is reminiscent of herpesvirus keratitis. (Luo et al., 2017, 6)

## **2.5 Assessment of Demodex**

Demodex symptoms are reminiscent of other eye conditions, such as blepharitis, dry eyes, and inflammation of the eyes. Therefore, diagnosis is more often made based on signs. (Fromstein et al., 2018, 59) At the time of diagnosis, Demodex should be suspected when the history shows blepharitis, conjunctivitis, or keratitis in adults or blepharoconjunctivitis or chalazia in children and when the clients are resistant to corticosteroids. (Shah et al., 2022, 936)

Crossover symptoms include tearing, blurry vision, ocular discomfort or irritation, itching, burning, foreign body sensation, and crusting or matted lashes—typical signs of *D. folliculorum* is cylindrical dandruff CD, which is easy to see in the lash line. (Fromstein et al., 2018, 59) Gao et al. report that the number of Demodex mites is significantly greater in eyelashes with CD than without. (Zhang et al., 2020, 414)

No approved gold standard diagnostic method exists, but different methods are used to establish the diagnosis. Most of the studies are done on eyelash epilation, which is considered troublesome for the examiner and the client. Now more IVCN and eyelash manipulation are suggested. IVCN is considered time-consuming and expensive as you need an extra tool. Eyelash manipulation and CD examination with a standard microscope are considered the most appropriate method in clinical settings. (Zhang et al., 2020, 415).

Previously when you only had a magnification of 16-20 on the microscope, you could only see CD but not the mites. To see the mites better, you have to remove the CD. (Ozcan et al., 2018, p. 38) It is mentioned that during an eye examination, you can take a 90- Dioptres lens to help see the image upright on the mites if you do not have a magnification of 25-40 in the microscope. If follicles are overcrowded, mites rest at the edge of the eyelid, which is rare due to their sensitivity to light. (Bitton and Aumond, 2021, 289).

Other signs are eyelash disorders such as trichiasis, distichiasis, madarosis, and erythema in the eyelid. The presence of CD indicates the presence of high-density infestations of Demodex mites. Demodex should be considered in blepharoconjunctivitis and corneal changes such as neovascularization, infiltration, opacification, and scarring, especially if they do not disappear after treatment. (Ozcan et al., 2018, 34-35)

In 2017, a clinical scoring system was proposed, Uludag ocular demodicosis clinical scoring (UODS). The scoring system contains the most common complaints and clinical signs potentially linked to Demodex. The maximum score is eight, and the sensitivity is remarkably accurate as only 54% of the Demodex-positive patients scored four or higher. (Ozcan et al., 2018, 42.)

Warning bells should ring for Ophthalmologists when encountering blepharitis with CD during the examination; the likelihood of ocular demodicosis occurs. (Zhang et al., 2020, 424)

### 2.5.1 Eyelash Removal and Microscopy

A definitive diagnosis can be made by taking samples from eyelashes. The eyelashes are examined with a confocal microscope. It is randomly recommended the epics of four nonadherent lashes per eyelid. Coston defines this sampling. (Fromstein et al., 2018, 59) There is also a difference in how many eyelashes clinicians and researchers remove. Coston epilated 2-4 eyelashes from each eyelid, and the lashes were mounted on a coverslip of a drop of oil. (Zhang et al., 2020, 409)

Eyelash sampling with CD is likely to yield results. The problem is that the mites could remain in the follicle when the lash is detached, and CD often hides embedded mites. (Zhang et al., 2020, 409)

Adding sodium fluorescein, peanut oil, or 75% alcohol makes it possible to dissolve the CD, which releases the embedded mites. (Fromstein et al., 2018, 60) When you epilate the eyelashes, a CD is often left at the edge of the eyelid, which has increased the number of eyelashes you epilate to 8-16. (Zhang et al., 2020, 409)

Coston's sampling method from 1967 has been modified because of these various problems. New sampling and analysis techniques have appeared where you deliberately choose eyelashes with CD isolated too randomly. To avoid the mites getting into the follicle, you should rotate the eyelashes before epilating and use added saline, which helps prevent the mites from dropping off the eyelash. Ethanol or dyes such as fluorescein or aqueous methylene blue instead of oil dipping, so it's easier to detect the mites. (Zhang et al., 2020, 409, Ozcan et al., 2018, 39)

More than six mites, but even four or five on one eyelash, are considered overpopulated, and as average mite population is counted as one or two mites per sixteen eyelashes. This method's challenge is getting the mite to stay on the lash after it is removed, which can give wrong results. (Ozcan et al., 2018, 39)

Lee et al. describe that the number of mites is related to the symptoms such as itching, redness, watery-, and foreign body sensation in the eye. However, some studies show that the number of mites is not necessarily related to the severity of the symptoms. (Zhang et al., 2020, 414)

## **2.5.2 Eyelash Rotation and Manipulation**

Hom's method of exposing the mites is to rotate the eyelashes so that the mites come up from the follicle. Removing the CD first makes it easier to see the cigar-shaped mites' tails sticking up from the follicle opening, but it requires a good magnification. This method is perceived as faster as you do not have to epilate lashes and are more accessible for clinicians and patients. (Ozcan et al., 2018, 39) Overall, eyelash manipulation gives a higher number of mites than ordinary microscopy. (Zhang et al., 2020, 414)

Murphy et al. used a technique where an eyelash from each eyelid was rotated four times counterclockwise and then four times clockwise. Sterile forceps are used as a tool. There were more significant amounts of *D. folliculorum* with rotation than with complete epilation of the eyelashes, and this is logical since *D. folliculorum* resides in the follicle. This method was considered suitable for detecting moderate to severe pathogenic infestation levels. (Zhang et al., 2020, 409-414)

Muntz et al. describes another way instead of rotation, a lateral tension is applied to the eyelash (extraction of the eyelash), Which also causes the mites to be exposed to the eyelash follicle. Removal of the CD before the eye manipulation also showed a more significant number of mites and a more reliable result, as the tails of the mites do not mix with the CD. (Zhang et al., 2020, 409)

Depending on the study, the lash manipulation is performed in different ways, making comparisons difficult. Some pull the lash directly, rotating one or more times or pulling sideways to one side or not specified. (Bitton and Aumond, 2021b, 288)

## **2.5.3 In Vivo Confocal Microscopy (IVCM)**

The confocal microscopy principle was patented in 1957 by Marwin Minsky; It's a non-invasive imaging and diagnostic tool. IVCM is a possible morphological and quantitative analysis of ocular surface microstructure. (Messmer et al., 2006)

IVCM is better at detecting low levels of Demodex infestation than traditional epilation, combined with symptomatic patients related to MGD. (Ozcan et al., 2018, 40) Kojima et al. first proposed the use of IVCM for ocular Demodex infestations. Several other studies have also reported it as an effective and reliable method for detecting the mites around the eyelash line and in the Meibomian glands. (Zhang et al., 2020, 414)

IVCM also provides information that light microscopy cannot provide, such as evaluation of meibomian gland dysfunction, peri glandular inflammation, and conjunctival infiltrates. (Shah et al., 2022b, 936)

#### **2.5.4 Spontaneous Fluorescence**

This method is not used in research as a diagnostic method but is mentioned in one book. Demodex lights up in the dark. It is assumed that the reflection comes from external light sources of the chitinous exoskeleton because the direct microscope light is closed, and only immersion oil is used. (Ozcan et al., 2018, 41)

#### **2.6 Management of Demodex**

How many mites represent normal, and when is it a question of pathognomic overgrowth? What amount of mites causes symptoms? When to treat? The goal of the treatment is not to kill all mites but to reduce the number of mites on the eyelid and eyelashes. As the amount decreases, the risk of inflammation decreases. (Fromstein et al., 2018, 60)

The presence of cylindrical dandruff is almost pathognomic of Demodex. The connection between symptoms and signs is weak. One client may have a lot of cylindrical dandruff but no symptoms, and another may have no signs but lots of symptoms. Due to this, CD recording works more as a diagnostic technique than as successful management. Important with Demodex is long-term eyelid hygiene because Demodex is a chronic condition. ("Demodex Infestation - EyeWiki," n.d.)

The effectiveness of the treatment is usually measured on *D. folliculorum* because they are more easily accessible than *D. brevis* and are counted as a reduced number of mites or reduced survival time (lack of movements in the legs or mouth).



Autofluorescence of propidium iodide dye is reliable in assessing the point of death of the mite and is suitable for determining Demodectic activity. (Bitton and Aumond, 2021, 289)

Some agents have been found to kill Demodex within several minutes in vitro. Still, unfortunately, these agents cannot be applied for clinical use due to side effects such as eye irritation. Agents that destroy Demodex within several minutes are 100% alcohol, ether, xylol, benzene, Danish sulfur ointment, 100 % dill weed oil, and caraway oil. (Ozcan et al., 2018, 64)

Bitton and Aumond describe that a certain number of antiseptics can eradicate the mites in vitro. These agents are tea tree oil, caraway, dill, weed, salvia, peppermint oil, and pilocarpine gel. Camphor oil and linalool, the primary component of rosewood, have been shown to have a solid antimicrobial substance, including leishmanicidal effects. Linalool as a sole treatment method needs more investigation. (Bitton and Aumond, 2021, 289)

The treatment of Demodex depends on the severity of the condition. Treatment consists of different ways of cleaning the eyelids and eyelashes. Tea tree oil is the most effective and standard treatment for Demodex. Mild cases are treated at home with Tea tree shampoo and face wash once daily. (Figure 6) Moderate to severe patients use eyelid wipes at home twice daily, visit the clinic weekly, and are treated with highly concentrated tea tree oil for three weeks. Patients with severe symptoms can also be treated with BlephEX every 3-6 months, a handheld machine used in the office. BlephEX carefully removes scurf and debris and exfoliates eyelids. Patients can also consider changing makeup, using hot water when washing clothes, and drying bedclothes in a dryer. (Fromstein et al., 2018, 61-62)

In another survey, the effectiveness of different treatments was evaluated. Where it appeared that there were no differences if treated locally or systematically, neither with nor without cylindrical dandruff. As local treatments were used, TTO, T4O, Metronidazole ointment, and Pilocarpine gel, and as Systematic treatments, Ivermectin and Metronidazole were mentioned. There was also no significant influence of age or gender. The local treatments give less systematic side effects with promising molecules in treating Demodex blepharitis. (Navel et al., 2019, 656)

The survey showed that regular eyelid hygiene did not reduce the number of mites. The same study mentioned that more hypersensitivity reactions appeared with systemic treatments compared to local treatments. Mites were also found in healthy eyelids, which supports the idea that using toxic or very systematic treatment may be unnecessary. (Navel et al., 2019, 656)

Navel suggests, based on their investigation, that Demodex blepharitis is treated with antiparasitic local first-line treatment in the combination of TTO, T4O, or pilocarpine gel with regular eyelid hygiene once or twice daily for 1-3 months. (Navel et al., 2019, 661)

In the second line or severe cases, "systemic" treatment such as Ivermectin or Metronidazole can be added. It is not proven, but it is believed to reduce relapses. Severe cases include keratitis, corneal ulcers, severe itching with skin lesions, trichiasis, ectropion, or entropion with corneal lesions. (Navel et al., 2019, 661)

Rosacea can also be treated with a combination of both systematic and local treatments. (Navel et al., 2019, 661) Shah mentioned that oral Ivermectin and Metronidazole are classified as second-line treatments and are avoided due to an alarmingly high relapse rate and the risk of life-threatening side effects such as fatal encephalopathy. (Shah et al., 2022a, 937)

Martinez-Pulgarin mentioned in their systematic review and meta-analysis 2021 that systemic and topical Ivermectin + Metronidazole is the most effective in reducing the number of mites. They work well together due to the acaricidal effect of Ivermectin and the broad anti-inflammatory effect of Metronidazole. In the same study, it appeared that TTO, especially T4O, achieved a total eradication rate of 23,6-77,8% at different concentrations. They also mentioned that IPL could reach a 100% eradication rate. They question whether complete eradication is required for clinical improvement or only to reduce the number of mites. (Martínez-Pulgarín et al., 2021, 5)

Savla mentions a study where intense pulsed light treatment effectively alleviates signs of D. blepharitis. (Savla et al., 2020, 26) New substances, Manuka honey from New Zealand, show comparable effects with 50% TTO to reduce Demodex in vitro, which is not commercialized yet. Other new substances with antimicrobial properties are hypochlorous acid and a polysaccharide, *Abelmoschus esculentus*, but their Demodectic properties have not yet been demonstrated. (Bitton and Aumond, 2021, 289) Research on selenium sulfide is limited but is cited as a potential agent for killing Demodex mites. The biggest in the care of Demodex may be forthcoming.

