An overview of Demodex Folliculorum

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Introduction
Demodex is an ectoparasite which belongs to the class Arachnida (sub class: Acari). It can be found on the surface of the human body and is mostly found on the face, cheeks, forehead, nose and eyelids. (Baima, 2002). Demodex often hide in the deep ducts of the sebaceous glands since active sebum excretions provide a favorable habitat for breeding and nourishment. Signs of Demodex infestation include cylindrical dandruff, disorders of the eyelashes, lid margin inflammation, meibomian gland dysfunction, blepharoconjunctivitis and blepharokeratitis. Colonization of Demodex increases with age and reaches 100% by the age of 70.
Demodex causes ocular itching, foreign body sensation, crusting and redness of the lid margin, and blurry vision. Suspicions of a Demodex infestation should be aroused by the loss of lashes and/or cylindrical dandruff around the base of the eyelashes during a slit lamp evaluation. Examination of eyelashes under a microscope will confirm the presence of the Demodex mites.

Treatment
Several options are available for the treatment of Demodex Folliculorum. These include treatment with topical and systemic anti- inflammatory and antibacterial medications, mercurial ointment, sulphur ointment, camphorated oil, crotamiton, antibiotics, as well as anti mycotic drugs. A good response has been observed after oral application of ivermectin along with topical application of permethrin cream.
As a topical treatment, tea tree oil is the preferred medication in combination with lid hygiene as evidence shows that it reduces the numbers of Demodex, is safe and has minimal side effects. It is also the only treatment that an Optometrist would be able to provide within the remit of their practice.

Conclusion: Demodex infestation can be responsible for ocular surface inflammation, meibomian gland dysfunction and blepharitis. Treatment of Demodex in general takes a few months. Apart from other treatment options described in this dissertation; lid scrub with tea tree oil is an effective treatment to eradicate ocular Demodex. It improves visual acuity and leads to a more stable tear film layer.

1.0 Introduction

The mite Demodex spp., belongs to the Class Arachnida, (sub class: Acariformes) and lives around hair follicles (Demodex Folliculorum hominis*)* or in the secretory ducts of sebaceous glands connected to the hair follicles (Demodex Brevis*)* of humans.

Demodex originates from the Greek words 'demos' meaning fat/wax and 'dex' meaning worm. The mites were first discovered in humans in 1841 and described by a Frenchman called Berger, and were in the same period described by Henle and Simon (1841/1842) ("Demodex", n.d.).
Around 65 species of Demodex are known (Yong, 2013), but only two species are found in humans and are considered to be normal and harmless skin fauna: Demodex Folliculorum longus and Demodex Brevis (Nutting, 1981) both referred to as eyelash mites.

The mites are mostly detected on the facial skin, forehead, cheeks, eyebrows, eyelashes and external ear of humans. The adult mites are normally 0.3–0.4 millimeter long although Demodex Brevis are slightly shorter (0.2-0.3 mm long) than Demodex Folliculorum mites. (Rufli, 1981). Each mite has a semitransparent, elongated body that consists of two fused segments and eight short, segmented legs attached to the main body. The body is covered with scales for anchoring to the hair follicle, and the mite has pin-like mouth-parts for eating skin cells and oils (sebum) which accumulate in the hair follicles. Demodex mites contain chelicerae in their head and mouth region to cut the epithelial cells of the skin of their host.

Demodex Folliculorum mites (figure 1) are found on the lid surface in the infundibulum portion of the hair follicles and around the eyelashes whereas Demodex Brevis mites are found in the deeper areas of the skin and have a wider distribution on the human body (Aylesworth, 1982).

Figure 2. Drawing of Demodex Folliculorum, adapted from http:/www. gutenberg.org/files/28177/28177-h/28177- h.htm.

1.1 LIVESPAN OF A *Demodex* MITE

The lifespan of a Demodex mite covers a total of several weeks (Liu, 2010); 14–18 days starting from the egg stage to the larval period followed by 5 days in the adult stage. A female adult lays 20-24 eggs in a single hair follicle. After the females lay their eggs, they may live for an additional five days as a maximum. The life span of the adult mites is short; therefore mating plays an important role in perpetuating Demodex infestation. Demodex's are not capable of surviving outside the host body for a long period, thus direct contact is required for transmission of the mites.