There have been no FDA-approved therapies for D. blepharitis, but now an antiparasitic agent, TP-03, is currently in phase 2b/3 clinical trials. If it were to be approved, it would be the first approved standard of care for treating D. blepharitis. The drug has shown promising results so far. (Shah et al., 2022a, 937-938)

Bitton and Aumond propose a validated scale of mite counts or indices to determine treatment initiation and infestation levels. D. folliculorum is more accessible; therefore, the effect of the treatment is measured solely on it. The effectiveness of the treatment is calculated as a reduced number of mites or reduced survival time. (Bitton and Aumond, 2021b, 289)

### **2.6.1 Lid Hygiene**

Lid hygiene is suitable for all eyelid pathologies and healthy eyelids for preventive purposes. There are various cleaning agents, wipes, gels, oils, and traditional baby shampoo for standard lid hygiene. Routine eyelid hygiene has shown some effect on the Demodex count. However, eyelid hygiene alone is not enough in more severe conditions of Demodex. Everyday eyelid hygiene reinforces and complements other treatments. (Ozcan et al., 2018, 48)

There is a Vitro study where it was confirmed that 50 % of baby shampoo could not kill Demodex in 150 minutes and also shows poor results in reducing mites. It has been published that baby shampoo should not be used for eyelid hygiene because it is ineffective and can harm the tear film because of the adverse effect on goblet cell function. (Fromstein et al., 2018, 61)

Zhang et al. reported on 15 studies that concluded that regular eyelid hygiene did not reduce mite counts. (Zhang et al., 2020, 422)

Bitton and Aumond recommend cleansing the face morning and evening, avoiding oil-based cleansers and oily makeup. Exfoliation of the skin to remove dead cells is also recommended. It is advisable to use creams/ moisturizers because they can act as a lipid nutritional supplement for the mites. (Bitton and Aumond, 2021a)

Should one refrain from lipid-based eye drops during the Demodex attack, we know that Demodex survival time is extended by, e.g., mineral oil, which is a component of several artificial tears and ointments. More research is needed to confirm this claim. (Bitton and Aumond, 2021a)

## 2.6.2 Tea Tree Oil

Tea tree oil also goes by the name melaleuca oil. The use of oil was already started in the 1920s by the entrepreneur Arthur Penfold. Tea tree oil is a pale yellow to almost colorless and transparent oil. It is an essential oil with a camphorous scent, comes from Australia, and contains many chemicals that change if exposed to air and oxidize. (Savla et al., 2020, 9)

TTO contains 15 known ingredients, and T4O is the main component. TTO is never prescribed orally; it is poisonous if ingested. (Savla et al., 2020, 9) T4O is a primary constituent of tea tree oil. It is extracted from the leaves, branches, and bark of *Melaleuca alternifolia* cheel, and its chemical formula is  $C_{10}H_{18}O$ . T4O's treatment is based on its acetylcholinesterase inhibitory effect. (Fromstein et al., 2018, 61)

There is a large selection of different tea tree products, of which wipes are mainly used for home care; there are also various soaps and shampoos. (Figure 6). Applying tea tree oil to the edge of the eyelid will make the mites disappear from the follicle, leaving them no time to reproduce, and reducing the number of mites. (Fromstein et al., 2018, 61) T4O is the most active ingredient in TTO, with a 30-48% concentration. (Navel et al., 2019, 660) T4O has been shown to reduce mites over four weeks if the concentration is 38%. (Fromstein et al., 2018, 61)

The side effects when using TTO or T4O are rare and never systematic. There may be eye irritation, eyelid redness, skin rash, itching, or burning sensation. However, it's not found that a drug with TTO or T4O would have marketing authorization for doctors. (Navel et al., 2019, 661)

The weaker the tea tree oil, the more often you must treat it. Studies show that 5% tea tree oil applied twice daily or as high as 50% tea tree oil applied weekly to the lid and base of the eyelash follicles effectively reduces mite infestation. High concentrations of tea tree oil, such as 50%, should be treated in the clinic. Tea tree oil can cause dermatitis, allergy, and eye irritation in patients with skin sensitivity. (Fromstein et al., 2018, 61)

Treatments aim to get the mites to emigrate from the lash follicle so they cannot lay eggs and hatch more Demodex mites. But in addition to the eyelashes' roots and the eyelid's edge, patients should be instructed to brush their forehead, eyebrows, and cheeks because the mites also live in those areas. (Fromstein et al., 2018, 61)

Many tea tree oil products are diluted with macadamia- or walnut oil, which should be considered if the patient has a nut allergy. The mites resist some antiseptics, such as 75% alcohol, 10% povidone-iodine, and erythromycin. It is also mentioned in studies that hypochlorous acid, active against bacterial fungi and viral pathogens, has shown a reduction in mites. (Fromstein et al., 2018, 61) However, an investigation emerged in which the security was deficient, where the TTO effect on D. blepharitis was investigated. The survey found uncertainty related to the current use of TTO, and it was unclear whether TTO can alleviate the eye symptoms associated with D. blepharitis. However, all the reviews they found showed that TTO is an effective way to treat D. blepharitis (Savla et al., 2020, 25)

Luigi's article found that a 0,5% solution of T4O in vitro had an adequate anti-Demodex effect. An in vivo study was also discussed where a 7.5% TTO eyelash shampoo reduced Demodex mites by 36%. (Capasso et al., 2022)

Messaoud et al. compared once daily versus two times daily application of Blephademodex containing 2,5% T4O and hyaluronic acid. Messaoud described an improvement in symptoms and a reduction of CD in both treatment groups. (Zhang et al., 2020, 423)

Bitton and Aumond describe combining treatments in the clinic and at home to reduce mites and eye symptoms effectively. 50% TTO in the office, daily eye wipes with TTO at home, and BlephEX. (Bitton and Aumond, 2021, 289)



Figure 6. Tea Tree products. Picture Ann-Caroline Sinisalo

### 2.6.3 Manuka Honey

Manuka honey comes from New Zealand. It is a monofloral honey that is used in alternative medicine. (Figure 7) It is considered to have healing properties and is said to help with wounds, indigestion, fever, and back pain. Some scientific studies have investigated its antiseptic and anti-inflammatory effects in wound healing. It has also been suggested that honey can act as an antibiotic. (“Manukahonung,” 2020)

Manuka honey has a high concentration of methylglyoxal, complexed with  $\alpha$ -cyclodextrin. The honey has shown an antibacterial and antidemodetic effect with total eradication rates of up to 60%. It is evaluated by Craig et al. (Martínez-Pulgarín et al., 2021, 6)



Figure 7. Manuka honey Picture Ann-Caroline Sinisalo

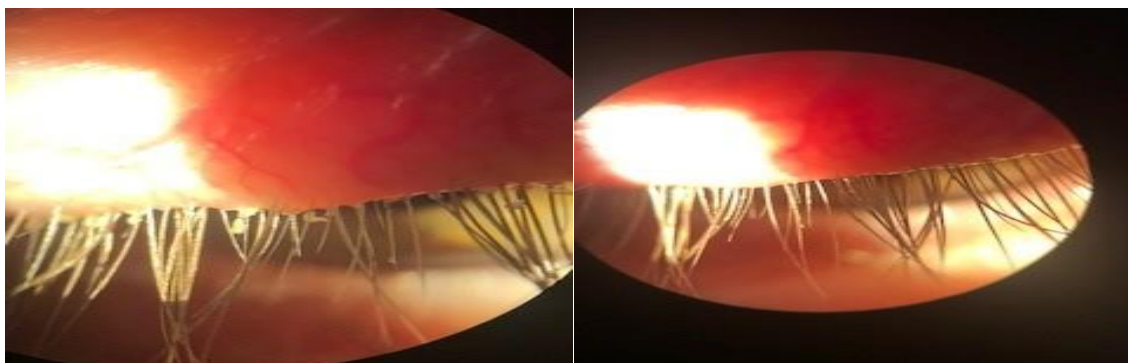
#### 2.6.4 Lid Scrubbing; BlephEX

The eyelids and the root of the eyelashes are difficult to clean. Where overgrowth of bacteria, biofilm, screws, and debris can accumulate for many years, the exothix-induced inflammation can cause damage to the eyelid and lacrimal glands. ("Blephex - BlephEx Page," n.d.)

With BlephEX, you can clean and exfoliate eyelids and lashes. You can also remove the exothixin-laden biofilm along the margin of the lid, which helps you avoid long-term inflammatory damage to the lacrimal glands. (Figure 8) ("Blephex - BlephEx Page," n.d.)

Furthermore, BlephEX works positively on Demodex, and BlephEX removes cylindrical dandruff. In addition, it helps to remove the mite eggs at the base of the eyelash follicle. (Fromstein et al., 2018, 62)

Depending on the source, treatments are given every 3-6 months. With regular eyelid hygiene, you can try to increase the time between treatments. ("BlephEx™ Eyelid Treatment | Dry Eye Treatment Long Beach CA," n.d.)



*Figure 8. Right eyelid before and after Blephex treatment. Picture Ann-Caroline Sinisalo*

### **2.6.5 Intense Pulsed Light ( IPL )**

The first report that IPL used in ophthalmology is from 2002, Where (Toyos et al.) improvements were observed in MGD patients. IPL is a handheld machine with intense pulsed light and a high-tensive light source without a laser. It works with a flash lamp and produces a long-wavelength incoherent light output. The device uses electromagnetic waves that expand the capillaries, resulting in the cessation of inflammation. (Toyos et al., 2015, 42)

The Demodex's pigmented exoskeleton consists of a chromophore that absorbs IPL energy. IPL treatment helps eradicate the mites by inducing coagulation and causing local tissue death of Demodex. The IPL treatments were well tolerated in the Wladis study, and there were no local or systematic side effects. Several studies have shown that IPL helps open the blocked meibomian glands. (Wladis et al., 2020, 1228)

A study shows that IPL with three given treatments (baseline, at three months, and six months already had an eradication rate of 55% at one month. It is still unclear what causes it. There is speculation that the energy delivered during IPL and/or the heat may raise the temperature to critical levels to exterminate them. (Bitton and Aumond, 2021, 289)

Demodex mite's optimal temperature is 16-20 degrees because 54 degrees is fatal to the mite. There is a possibility that the heat generated from IPL pulses can kill the mites directly. (Zhang et al., 2020, 424)



Bitton and Aumond write that 49 degrees give in vitro a complete immobilization of the mite within 25 seconds with IPL, which arouses interest in clinical examination. (Bitton and Aumond, 2021, 290)

### **2.6.6 Permethrin**

Permethrin is a chemical substance used as an acaricide and insecticide. The product is used in creams and shampoos under the name nix. Permethrin is used to treat scabies and for a variety of other purposes. The substance harms cats and fish and should not be used on pregnant or breastfeeding women. ("Vad är permetrin?," n.d.)

Permethrin disrupts the nerve membrane channels in arthropods and destroys the mite. One study showed its effect on chronic blepharitis and Demodex; it reduces facial Demodex in papulopustular rosacea. (Zhang et al., 2020, 423)

Hecht et al. proved that daily use of 5% permethrin cream on the eyelids for six months reduced blepharitis symptoms and Demodex mite counts. (Zhang et al., 2020, 423)

### **2.6.7 Pilocarpine**

It is a parasympathomimetic. Pilocarpine is a well-known drug for treating glaucoma and dry mouth. Pilocarpine has an opening effect on the chamber angle, so it is used in acute narrow-angle glaucoma. In the eye pilocarpine causes miosis. As a side effect, Pilocarpine can cause an acceleration of glandular activity, bowel function disorders, and a drop in blood pressure. ("Pilokarpiini – Wikipedia," n.d.)

Pilocarpine in gel form has shown exciting results. The gel paralyzes the mite's breathing and mobility with its antiparasitic effect. Pilocarpine also has a deadly effect, and the side effects are rare. The side effects of Pilocarpine are never systematic. There may be eye irritation, eyelid redness, skin rash, itching, or burning sensation. (Navel et al., 2019, 660)

### **2.6.8 Ivermectin**

Ivermectin is an orally administered antiparasitic drug known for its antiparasitic effect through a selective activity against glutamate-gated chloride ion channels of the peripheral nervous system of invertebrates. Ivermectin belongs to anthelmintic medications. Used empirically to treat Demodex blepharitis as an off-label medicinal prescription outside marketing permit. (Navel et al., 2019, 660)

Oral Ivermectin is effective in reducing Demodex infestation but combining Ivermectin with Metronidazole was found to be even more effective in reducing the number of mites *D. folliculorum*, and this gives hope for future therapeutic options for very vulnerable clients. (Martínez-Pulgarín et al., 2021, 5-6)

Ivermectin can cause side effects such as fever, headache, flu-like- and skin symptoms. ("Ivermektiini," 2022) In one study, systemic Ivermectin 0,2 mg per kg body weight is recommended in a single dose, and in another study, 6mg twice daily for one day, repeated after 14 days. (Ozcan et al., 2018, 47)

### **2.6.9 Metronidazole**

It is an antibiotic that is effective against anaerobic bacteria and other microorganisms. Alcohol should be avoided while taking Metronidazole. ("Metronidazol Actavis - FASS Allmänhet," n.d.) It is used orally in infections and infestations related to anaerobic bacteria trichomonas and amoebas. It is indicated topically in inflammatory forms of rosacea. (Ozcan et al., 2018, 47)

The effect of Metronidazole on Demodex is unknown. (Navel et al., 2019, 660) Demodex has survived metronidazole concentrations (1mg/ml) in vitro, which strengthens the idea that the effect of oral Metronidazole in eradicating Demodex is not that strong. But there is evidence from 2007 that topical Metronidazole 2% has been shown to reduce the number of Demodex mites. (Ozcan et al., 2018, 47-51)

### **2.6.10 TP-03**

TP-03 is not on the market yet, but Tarsus is creating TP-03, which may become the first FDA-approved therapy for Demodex blepharitis. If TP-03 is approved, it will be a topical ophthalmic lotilaner, a well-characterized antiparasitic agent that targets parasite-specific Gaba-C1 channels. ("TP-03," n.d.)

To date, no serious treatment-related side effects have occurred, and it has generally been safe and well tolerated in all 833 patients involved. ("TP-03," n.d.)

### **3 THE PURPOSE, OBJECTIVES, AND TASKS OF THE RESEARCH DEVELOPMENT WORK AND THE DIFFERENT STAGES**

#### **3.1 Purpose of the Study Statement**

The purpose of this master thesis was to study Demodex via a case study. The aim was to determine the need to treat a symptom-free client with signs of cylindrical dandruff associated with Demodex blepharitis.

#### **3.2 Statement of the Research Question**

Should Demodex blepharitis be treated when the patient has only cylindrical dandruff signs but no symptoms?

#### **3.3 Summary Description of the Experimental Design**

This single case study report involved the clinical assessment and management of a 57-years old Finnish male who went to a privately owned optical shop for an eye examination. The survey was based on different treatment methods and their impact on Demodex, consisting of six return visits. The survey was done from 21.07.22-14.10.22, and the research method was qualitative. This project was done for AC optik, and the researcher collected all data on-site while the patient was being seen in the clinic. Therefore, a separate IRB approval was not needed.

#### **3.4 Study Objectives**

##### **3.4.1 Study Objective 1**

To carry out a comprehensive literature review of Demodex mites focusing on asymptomatic Demodex blepharitis with signs of cylindrical dandruff. It was based on basic information, assessment, and management of Demodex.

### 3.4.2 Study Objective 2

To perform a single case study example of asymptomatic Demodex blepharitis with signs of cylindrical dandruff.

## 3.5 Methodology

### 3.5.1 Literature Search

The literature search was based on existing evidence of Demodex blepharitis and, at a later stage, specifically on asymptomatic Demodex blepharitis and signs such as CD and its current shortcomings. PubMed, google scholar, optical branch books, and optical www-sides were used as a database. The studies that were searched via PubMed had a time interval of five years and consisted of article types, meta-analyses, systemic reviews, and reviews. The search terms that were used were Demodex blepharitis and blepharitis. There were 15 surveys with these keywords, four off-topic, and two lost due to the French and Spanish languages. Nine surveys in English are included in the literature review. The surveys were collected in April 2022.

**Inclusion criteria:** Demodex and blepharitis

**Exclusion criteria:** Demodex and skin problems and PubMed surveys in languages other than English

### 3.5.2 Case Study

The case study was done in a privately owned optician shop, AC optik, in Lovisa, Finland. The client came for a routine eye examination and the purchase of new glasses. The eye examination used Rodenstock DNeyscanner, Nidek auto refractometer, and automatic phoropter. The base curve of the cornea, tear meniscus, NIKBUT, and redness of the eyes were measured with the Oculus Keratograph. Cornea staining was measured with fluorescein and photography with Keratograph. The eye pressure was measured with iCare, and finally, the eyes were microscopy with a Haag-Streit microscope.

## 4 IMPLEMENTATION OF THE RESEARCH DEVELOPMENT WORK

### 4.1 Case Study

The case study presents a man born in 1965 who spontaneously came for an eye examination, and because of his CD in the eyelashes but no symptoms, he became the Case study client.

#### 4.1.1 Assessment

The client's previous glasses were purchased in February 2019. He came for an eye exam because the glasses had broken and were temporarily glued, and in the anamnesis appeared that he uses prostate medicine and takes allergy medication all year round due to pollen. He had no ocular symptoms. He had no extraordinary ocular history other than wearing glasses since he was young. He had been to an optometrist in 2020 to find out if he could do possible progressive lens surgery; that was his last eye exam. He has never been to an ophthalmologist. Current to the general health history appeared only prostate problems and allergies. He is not atopic but suffers from dry skin. In the family history, occurs no ocular diseases. !

The first examination was made on July 21, 2022. His free visual acuity was 0,3 / 0,2-. Corrected visual acuity with power -1,50 -0,75 ax 95 / -2,00 -0,75 ax 70 was 1,0 in both eyes. The cover test showed ortho far and near. Pupil size in normal light was 2,9 / 2,9 mm and 5,6 / 4,7 mm in the dark, and both reacted to light. The right eye is dominant. Worth testing standard four signs, far esophoria 0,5 PRD, and near four PRD exophoria. Amsler is negative in both eyes.

In the ocular health, examination appeared that the upper eyelashes had cylindrical dandruff and also in the lower lash line. The right eye had more CD. (Figure 16). The eyelids were curved, with remaining meibomian glands above and below. The lower meibomian glands were packed and short. The meibomian glands were crooked at the upper lid and sealed at the lower eyelid. (Figure 14). Conjunctiva Eye redness is comparable in both eyes, green in the measurement and slightly redder temporally. (Figure 12). The cornea had no staining (Figure 15), and the base curve (BC.) was close to the average of 7,8 (Figure 9). The central thickness of the cornea was 487/488 thinner than the average 545. The tear meniscus is lower in the right eye than in the left. (Figure 10)

NIK BUT was green in both eyes. The right eye breaks up for the first time at 12,49 and has a total breakup time of 20,78. Left breaks up at 16,25 and has a full breakup time of 16,25. Neither eye counts as dry. (Figure 11). The anterior chamber was open in both eyes. Iris was green and brown (Figure 12.) The lens was still evident.

Ophthalmoscopy was done superficially because we concentrated on the external factors of the eye and its signs. The patient thought he had been to an ophthalmologist in 2020, but the patient's journal showed that he had been to an optometrist.

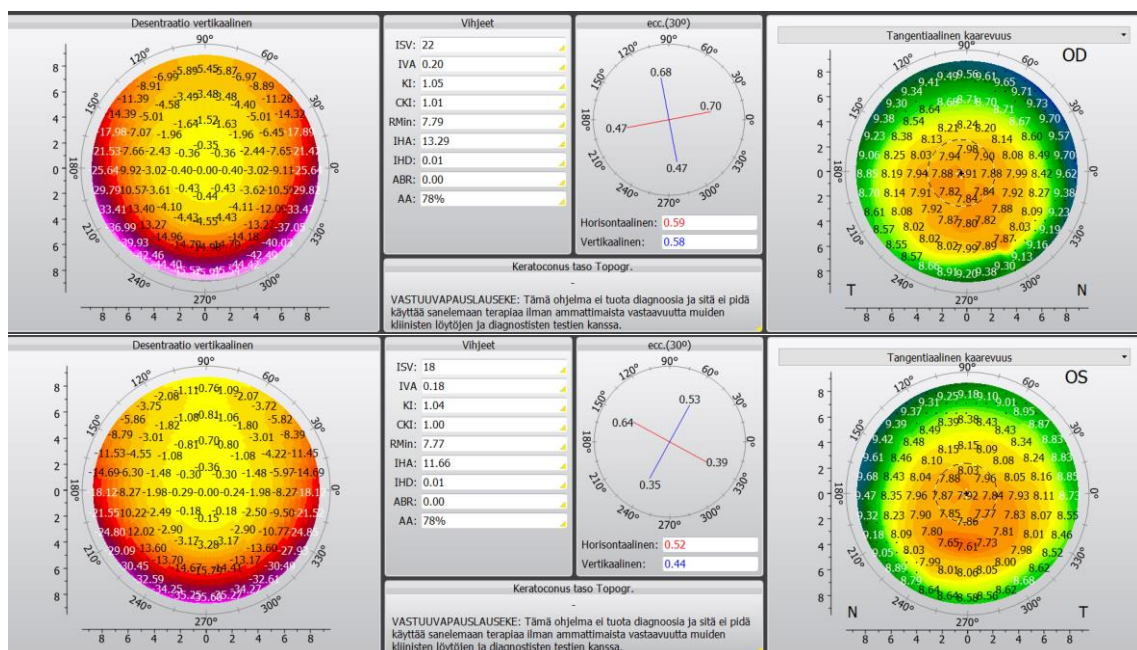
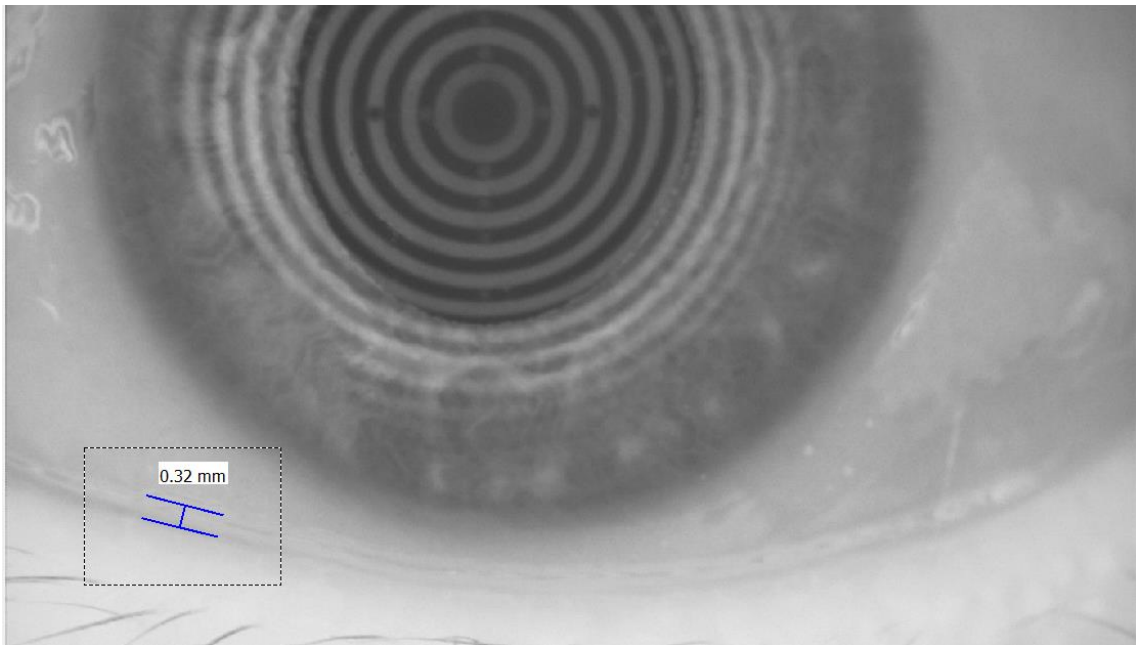
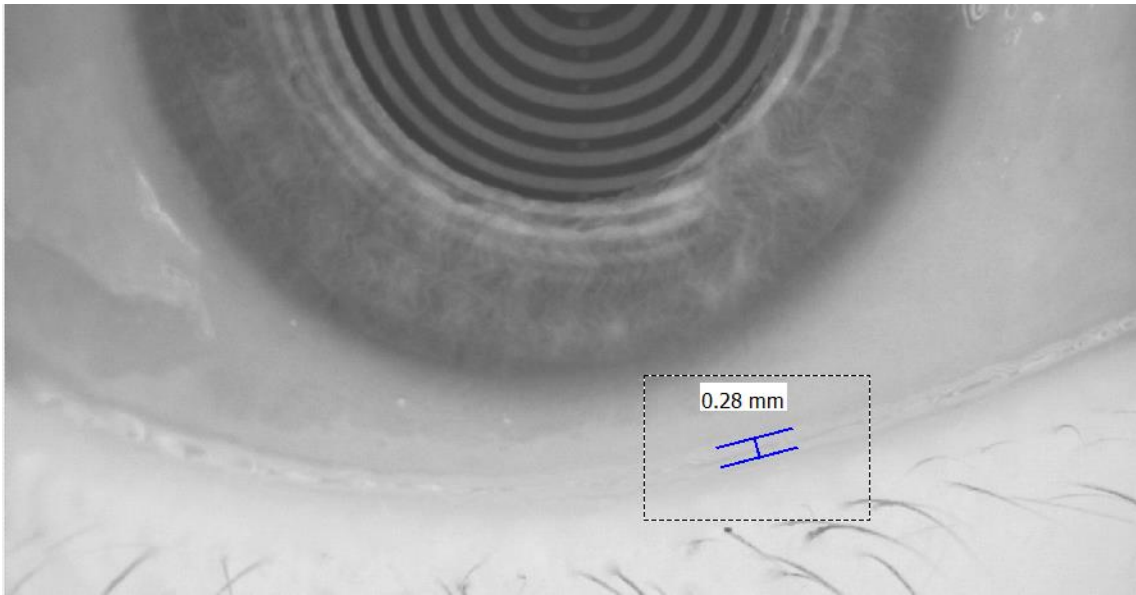
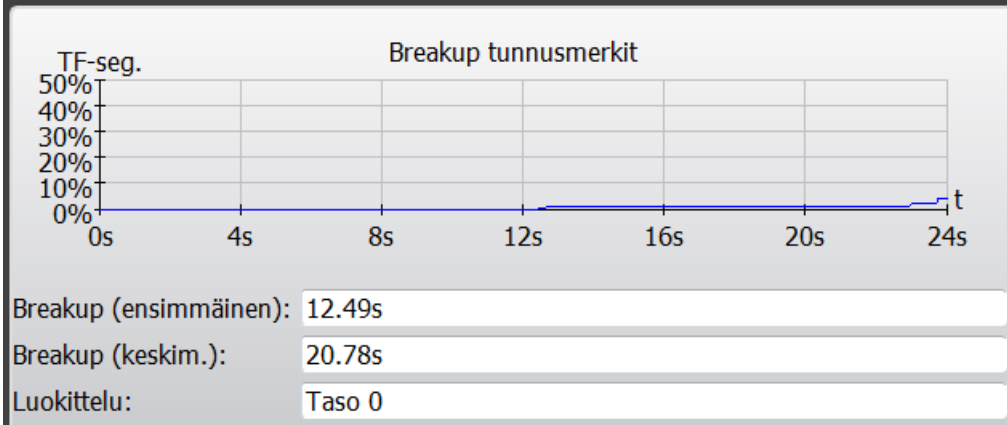
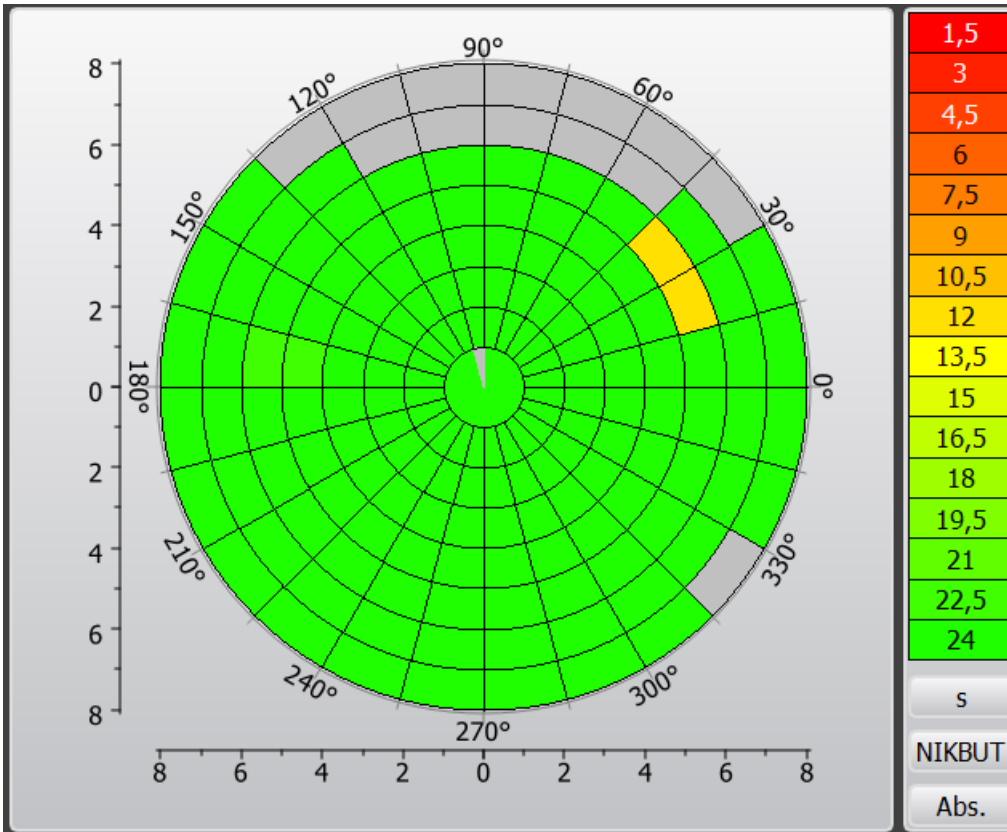