In all phases of their life cycle, Demodex Folliculorum and Demodex Brevis are believed to be more active at night, as they try to avoid light (Lacey, 2011). The mites can leave the hair follicles and slowly move around on the skin, at a speed of 8–16 mm per hour.

The average density of Demodex mites in healthy people is 0.7 per cm^2. In patients with Rosacea, Forton et al (1993) found a mean count of 10.8 mites per cm^2.
Venecia and Siong (2011) studied the incidence and density of Demodex mites in patients eyelashes with normal eyelids, meibomian gland dysfunction, anterior blepharitis and mixed blepharitis. A maximum Demodex count of 5 was found in patients with normal eyelids, confirming that Demodex may be present in the normal population as well. What about in the other conditions, say something about the Demodex count in those conditions.

In large numbers usually values over 5 mites per eyelid Demodex can cause symptoms such as itching, dryness, meibomian gland dysfunction, ocular irritation and inflammation as well as visual complaints. Infestation with ocular Demodex is common and usually does not cause any symptoms, although occasionally some skin diseases such as ocular Rosacea (Coston, 1967) can be caused by the mites. One of the most common manifestations of ocular Demodex is an irregular corneal epithelium causing blurred vision, inflammation of the ocular surface, painful eyes and associations with conjunctivitis (Gao, 2005). Demodex Folliculorum can cause anterior blepharitis associated with loss and misdirection of the eyelashes, and Demodex Brevis can cause posterior blepharitis with meibomian gland dysfunction and keratoconjunctivitis (Liu, 2010).

Research also suggests that Demodex infestation may be one of the triggering aspects of carcinogenesis in basal cell carcinomas of the eyelid (Erbagci, 2003) and sebaceous adenoma (Dhingra, 2009). Demodex infestation has been recognized as an important cause of skin diseases and has increasingly become a public health concern.

There is a growing body of literature on the ocular manifestations of Demodex infestation This dissertation will focus on the diagnosis and treatment of Demodex, and the options for a non-invasive detection and treatment in optometric practice.

1.2 Results of mite infestation

Normally the skin of a new-born is free of Demodex Folliculorum, Demodex passes to newborns through close physical contact after birth (Rufli, 1981).

Demodex Folliculorum and Demodex Brevis are seldom found in young children, while colonization of the skin in humans takes place in and numbers proliferate around the time of puberty when the sebum level that is present in the skin increases (Desch, 1972).
Demodex mites are commonly found within the skin of healthy representatives of all human races and in all geographical areas (Lacey, 2009).

Because Demodex are fully dependant on the pilosebaceous units they are not capable of surviving outside the host for a long period. Demodex cannot be maintained or cultured in vitro (Zhao, 2009), routes of transmission are not completely known but to parasitize and infect other healthy humans direct contact is required (hair, eyebrows and of the sebaceous glands on the nose) as well as through dust. Infected people with no visible signs can also transmit the mites to other people. Once a person is infected, it can take months or even years before the signs and symptoms of infection become visible. There are a few reports that mention occasional cross-infection between humans and animals (Morsy, 1995; Wang, 2013) but these tend to be rare.

Infestation with the Demodex mites can cause Blepharitis and or Rosacea.
Liu et al. (2010|) demonstrated a close correlation between the severity of Rosacea and Demodex blepharitis. In a meta-analysis of the association between acne vulgaris and Demodex infestation Zhao et al. (2012) found a strong association between Demodex infestation and blepharitis. They concluded that if conventional treatments for blepharitis fail, the examination of Demodex mites and therapy for Demodex should be considered.

1.3 Blepharitis

Blepharitis is an inflammatory disease process of the eyelid(s) and hair follicles of the eyelashes, associated with a bacterial eye infection, symptoms of dry eyes or certain types of skin conditions such as acne Rosacea (Thygeson, 1946).

There are three different main types of blepharitis:
1. Anterior blepharitis affects the outside front part of the eyelid, where the eyelashes are located. The two most plausible causes of anterior blepharitis are bacteria (Staphylococcus) and scalp dandruff (Liu, 2010).

2. Posterior blepharitis affects the part of the eyelid that makes contact with the eye and is caused by problems with the oil (meibomian) glands in this part of the eyelid. Two skin disorders can cause this form of blepharitis: Acne Rosacea, which leads to red and inflamed skin, and scalp dandruff (seborrhoeic dermatitis)
3. Mixed blepharitis, affects the entire lid margin.

Blepharitis associated with Demodex infestation can lead to eye irritation, burning and itching of the eyes, erythematous eyelid margins with typical cylindrical dandruff, dry eye and visual complaints such as blurred vision.

The severity of the eye lid margin disease not only corresponds with an increased number of Demodex, but is also dependant on the number of bacillus Oleronius suggesting a link between Demodex and bacillus Oleronius and the severity of blepharitis. The mite's digestive system is so efficient and results in so little waste that they have no excretory anus. Bacillus Oleronius has been detected inside Demodex mites, suggesting that this bacterium could aid digestion in the mite (Delaney, 2004; Lacey, 2007).

Szkaradkiewicz et al. (2012) found that the bacillus Oleronius bacteria parasite may act as a carrier, which most probably functions as a co-pathogen in the development of severe forms of blepharitis. The Demodex mite and/or its secretions have been suggested as a causative agent for the inflammation seen in blepharitis (Kim, 2011; Liu, 2010; Neiberg, 2008; Czepita, 2007). Demodex mites can cause blepharitis by carrying bacteria on their surface including Streptococci and Staphylococci. These bacteria produce proteins that can activate neutrophils which are responsible for the production of inflammatory cytokines implicated in the induction of Rosacea (Wolf, 1998).

1.4 Rosacea

Rosacea is an umbrella term for multiple clinical subtypes of chronic inflammatory dermatosis affecting predominantly the mid face. It usually affects people between the ages of 25 and 50 and is very rare in children. Diagnostic criteria for Rosacea include features such as flushing erythema, papules and pustules, feeling of burning or tingling of the skin and dryness of the skin. More serious sight threatening complications such as Rosacea keratitis and corneal damage can also occur.

There are numerous arguments in the literature supporting the theory that Rosacea is associated with suppressed immunity which may lead to an increase in Demodex infestation (Forton, 2012). A study by Zhao et al. (2011) concluded that Demodex is associated with Rosacea, steroid-induced dermatitis, seborrhoeic dermatitis, and primary irritation dermatitis.

The study also suggested that good hygiene practice might reduce the chances of demodicosis and Demodex infestation. These findings were supported by a study by Moravvej et al. (2007) who found that Demodex mites may play a role in the pathogenesis of Rosacea.

Although Demodex is widespread and considered a non-pathogenic parasite in parasitological textbooks, research has shown that Demodex is associated with many pathogenic kinds of skin conditions (Morsy, 2000).
In patients with facial Rosacea, the pathogenesis of the skin lesions has been speculated to be caused by an increasing density of mites, which is the trigger for inflammatory or specific immune reactions and is capable of mechanically blocking the hair follicle, or acting as a vector to bring in the bacteria. Ocular rosacea is a manifestation of Rosacea that affects the eyes and eyelids.

As a result of Rosacea caused by Demodex, infestation leads to:

1. Discomfort and burning in the eyes and on the eyelids.
2. Symptoms will come and go and several factors can aggravate or trigger the condition such as stress, physical exertion, sun exposure, certain spicy foods and alcohol.
3. Cylindrical dandruff surrounding the lashes and disorders of the eyelashes.
4. Lid margin inflammation and Meibomian gland dysfunction.
5. Blepharo-conjunctivitis and Blepharo-keratitis.
6. Conjunctival inflammation and corneal lesions *(*superficial corneal vascularization, marginal infiltration, superficial opacities and nodular scars).

Lacey et al. (2007), discovered that antigenic proteins related to the bacterium Oleronius, found on the Demodex mite, stimulate an inflammatory response in patients with papulopustular Rosacea. A study by Li et al. (2010) in 59 Rosacea patients showed a significant correlation between facial Rosacea, the infestation of the eyes with Demodex mites, and the reaction to certain mite-related bacillus Oleronius previously found to stimulate an immune response in Rosacea sufferers.

On the skin of humans, bacillus Oleronius may occur in the endospore form, which comes into the digestive tract of Demodex mites when they consume epithelial cells. The dead mites then decompose inside the hair follicles, where they release significant numbers of bacterial antigens, which have the potential to stimulate a strong immune response (O'Reilly, 2012). Thus, the intensification of blepharitis and Rosacea, especially the papulopustular variant, may not be induced so much by the presence of the mites but by the presence of number Demodex mites that carry bacillus Oleronius in their digestive tract.