Figure 9. Topography of the right and left eye. Picture Ann-Caroline Sinisalo



*Figure 10. Tear meniscus in the right and left eye. Picture Ann-Caroline Sinisalo*





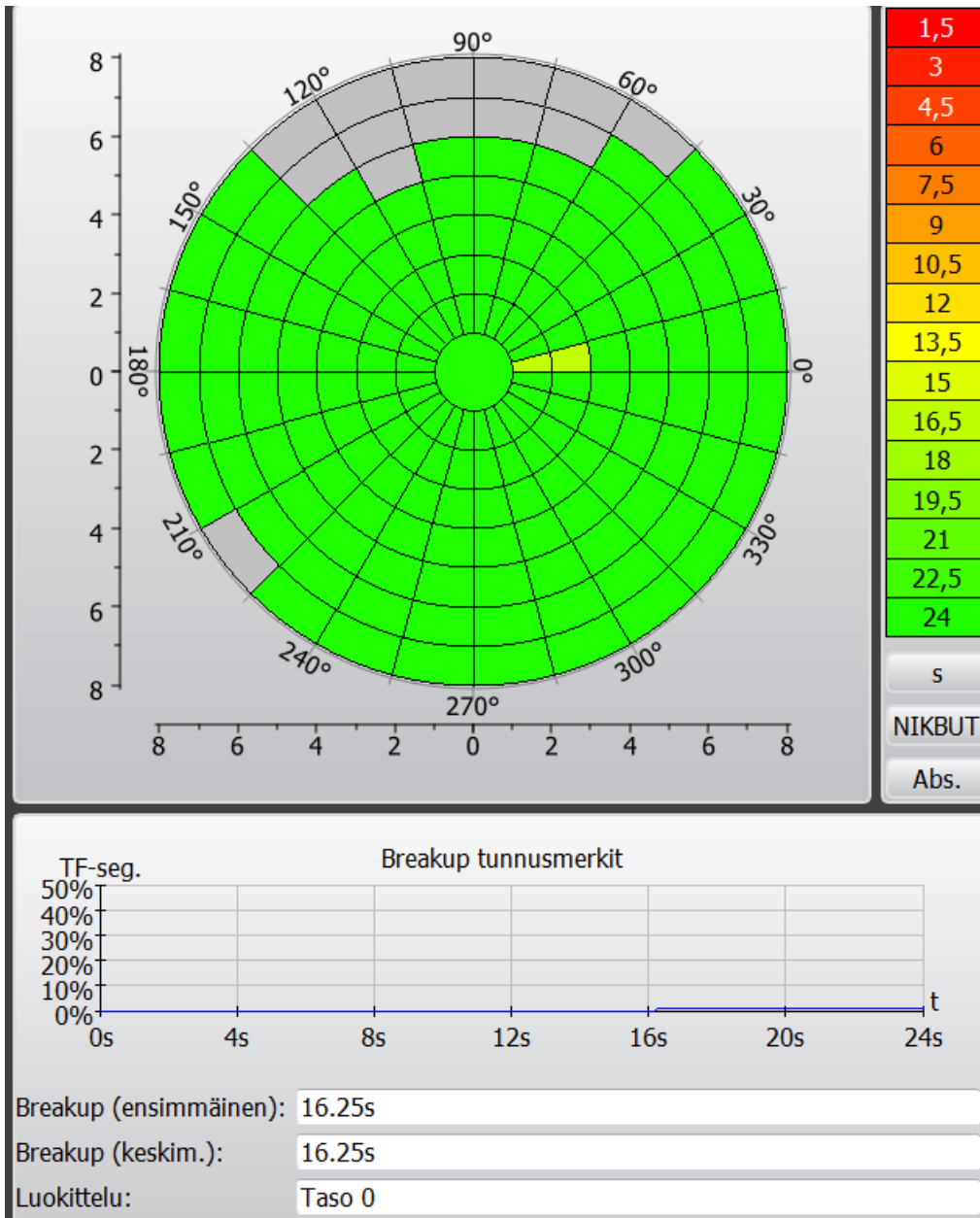


Figure 11. NIKBUT in the right and left eye. Picture Ann-Caroline Sinisalo

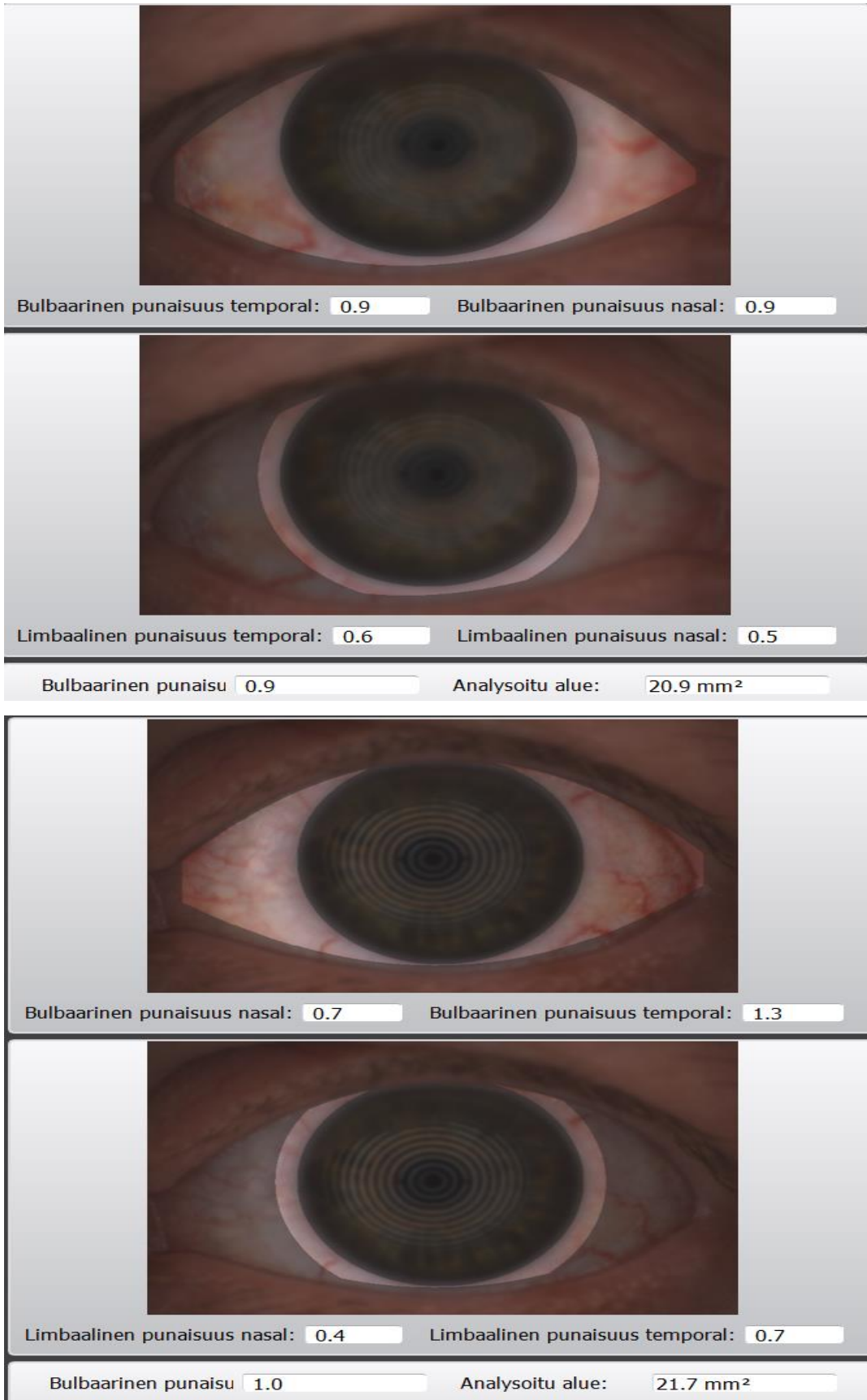






Figure 12. Redness in the right and left eye. Picture Ann-Caroline Sinisalo

| OD | Tutkimuksen luol  | Tutkimuksen tyyppi     | Tutkimuksen luokitus        | Tutkimuksen päivämä |          |
|----|---|------------------------|-----------------------------|---------------------|----------|
| 1  |  | Kyynelmeniskin korkeus | Normaali (0,2 - 0,35 mm)    | 16.9.2022 15.34     | ... Avaa |
| 2  |  | NIK BUT                | Normaali ( 11-15 sekuntia ) | 16.9.2022 15.36     | ... Avaa |
| 3  |  | Punaisuus              | Normaali                    | 16.9.2022 15.34     | ... Avaa |
| 4  |  | DEQ OSDI               | ei saatavana                |                     | ... Uusi |





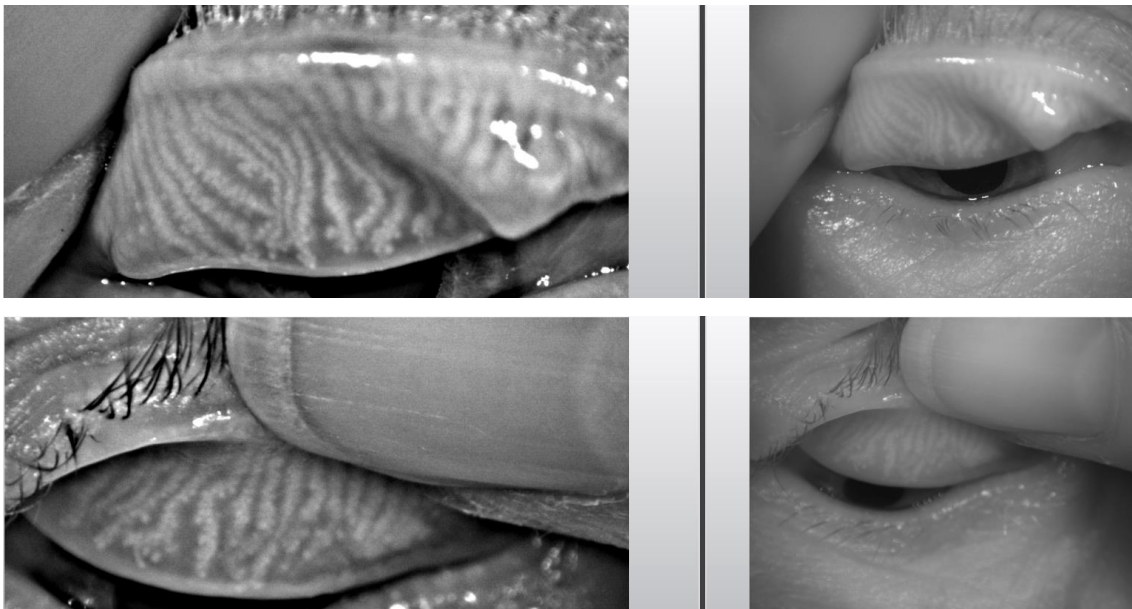
| OS | Tutkimuksen luol  | Tutkimuksen tyyppi     | Tutkimuksen luokitus                | Tutkimuksen päivämä |          |
|----|---|------------------------|-------------------------------------|---------------------|----------|
| 1  |  | Kyynelmeniskin korkeus | Normaali (0,2 - 0,35 mm)            | 16.9.2022 15.35     | ... Avaa |
| 2  |  | NIK BUT                | Keskiarvon yläpuolella ( yli 15 ... | 16.9.2022 15.37     | ... Avaa |
| 3  |  | Punaisuus              | Normaali                            | 16.9.2022 15.35     | ... Avaa |
| 4  |  | DEQ OSDI               | ei saatavana                        |                     | ... Uusi |