Demodex spp. could participate in the pathogeny of Rosacea by several mechanisms such as causing direct damage to the follicular epithelia, by increased mite density, by obstruction of the hair follicle or the sebaceous duct, by generating foreign body reactions, by inducing host hypersensitivity reactions and by acting as vectors for bacteria (Staphylococcus Albus and bacillus Oleronius) (Lacey, 2009; Bonnar, 1993; Crawford, 2004).

1.5 Activation of Demodex

The Demodex mites consume epithelial cells at the hair follicle and mechanically block the orifices of meibomian glands leading to distension of the glands and hypersensitivity reactions. Protein in bacterium Oleronius leads to inflammatory cascades.

Liu et al. (2010) found a strong correlation between positive serum immune reactivity to the 83-kDa and 62-kDa bacillus proteins, ocular Demodex infestation, facial Rosacea, and blepharitis. Even dying and decomposing mites in the follicles or glands may increase the release of these two bacterial antigens, leading to a critical level for activating a cascade of host inflammatory responses (Bevins, 2007).
When the corneal epithelial cells are exposed to the bacillus Oleronius proteins a sensitivity reaction can be precipitated resulting in aberrant wound healing, marginal corneal infiltrates and possible triggering of sterile ulcering of the cornea.

Ultraviolet radiation can lead to immunosuppression and sebaceous gland hyperplasia. Kulac et al. (2008) investigated the infestation of Demodex Folliculorum in patients (n= 45) who had received phototherapy for the treatment of skin diseases. He found that the prevalence of Demodex in patients increased after receiving phototherapy.
Phototherapy increases the amount of skin surface lipids by direct activation of the function of sebaceous glands. The increase in Demodex Folliculorum may have been caused by immunosuppression and enlargement of the sebaceous glands as a result of phototherapy.
It is possible that increased blood flow in dilated papillary dermal vessels by the effect of solar radiation may provide a favorable environment. Because phototherapy is often indicated in treatment of several skin diseases, Kulac et al.(2008) recommended a potassium hydroxide examination or a standardized skin surface biopsy in patients developing demodicosis after treatment with phototherapy.

1.6 Associated risk factors:

There are a large number of risk factors that may be associated with an increased infestation with Demodex. Several reports have described the relationship between the rates of Demodex infestation and gender, but this topic remains controversial. Türk et al. (2007) reported that males have a higher rate of Demodex infestation, whereas Forton et al. (2005) reported that females have a higher rate. Kemal et al. (2005) and Lee et al. (2010) found no relationship between rates of Demodex infestation and gender. The differences found between the studies may be due to the sample sizes used and the different methodologies used to count the number of Demodex organisms. In studies with large sample sizes no differences were found.

TABLE 1 : ASSOCIATED TRIGGERS OF DEMODEX INFESTATION (NATIONAL HEALTH SERVICE, 2008)

Exposition:
- Stress and emotion
- Climate: (warmth, humidity, sun and wind)
- Fever
- Flushing

Drinks and food:
- Alcohol
- Coffee and tea
- Hot liquids, spicy food (e.g. chili, curry, pepper)

Irritation:
- Perfume, after shave.
- Peeling products
- Soap & Sun oil.
- Sinus and allergic conditions (e.g. the bacillus Oleronius)

Medication:
- Amiodarone
- Prostaglandins.
- Sympathycomimetics.

Poor ocular hygiene in combination with increasing age may also be associated with an increase in Demodex count (Koo, 2012) as a result of blocked orifices which prevent normal sebum secretion resulting in increased infestation.

Treatment with topical steroids particularly long term use of these drugs may also result in an increase in the number of Demodex (See for example Hengge et al. (2006), Fujiwara, (2010) and Singh et al. (2009).
The exacerbation of Demodex is probably due to the immunosuppressive action of topical steroids, responsible for an increase in the density of the parasite, since steroids suppress the immune system which may allow the Demodex mites to thrive (El-Shazly, Ghaneum and Morsy, 2001).

There are some disorders of the eyelids, such as infections of the glands, dermatitis and psoriasis that need to be treated with corticosteroids, this aggravates Demodex but it sometimes is entirely impossible to treat two problems present at the same time.