Figure 13. Summary of the right and left eye. Picture Ann-Caroline Sinisalo



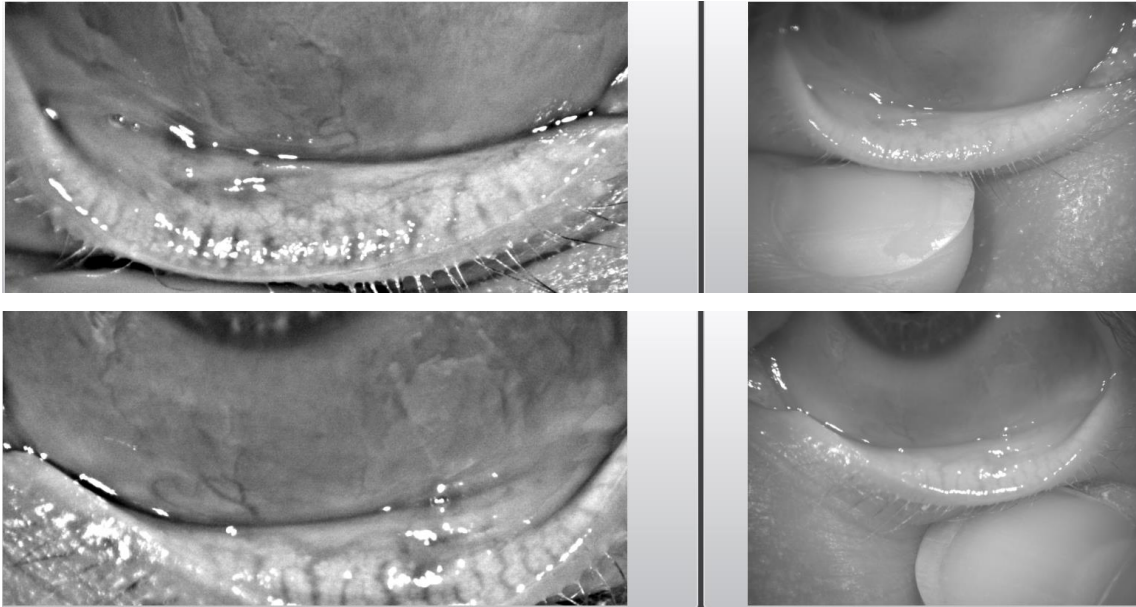
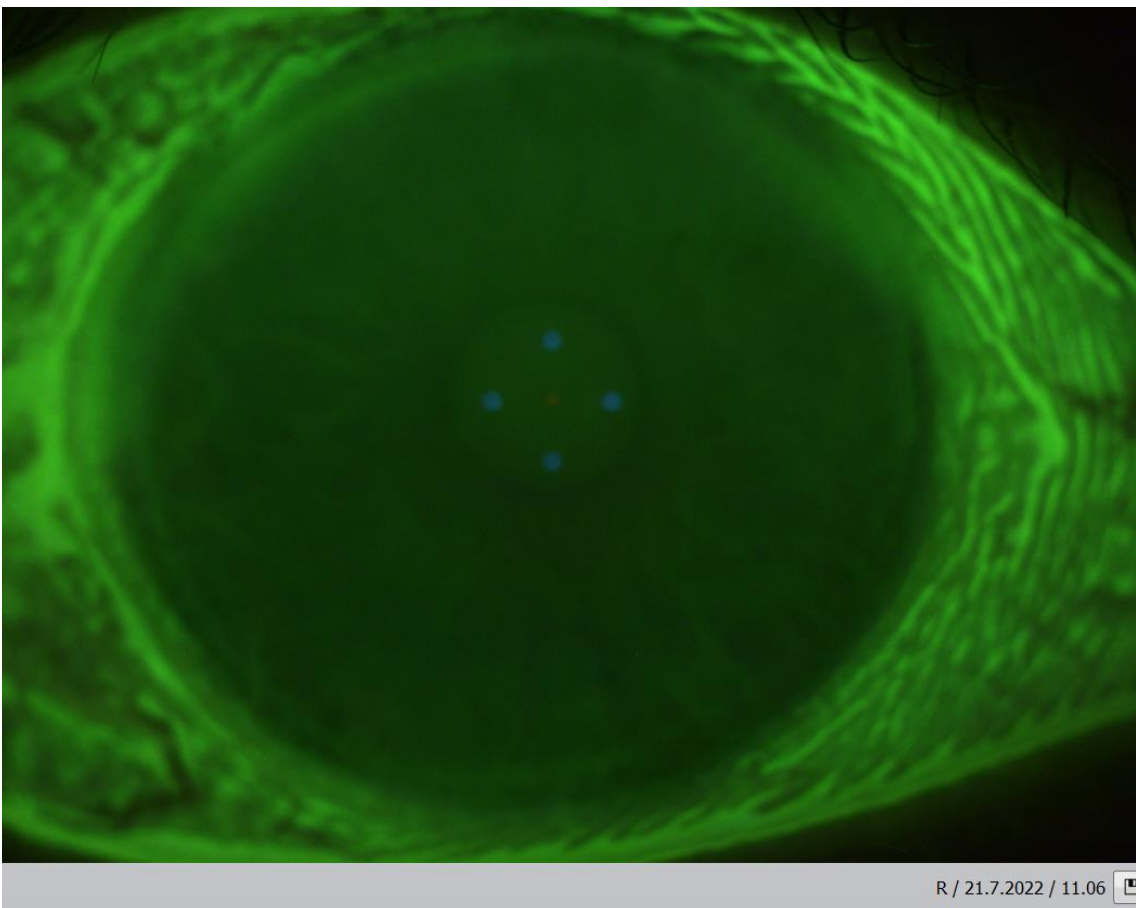


Figure 14. Meibo analyses in the right and left eye. Picture Ann-Caroline Sinisalo



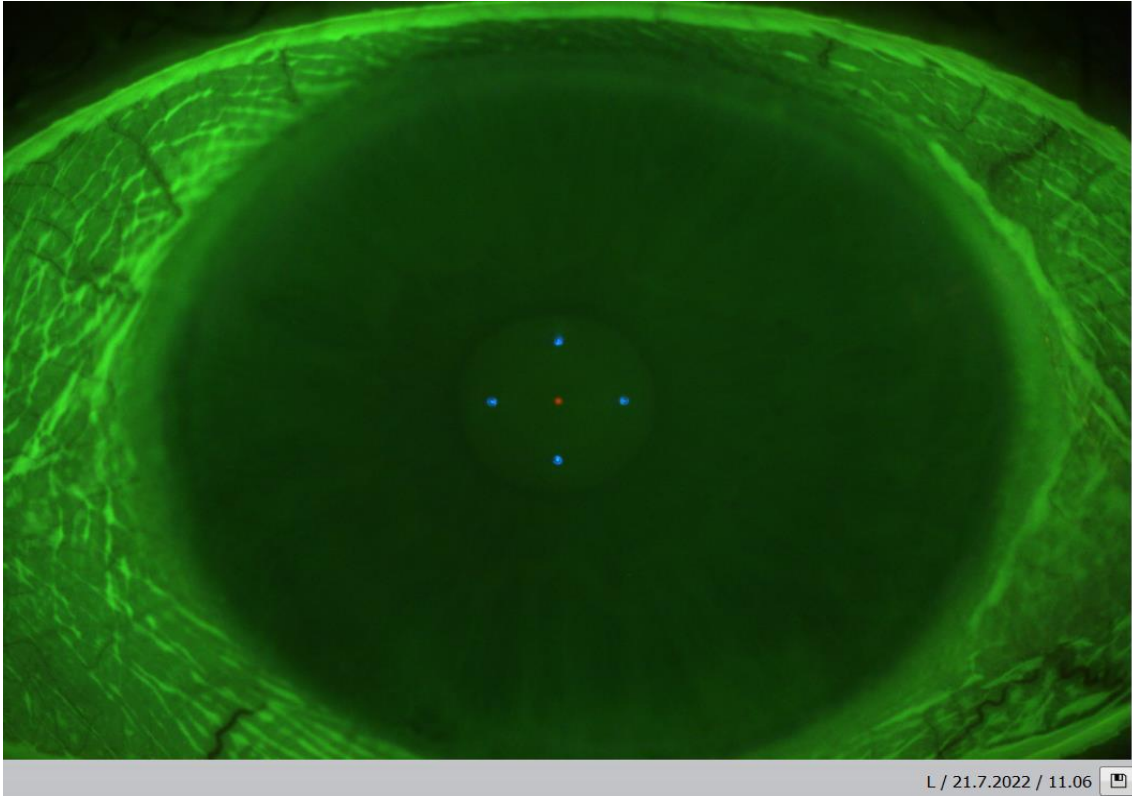


Figure 15. Cornea staining on the right and left eye. Picture Ann-Caroline Sinisalo

#### 4.1.2 Management

Since the client had no eye symptoms, he started with Blephasol duo cleaning (regular lid cleansing) of the eyelids morning and evening to see if the CD had disappeared and if he felt any difference. The treatment was planned from the mildest to increasing or changing the treatment method if the current process did not work.

#### 4.1.3 Differential Diagnosis

At the first visit, a broad eye examination was performed with various tests. Various tests and possible symptoms that can be differential diagnoses are presented here.

#### Anterior segment inflammation

- Dry eye syndrome
- Trichiasis = the eyelashes are directed posteriorly toward the globe
- Conjunctivitis / Pink eye = inflammation of the conjunctival tissue
- Keratitis = inflammation of the cornea
- Keratoconjunctivitis = inflammation of cornea and conjunctiva at the same time
- Phthiriasis = ectoparasitosis of the eyelashes

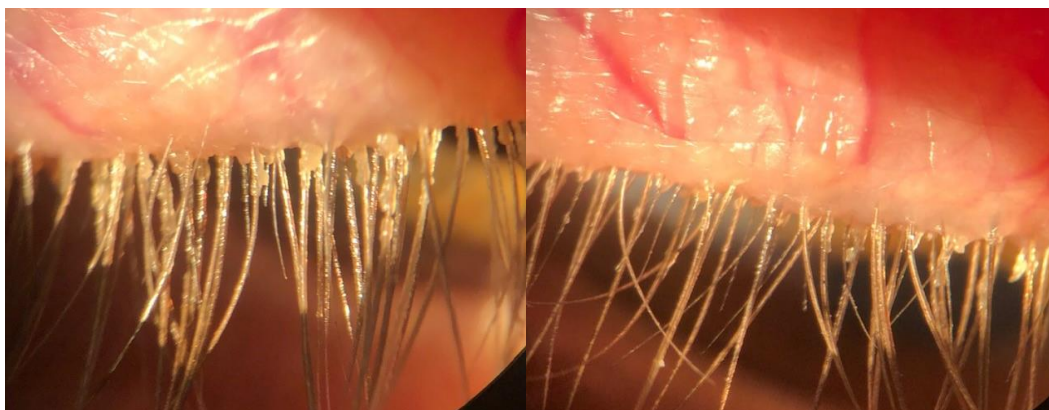
("Demodex Infestation - EyeWiki," n.d.)

Differential diagnoses are excluded due to signs of cylindrical dandruff, which indicates that it is a question of Demodex intervention. In the examination, the eyelashes are directed in the right direction. No inflammation of the conjunctiva or cornea appears. In the microscopic examination, phthiriasis cannot be seen.

#### 4.1.4 Referral

There was no reason to send the client to an ophthalmologist because of the Demodex. The situation is stable, and there is no suspicion, such as on the cornea, conjunctiva, etc., that would require medical attention. He should, in general, go to an ophthalmologist because he has never been, he is over 50 years old, and the cornea is thinner than the average, which gives +4/+4, contributing to the eye pressure being on the limit. 19 +4 / 18+4. He was referred for a BlephEX treatment because the CD didn't go away with the Blephademodex treatment.