2.0 Demodex in diabetic disease

Several researchers have found a correlation between diabetes mellitus and Demodex.
Hom et al. (2013) described several clinical cases of dry eyes, itching, meibomian gland disease and redness of the eye lid margins and found a strong relationship between Demodex Folliculorum and patients suffering from diabetes mellitus.
Gökçe et al.(2013) investigated the effect of blood glucose regulation in relation with the presence of Demodex and compared 42 patients with poorly controlled type 2 diabetes with 27 well controlled patients. Their findings suggest that poor blood glucose regulation increases the susceptibility to Demodex Folliculorum mite infestation in patients with type 2 diabetes.
Yamashita et al.(2011) demonstrated that patients with active proliferative retinopathy have a higher prevalence of Demodex eyelash infestation. They found a correlation between increased sebum production, Demodex density and proliferative diabetic retinopathy and concluded that long term proliferative diabetic retinopathy and poor glycemic control is a greater risk for immunosuppression resulting in a higher Demodex count. In contrast Lee et al. (2010) did not found any relationship with Demodex Folliculorum and diabetes mellitus, unfortunately they did not mention how many patients they sampled which makes it difficult to comment on why differences were found.

A study by Cakmak et al. (2008) found that cystic dilatations of hair follicles, altered fat in the pilosebaceous unit and altered lipid synthesis in the sebaceous glands due diabetes in rats.

2.1 Demodex in Floppy Eyelid Syndrome

Floppy eyelid syndrome (FES), a condition of lax and easily everted eyelids with a soft, foldable tarsus, is a disorder of unknown pathogenesis.
Patients with floppy eyelid syndrome usually present with a long history of unilateral or bilateral ocular irritation, discharge, Meibomian gland dysfunction and with a history of repeated treatment for chronic conjunctivitis, dry and red eyes. Van Nouhuys and colleague (1994) found an association between Demodex and FES. They found a significantly high infestation of the meibomian glands with Demodex Brevis mites in 6 patients with FES. Mastrota (2008) found that the tarsal plates of patients with FES were often infested by Demodex Brevis and concluded this may contribute to the degeneration and atrophy of the meibomian glands. It should be noted that these studies have used very small sample sizes and in order to establish the reliability of these conclusions similar research should be performed on a larger sample size group.

2.2 Association between Demodex infestation and age of patients

Lee et al. (2010) noted a significant relationship between age and Demodex count. These findings were supported by Rulfi (1981) and Aylesworth (1982) who found the prevalence to be approximately 100 % in middle aged and older adults. Not all researchers agree with these findings. Kemal (2005) detected no relationship between age and the number of Demodex. The difference in finding may be due to the type of patients used by Kemal (2005). For example; sanitation can have a direct bearing on the Demodex count. Elderly patients with good eyelid hygiene have fewer Demodex count relative to their age, while young patients with poor eyelid hygiene could have a greater count relative to their age.

Demodex in children is very rare. Demodex passes to newborns through breast feeding or close contact in the first days after birth. However, due to low sebum production, infants and children lack significant Demodex colonization (Basta-Juzbasic, 2002). There has been a strong relationship between Demodex in children associated with immunodeficiency's such as human immunodeficiency virus (HIV), infection and leukemia (Yamashita, 2011).

Presence of mites in adolescents and young adults continues to be surprisingly low but increases from the second decade to the sixth decade of life and remains steady through the eighth decade (Basta-Juzbasic, 2002; Aylesworth, 1982).
Sebum secretion increases around puberty under the influence of androgens, concomitant with sebaceous gland enlargement (Stewart and Downing, 1985) suggesting that it may be the quality and not the quantity of sebum that plays a role in Demodex.

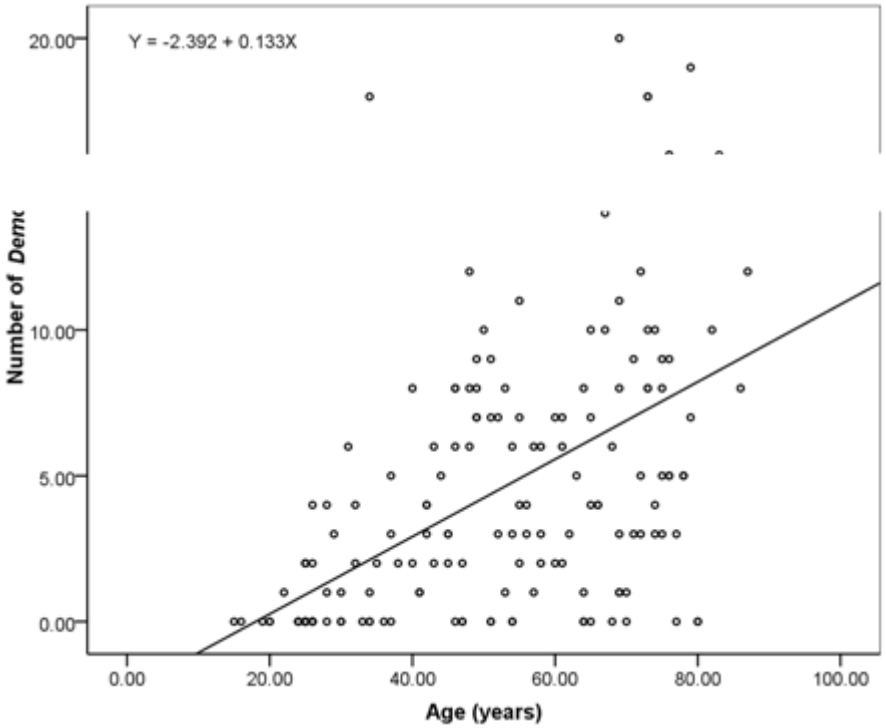

FIGURE 3, RELATION BETWEEN DEMODEX COUNT AND AGE (LEE, 2010).

A study on the demographic epidemiology of Demodex by Lee et al. (2010) in one hundred and seventy patients (see figure 2), showed significant positive correlations with increased age and the number of Demodex (100 % in elderly people (> 70 years old). Roth (1979) and Bonner (1993) reported that a higher Demodex count was associated with shorter tear film break up time (TBUT). The results of Roth and Bonner could not be replicated with a Schirmer test and no statistically significant correlations were found between the amount of tears and the numbers of Demodex. The difference may be due to the different tests used, whereas the TBUT test measures the lipid component of the tears the Schirmer test measures the aqueous component of the tears. The lipid component originates from the meibomian glands of the tarsus and forms the superficial layer of the tear film. The aqueous component is primarily secreted by the lacrimal gland.

Lee et al.(2010) also found an increased number of inflammatory markers in the tears e.g. interleukins (IL-1β and -6) and matrix metalloproteinase 9 (pro-MMP-9).
They concluded that Demodex affects the meibomian glands causing instability of the tear film, but does not affect the lacrimal glands.

2.3 Sociodemographic characteristics and risk factors:

Zhao et al. (2011) found that there was no significant correlation between gender and residence patterns and infestation with Demodex. These findings where collaborated by Andrews (1982), who compared 88 Caucasian New-Zealanders with subjects from countries in the northern hemisphere such as Samoa Islands and Polynesia and came to similar conclusions.
Zhao et al.(2011) found a significant association with acne vulgaris and Demodex in a meta-analysis of 63 papers. Okyay (2006) found that the Demodex count was not associated with acne vulgaris, this study however was not included in the meta-analysis of Zhao et al,(2011) because it did not match the inclusion criteria.

Okyay et al. (2006) reported that good hygiene which included daily face washing with soap did not have any effect on Demodex spp. prevalence. Similar findings were reported by Klapan et al. (2012) who found that the Demodex spp. prevalence did not have any relationship with daily hand-face washing, common towel use, keeping pets, and the number of people living together. But they observed that Demodex was more prevalent in people who showered more frequently and had used antibiotics in the last 6 months. They explained the higher Demodex count by postulating that the pores of the skin opened follicles and tubules due to the hot water which lead to the facilitation of parasites.
These studies give no information about the type of soap, shower gels or shampoo that was used. Washing with tea tree oil shampoo has been shown to be effective in eradicating ocular

Demodex and it is likely that these studies did not use soaps or shower gels that had this active ingredient (Gao et al.,2005).