#### *Starting position*



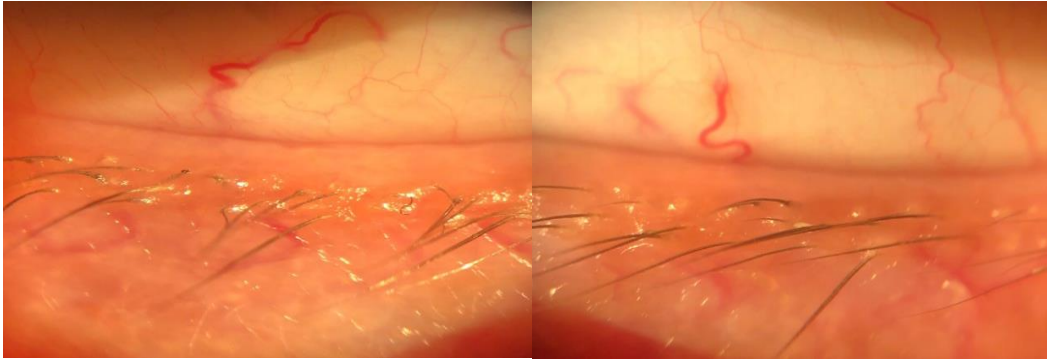


Figure 16. 21.07.2022 Starting position. Picture Ann-Caroline Sinisalo

*Follow-up visit 1*

The client returned on 28.07.22 after one week of using the Blephasol duo in the morning and evening. He found the Blephasol duo cloth easy to use but left a sticky surface. He experienced no difference in the sensation in his eyes. In theory, it appeared that regular lid hygiene does not kill the Demodex mites, and based on that, a week's treatment of regular lid hygiene was tried. On examination after one week, upper and lower eyelids appeared cleaner, but CD was still present. There was a slight reduction in CD. (Figure 17)

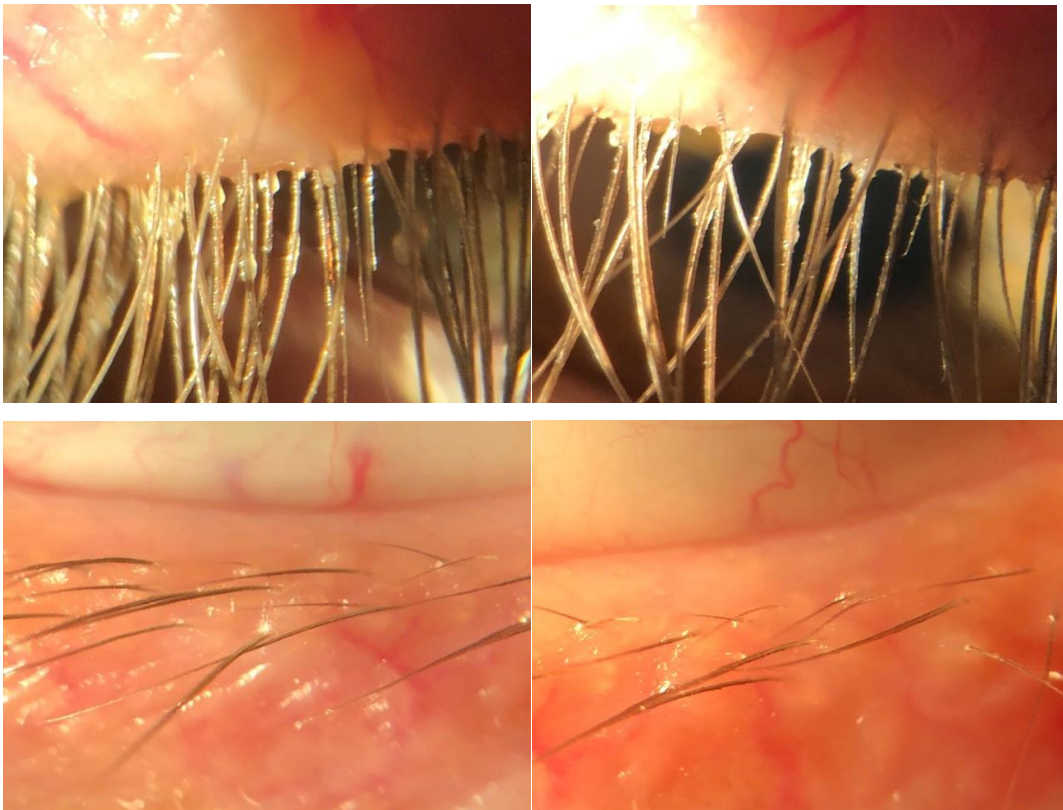


Figure 17. 28.07.2022 First return visit. Picture Ann-Caroline Sinisalo

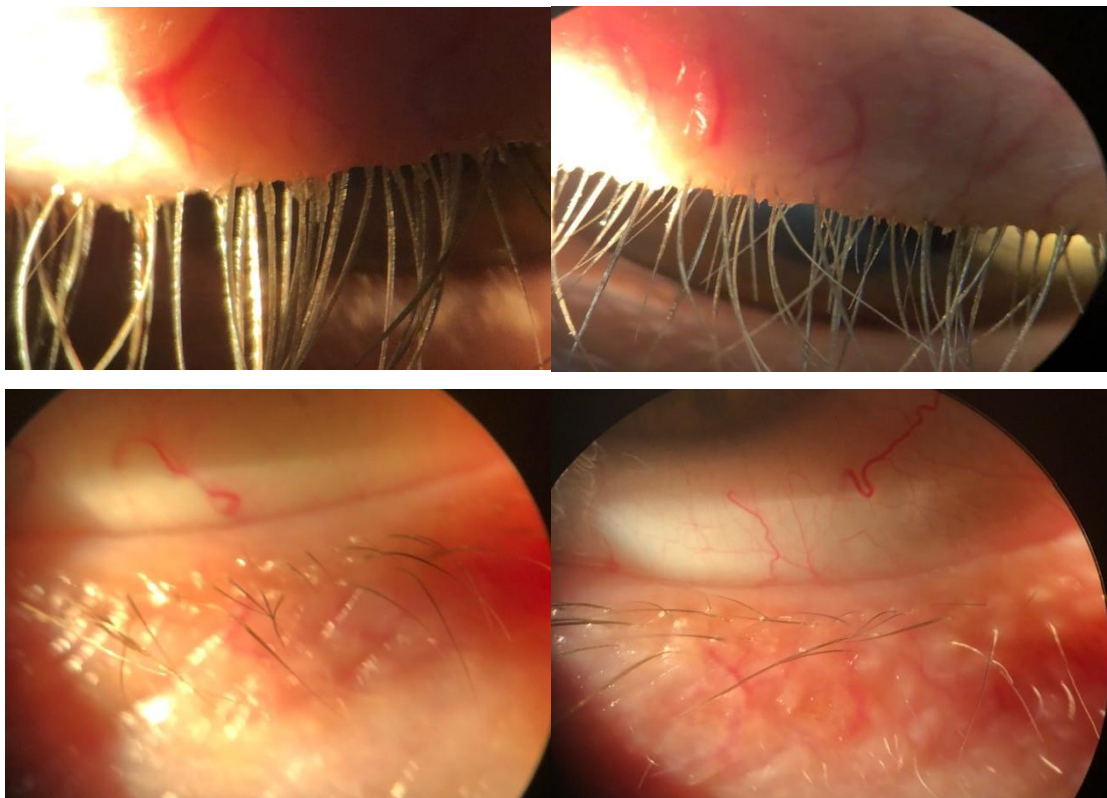


After the first return visit, the change was so small that a change to using Tea tree oil products was made. The client continued to use Blephasol duo morning and evening for regular eyelid hygiene and added Blephademodex only in the evening because the client was still asymptomatic.

*Follow-up visit 2*

After two weeks of regular lid hygiene and adding tea tree oil in the evening, a more significant reduction of CD was seen. (Figure 18) The addition of Tea tree oil caused the left eye to run for a couple of days, and he experienced a momentary stinging in both eyes. In addition to this, no altered sensation in the eyes.

According to the theory, two life cycles of Demodex should be killed, so the treatment continued the same way—Blephasol duo morning and evening and Blephademodex in the evening.



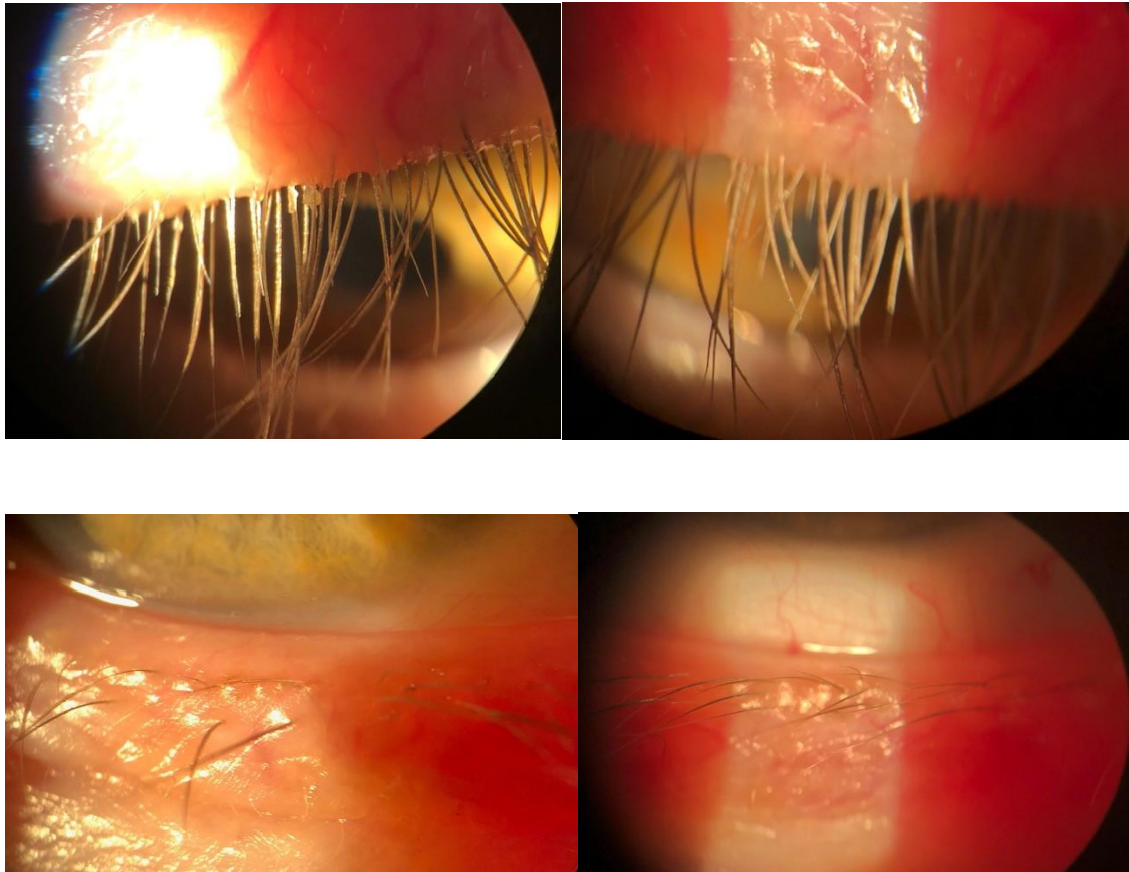
*Figure 18. 05.08.2022 Second return visit. Picture Ann-Caroline Sinisalo*

### *Follow-up visit 3*

On the third return visit, a significant change was seen after four weeks of using Blephasol duo (regular lid hygiene) in the morning and evening and Blephademodex in the evening. Almost all of the CD was gone. (Figure 19) The eyelash line looked more evident, and the eyelashes were separated from each other. The difference between the right and left eye was still there. The left eye was almost sign-free, but the right still had some CD left in the eyelash roots.

The client no longer experienced a burning sensation. The client did not find the product unpleasant and the Tea tree oil scent pleasant. The client also mentioned that despite the hot weather and the enormous night sweats because of the warm weather, Blephademodex did not cause any side effects. Still, after a substantial reduction in CD and a refresh of the eyelid margin, the client did not experience any eye changes.

To ensure that the treatment did not end too early, two more weeks were added in the same way as before—Blephasol duo in the morning and evening and Blephademodex in the evening.



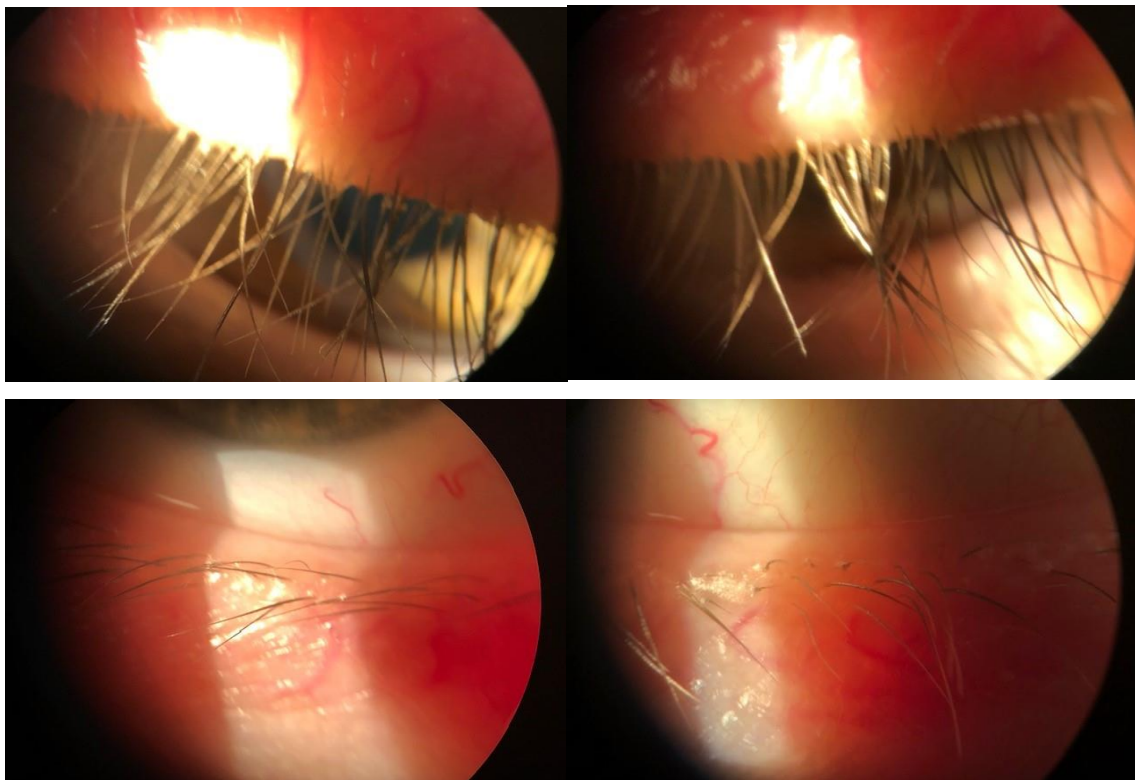
*Figure 19. 19.08.2022 Third return visit. Picture Ann-Caroline Sinisalo*

*Follow-up visit 4*

The fourth return visit after six weeks of using Tea tree oil did not give the desired result. The last CD had not disappeared; on the contrary, it may have even increased. (Figure 20)

The client experienced no difference in the eyes. He felt that the treatment was already routine. He did not share anything negative about the treatment and did not think it was hard work.

Since the last two weeks had not offered a reduction of the CDs, and may have had the opposite effect. There was a possibility that there were still mites, which meant that the treatment was continued for another two weeks. We could have changed the treatment method, added morning treatment of Blephademodex, or used BlepEX, but the medication was considered excessive.

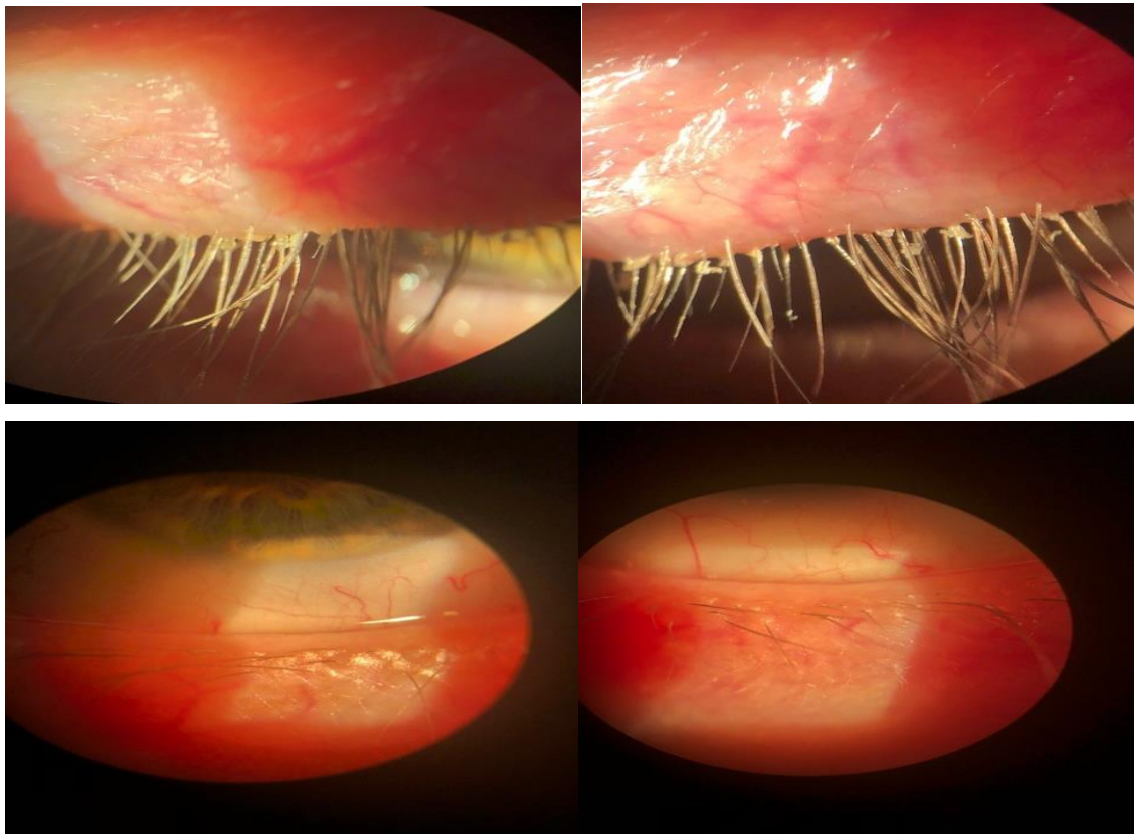


*Figure 20. 02.09.2022 Fourth return visit. Picture Ann-Caroline Sinisalo*

### *Follow-up visit 5*

The fifth return visit after a total of eight weeks of treatment. Which had consisted of one week of twice Blephasol duo and seven weeks of additional Blephademodex in the evening; there was still CD in the upper eyelids. (Figure 21) The right lower eyelid had a hordeolum and felt slightly inflamed and sick. The decision was to use Blephex in the upper lash lines. The lower lash line became unkempt due to some pain from the hordeolum.

The client still felt no difference in the eyelids but only reacted to having a hordeolum in the lower eyelid, which he hadn't had before.



*Figure 21. 16.09.2022 Fifth return visit. Picture Ann-Caroline Sinisalo*

Seven weeks of Blephademodex had not completely removed the CDs from the upper eyelids, so a BlephEX treatment was performed. The client had no problems with the treatment. In the BlephEX treatment, Blephagel was used as an aid in scrubbing. The CDs were persistent, and the treatment had to be repeated three times to free the upper lashes from the CDs. Despite this treatment and delicate" polished" eyelashes, the client felt no difference in the lash line.

After the BlephEX treatment, the upper eyelashes were free of CD (Figure 22), and behind, there were seven weeks of using Blephademodex wipes in the evenings. A trial of four weeks only maintenance of regular eyelid brushing morning and evening with Blephasol duo was decided

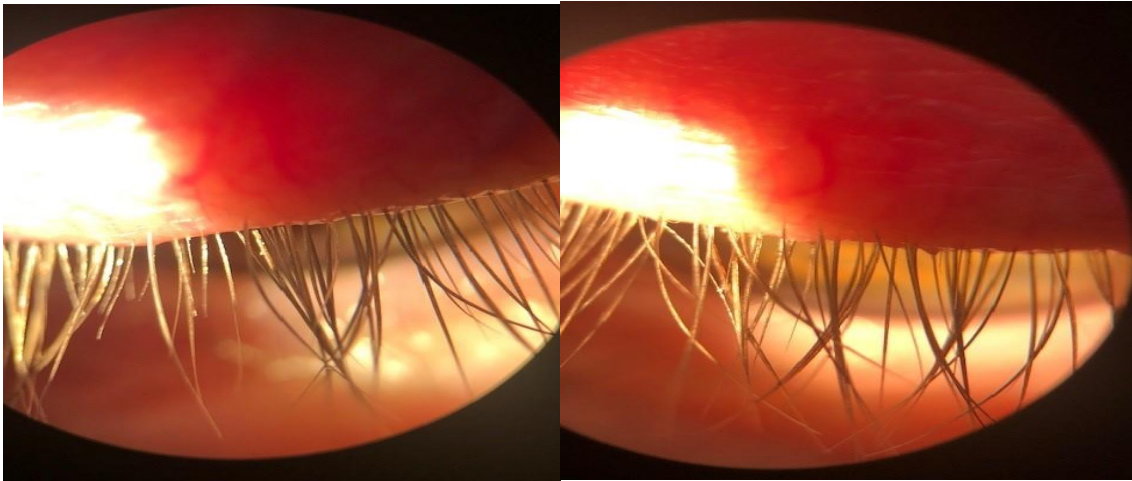
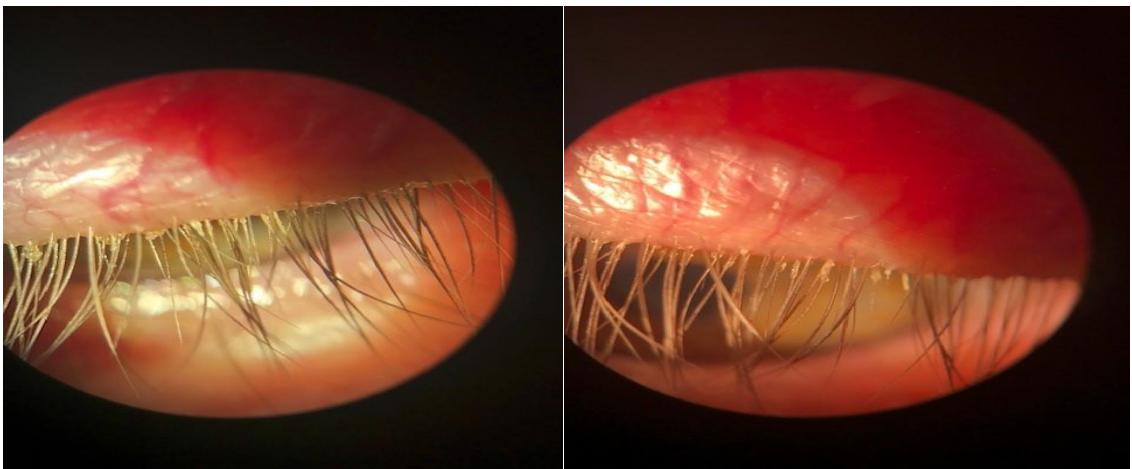


Figure 22. 16.09.2022 After Blephex cleaning. Picture Ann-Caroline Sinisalo

#### *Follow-up visit 6*

At the sixth return visit after four weeks of completed Demodex treatment and the only use of Blephasolduo, the upper eyelids were attacked again (Figure 23), and the hordeolum of the right eye was more extensive and more disturbing than last time. He was not referred to an ophthalmologist because he has had previous hordeolum, and they have resolved without medical care, and I believe they belong to the Demodex attack.



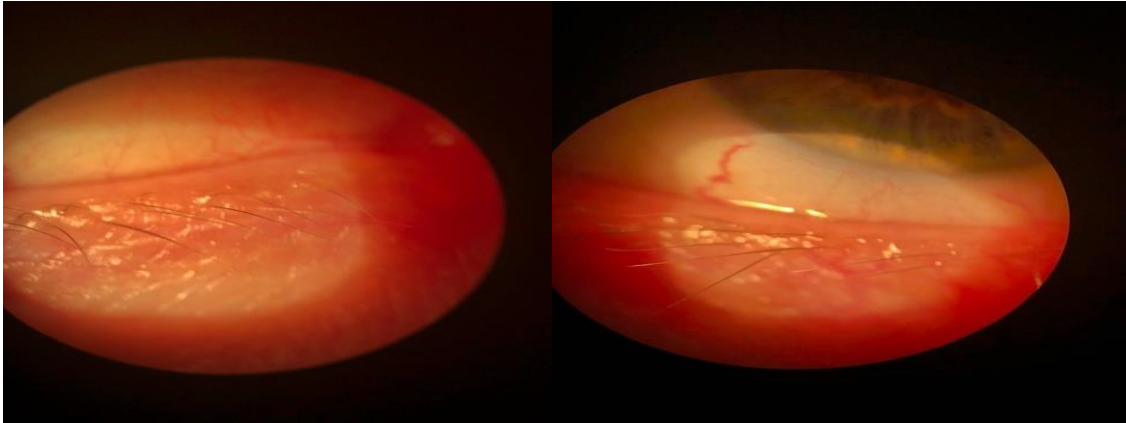


Figure 23. 14.10.2022 sixth return visit. Picture Ann-Caroline Sinisalo

#### 4.1.5 Discussion

Regarding the differential diagnosis, there were no ambiguities as the signs were vital, no symptoms occurred, and it could not be confused with any other disease. The questions that arise are invented from an optometrist's point of view and how they should react to Demodex mites in their daily work.

Should one treat based on signs such as cylindrical dandruff, and if so, which treatment method is most suitable for a symptom-free client? Does one need to add Demodex information and treatment to a routine eye examination?

Things that Fromstein mentions in his research in this Thesis work is that Demodex belongs to the normal lid flora and can be asymptomatic or cause symptoms. This was evident in the case study; he had no symptoms and was unaware that the eyelids were full of CD. Fromstein mentions that it was suggested that density and overpopulation could upset the ecosystem from homeostasis to disease. (Fromstein et al., 2018, 57-58) Can we imagine he had a small amount of mites that had not yet become a disease? Or does he have a sound immune system unaffected by the mites?

Savla also writes that many people with Demodex are asymptomatic and that Demodex affects men and women equally. (Savla et al., 2020, 1) But some studies suggest that Demodex blepharitis occurs more in men. (Ozcan et al., 2018, 32) Martinez-Pulgarin writes that 100 % of people older than 70 years and 84% of the population older than 60 are positive for Demodex infestation.

The case study client is a 57- years old man and statistically approaching the high-risk age. He only had a little atopic skin on his hands as a child and no skin problems as an adult. Martinez-Pulgarin mentions other risks than age, such as rosacea, alcohol intake, sun exposure, smoking stress, local or systemic immunosuppression, and poor hygiene. Of these statements, only age fits. (Martínez-Pulgarín et al., 2021,1) I experience alcohol intake, sun exposure, smoking, and stress more directly connected with rosacea and indirectly with Demodex.

Bitton and Aumond write that the mites survive in vivo for a few days because they are host-dependent. (Bitton and Aumond, 2021b, 285) Should you change your pillowcase effectively at the beginning of the treatment? To ensure that the mites cannot come back at night, they wander out of the eyes and end up on the pillowcase due to the treatment. Because of their speed of walking, they will not get far. And generally, avoid sleeping in other people's sheets?

Bitton and Aumond write that 16-20 degrees are the ideal temperature for development (Bitton and Aumond, 2021b, 291), which is common in Finland during the summer. Could you imagine that the Demodex attacks are milder during the winter months? Can you imagine the client's signs will be less in the winter if he spends much time outdoors? Does it work as a management method?

According to Fromstein, we can state that he had both; *D. folliculorum* and *D. brevis* mites, of which *folliculorum* formed CD and *brevis* packed the meibomian glands. After seven weeks of treatment, a hordeolum was pumping up in the right lower eyelid, which, according to Fromstein, has a connection with *D. brevis*.(Fromstein et al., 2018, 58)

But why did hordeolum appear after several weeks of treatment? To empty the blockages that *D. brevis* creates in the meibomian glands, one could imagine that it would be reasonable when using tea tree oil to do a heat treatment so that all mites and mite residues are removed from the meibomian glands. Or does the heat give them a better environment in which to reproduce?

Demodex and skin problems such as facial rosacea were excluded from this thesis work, and it centered on eye problems. Fromstein mentions facial rosacea (Fromstein et al., 2018, 59) and therefore brings up in the discussion that it doesn't help to take care of the eyes alone in many cases, but you should also take care of the skin. The client also cleaned his eyebrows and nose with Blephademodex.

The skin could also be why the mites returned after the treatment ended and only routine eye hygiene was carried out. The client also had a large beard, where the mites possibly could be? Could it be a reason to wash the beard with tea tree soap?

Fromstein mentions that the diagnosis of Demodex is usually based on signs instead of symptoms because the symptoms can be mixed with other anterior segment conditions. At the same time, Fromstein writes that CD indicates the presence of high-density Demodex mite infestation, which would mean that you can have high density but no symptoms, refuting the earlier theory that he did not have a large amount. The diagnosis was made based on signs and CDs. There was no definitive diagnosis made of the number of mites with a sampling of eyelashes or with in vivo confocal laser scanning microscopy, which is why it cannot be speculated more (Fromstein et al., 2018, 59)

Fromstein writes that if you leave Demodex untreated or poorly cared for, adverse effects such as redness, inflammation, telangiectasia, MGD, and ocular allergy may persist. But it is not mentioned whether it makes any difference if there are symptoms. (Fromstein et al., 2018, 61) Can it be interpreted that everyone who has Demodex should be treated?

According to Navel, using toxic or very effective systemic treatment in healthy eyes with Demodex may be unnecessary and this supports the approach from milder to more vigorous in the case study. (Navel et al., 2019, 660)

Fromstein uses the expression that the goal is to reduce the number of mites as the entire mite population cannot be eliminated (Fromstein et al., 2018, 61), raising the question of when have you reduced enough? Is a little CD okay if the amount is less than at the beginning?

The examination aimed to free the eyelashes from all CD to see if any recurrence recurred. Despite one week of Blephasolduo morning and evening treatment, seven weeks of treatment with additional Blephademodex every evening, and after eight weeks of total treatment, BlephEX was used to the upper eyelids, and relapse occurred after four weeks with only Blephasolduo.

Tea tree oil is the most effective and commonly used treatment; according to Fromstein, a 5% concentration used two times daily or 50% concentration used once a week effectively reduces Demodex infestation.



At the same time, Fromstein mentions that patients with sensitive skin can react to tea tree oil with symptoms such as dermatitis, allergy, and ocular irritation, especially with higher concentrations. The following paragraph mentions that mild cases are prescribed at-home treatments of once-a-day tea tree oil shampoo and facial wash. For moderate to severe patients, once a week, stronger concentration for three weeks, lid wipes twice a day, and BlephEX treatment every 3-6 months for severe patients. (Fromstein et al., 2018, 62) With this theory, we assumed that the treatment on the case study patient starts from the mildest in order not to cause side effects when he is asymptomatic and test whether it is compelling enough

Navel writes that TTO or pilocarpine gel with usual lid hygiene once or twice daily during 1-3 months supports the case study approach. (Navel et al., 2019, 661).

According to Savla, there should be more extended studies on the effect of tea tree oil regarding concentrations, and at the same time, Savla recommends at least two life cycles to ensure the adequate killing of the mites. (Savla et al., 2020, 9) In the study, Blephademox was used, which is a 2,5% Tea tree oil wipe. Two life cycles mean about six weeks; in the study, we had seven weeks, which in terms of time should have been long enough but in terms of concentration, too weak or too few times of use a day?

Navel writes that all treatments decrease mites count except usual lid hygiene. Navel also mentions that routine lid hygiene mechanical effects have been proven and should be added early. (Navel et al., 2019, 656-660) In the investigation of usual lid hygiene, Blephasolduo was used alone for a week to check what was happening and to learn how to clean and touch the eyes with an agent that did not cause side effects. I experience the brushing as a basic rule to remove all the impurities in the air and that it could soften the CD and help the tea tree oil preparation to get deeper into the follicle and the mites to emigrate out.

Martinez-Pulgarin mentioned the highest significant RR.s in thirteen studies were 50% TTO lid scrubs, Manuka honey, and topical Ivermectin + Metronidazole. (Martínez-Pulgarín et al., 2021, 4) Manuka honey came up so late in the research stage that It was not included, but I hope for more research in that area.

Savla writes about a group that received intense pulse light and that treatment eradicated Demodex mites at three months. (Savla et al., 2020, 2)

The investigation could have been continued with intense pulse light to see if you can reach a complete eradication, but is it necessary? When is it mentioned that the reduction is most important? Can we imagine that IPL could have a triple effect, kill the Demodex mites, and care for the skin and dry eyes all at once?

Shah mentions that Demodex blepharitis can be a chronic condition necessitating adequate long-term management. (Shah et al., 2022a, 934) I can see in the case study that eight weeks is a long time, but it does not guarantee that the mites will disappear and will not return. Shah also mentions TP-03, which can significantly simplify the treatment of Demodex blepharitis if it comes on the market and works effectively. I think that people in today's situation want easy solutions. Preferably a pill or drops that would quickly resolve the problem. Six to eight weeks of brushing with TTO different solutions can feel challenging, although the client did not find it difficult or time-consuming. It can be difficult, mainly to motivate an asymptomatic patient.

#### **4.1.6 Conclusions**

Demodex is not new; the first notes come as early as 1841, but it is a relatively new thing that people have started to react to in the optometrist world during eye examinations. First, it concentrated on dry eyes, and Demodex was found.

Regarding the diagnosis of Demodex, there is quite a consensus. During visual examinations, it is enough to discover cylindrical dandruff, CD, which is a sign that *D.folliculorum* has established its foothold in the eyelash follicle and overpopulation exists. When viewing a CD and even without CD, you can also easily use rotation or manipulation if you have sufficient magnification. Eyelash removal, microscopy, and in vivo Confocal Microscopy is used more in examinations where a unified approach is desired to obtain reliable studies.

The uncertainty is how many eyelashes should be epilated and whether there should be CDs on them. Regarding IVCM, you need an extra expensive tool that cannot distinguish between *D. folliculorum* and *D. brevis*.

The thing that is debated the most is probably the management of Demodex. It is agreed that usual eyelid hygiene is good but does not kill the mites. Tea tree oil is the most used but the concentration % and how many times it should be used at home or in the clinic in different examinations.

Tea tree oil's side effects are also mentioned in different ways. One clear thing is that you start with treatments that don't have side effects, such as tea tree in a milder form, BlephEX, and IPL, and if necessary, you switch to Ivermectin and Metronidazole. The Manuka honey, which requires more research, is new on the market, and the new TP-03, which may be on the market shortly.

Nowhere is mentioned how to treat an asymptomatic Demodex anterior blepharitis. Anyone who sees CD in a regular eye exam, whether they have symptoms or are symptom-free, should be informed about Demodex, what it can do, and how it can be treated. I believe that we, as optometrists, are obliged to notify the client about the matter and take action that is the client's responsibility.

No one can be forced into care, but it could be emphasized that even those without symptoms should know the consequences of neglect or poor maintenance. The case study recommends BlephEX because it cleans the eyelashes and lash line nicely and removes any embedded mites and this would mean that you could leave out the usual lid hygiene (Blephasol Duo) in this case and go straight to Blephademodex and use it morning and evening for at least six weeks, then switch to usual lid hygiene for preventive purposes. Before recommending it, Manuka honey should be studied more to know its effectiveness. One conclusion to consider is that when the client is symptom-free, no strong medications are needed, more a reduction of mites to avoid it becoming a disease and acquiring symptoms.

Although skin problems were excluded and only mentioned in connection with skin and eye problems, the future will unite eye specialists with dermatologists to treat Demodex.

My suggestion for how to continue this work is to make a Guideline about general information about Demodex and information about different treatment options. The theoretical part could include newer treatment methods such as IPL, Manuka honey, and TP-03.

The need exists as people live longer and longer, and we know that 100% of 70 years olds have some form of Demodex blepharitis.

## **4.2 Reliability of the Research Development Work**

In this investigation, evidence-based literature has been used for making clinical decisions, and Evidence-based assessments have been used to assess the patient. Despite this, it is only a matter of one case study, so it cannot be generalized but provides evidence for the assessment and management of Demodex blepharitis.

## **4.3 Ethicality of the Research Development Work**

This project was done for AC optik, and the researcher collected all data on-site while the patient was being seen in the clinic. The patient agreed to participate in this case study, and AC optik was responsible for the material that the survey required. Therefore, a separate IRB approval was not needed.

## **4.4 Evaluation of the Research Development Work**

This case study and literature were used to develop AC optik's dry eye services. Demodex treatment will be added to the service range.

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## 6 APPENDICES

### ALL IDENTIFIED RECORDS INCLUDED IN THE REVIEW APPENDIX1

| TITLE   | PUBLISHER   | TYPE OF SURVEY                        | YEAR | LANGUAGE |
|---|---|---------------------------------------|------|----------|
| <b>Efficacy of treatments for Demodex blepharitis: A systematic review and meta-analysis</b>                | <a href="#">Valentin Navel</a> <sup>1</sup> , <a href="#">Aurélien Mulliez</a> <sup>2</sup> , <a href="#">Cédric Benoist d'Azy</a> <sup>3</sup> , <a href="#">Julien S Baker</a> <sup>4</sup> , <a href="#">Jean Malecaze</a> <sup>3</sup> , <a href="#">Frédéric Chiambaretta</a> <sup>3</sup> , <a href="#">Frédéric Dutheil</a> <sup>5</sup> | Systematic review and meta-analysis   | 2019 | English  |
| <b>Demodex blepharitis: clinical perspectives</b>   | <a href="#">Stephanie R Fromstein</a> <sup>1</sup> , <a href="#">Jennifer S Harthan</a> <sup>1</sup> , <a href="#">Jaymeni Patel</a> <sup>1</sup> , <a href="#">Dominick L Opitz</a> <sup>1</sup>   | Review article                        | 2018 | English  |
| <b>Tea tree oil for Demodex blepharitis</b>   | <a href="#">Keyur Savla</a> <sup>1</sup> , <a href="#">Jimmy T Le</a> <sup>2</sup> , <a href="#">Andrew D Pucker</a>  | Review-Intervention                   | 2020 | English  |
| <b>Ocular Demodex: a systematic review of the clinical literature</b>                                       | <a href="#">Alexis Ceecee Zhang</a> <sup>1</sup> , <a href="#">Alex Muntz</a> <sup>2</sup> , <a href="#">Michael T M Wang</a> <sup>2</sup> , <a href="#">Jennifer P Craig</a> <sup>2</sup> , <a href="#">Laura E Downie</a>   | Systematic review                     | 2020 | English  |
| <b>Ocular Demodicosis as a Potential Cause of Ocular Surface Inflammation</b>                               | Luo, Xiaohui MD <sup>*</sup> ; Li, Jing MD <sup>*</sup> ; Chen, Chuan MD <sup>*</sup> ; Tseng, Scheffer MD, PhD <sup>†*</sup> ; Liang, Lingyi MD, PhD <sup>*</sup>  | Article                               | 2017 | English  |
| <b>Recent Evidence of Tea Tree Oil Effectiveness in Blepharitis Treatment</b>                               | <a href="#">Luigi Capasso</a> <sup>1</sup> , <a href="#">Giulia Abbinante</a> <sup>2</sup> , <a href="#">Alessia Coppola</a> <sup>2</sup> , <a href="#">Giulio Salerno</a> <sup>2</sup> , <a href="#">Maddalena De Bernardo</a> <sup>2</sup>  | Review Article                        | 2022 | English  |
| <b>Update on the Management of Demodex Blepharitis</b>  | Paras P, Shah, BA, Rebecca L. Stein, MD and Henry D. Perry, MD  | Review article                        | 2022 | English  |
| <b>Interventions for Demodex blepharitis and their effectiveness: A systematic review and meta-analysis</b> | Dayron F. Martínez-Pulgarín, Marcel Y.Ávila, Alfonso J. Rodríguez-Morales   | A systematic review and meta-analysis | 2021 | English  |
| <b>Clinical and Experimental Optometry</b>  | Etty Bitton & Sarah Aumond  | Invited Review                        | 2021 | English  |