3.0 Detection of Demodex

The detection rate of Demodex can be affected by many factors (Huang, 2006) including checkpoint, area, daytime and times of examination. The use of make-up seems to reduce the likelihood of Demodex carriage (Horváth, 2011) in young adults. Nevertheless, Yamashita et al. (2011) observed a higher prevalence of Demodex mites in (older) women who used makeup, probably due the blockage of the meibomian orifices by moisture eye makeup but also due to hormonal alterations allowing the mites to reproduce at a higher rate.
On the other hand Demodex density is related to age (Lee et al., 2010) also older people uses more heavy make-up and creams, on regular basis, that make them more susceptible for Demodex Folliculorum.

3.1 Clinical manifestation of Demodex

Apart from Blepharitis, Demodex can cause unusual ocular manifestations such as superficial corneal neovascularization, marginal corneal infiltration, phlyctenule-like lesions, superficial corneal opacities, and nodular corneal dystrophy, especially in patients with ocular Rosacea (Kheirkhah, 2007).

The most common ocular manifestations of Demodex infestation are blepharitis, iritis, iridocyclitis and conjunctivitis with dry eye, while on rare occasions Rosacea keratitis can lead to corneal ulcers, which then requires urgent ophthalmologic consultation. Photophobia and even pain may be present (Jansen, 1997).

Itching without any specific cause may indicate the prevalence of demodiciosis. Karincaoglu et al. (2004) performed a study in 33 patients with non-specific itching in which the itching did not originate from a definable skin lesion such as contact dermatitis or tinea facialis. The itching severity score was found to be significantly higher in persons with a higher Demodex mite density. Karincaoglu et al. (2004) suggested that the detection of Demodex Folliculorum should be considered in humans with and without non-specific itching.

Demodex examination is especially designated in patients who are suffering from ocular irritation and conjunctival inflammation. Following a review of 30 patients, Yam (2013) concluded that the possibility of demodicidosis should also be considered in adults presenting with recurrent chalazia after conventional treatment has failed.

3.2 Signs & symptoms

TABLE 2: SIGNS OF DEMODEX IN ORDER OF DECREASING PREVALENCE.

Ocular manifestations:	Bilateral crusting and redness of the lid margins
	Lashes with dandruff
	Meibomian gland disease
	Swollen eyelids/blepharitis
	Conjunctival inflammation
	Corneal vascularisation
	Superficial opacities
	Nodular scaring
Facial skin manifestations:	Itchy eyebrows, scalp and face
	Oilier skin than normal
	Enlarged facial pores
	Acne, cysts, and pustules
	Rosacea or facial flushing
	Hair loss (madarosis)
	Swollen nose

Symptoms:

The main symptoms of infestation are tickling and itching, crawling sensation on the face and in the scalp in the evening, burning, foreign body sensation, crusting and redness of the lid margin, blurry vision and failed response to dry eye treatments and blepharitis.

Itching during the night and early morning on the lower nose, eyebrows and eyelashes and irritation is common with these mites because of their aversion to light. Demodex mites are active at night and come out onto the surface to mate and to lay their eggs on the lashes. They subsequently crawl back into the follicle in the morning, causing the patient to itch. What

makes the diagnosis of Demodex difficult is that some patients will have “a lot of Demodex” without symptoms (Norn, 1970).

All of these conditions are typically bilateral and chronic or relapsing, however unilateral demodicosis has been observed by Pallota (1998). Also, Shelley et al.(1989) described a case report of unilateral Rosacea with Demodex Folliculorum, after treatment with sunscreens and corticosteroids.

3.3 Questionnaires used in Demodex examinations

Using a questionnaire allows investigators to collect information in a structured manner which may not necessarily be gathered through routine history, thereby adding to the clinical examination and providing relevant guidance in the decision-making process.
The data generally collected in Demodex investigations are: age, gender, ethnic group, residence pattern, skin type, medication, facial problems, hygiene practice, eating habits, alcohol use, facial and ocular symptoms, past unresponsiveness to conventional treatment for dry eye, allergies or blepharitis and relieving factors. (Zhao, 2011).

3.4 Microscopic detection and counting of Demodex mites

To determine the prevalence of Demodex in eyelashes there are two different methods for lash sampling: the invasive method and the non-invasive method.
In the invasive method lashes are collected from the upper and lower eyelid whereas in the non-invasive method Demodex is identified in the eyelash without epilation.

A method of invasive lash sampling and Demodex counting is described by Gao et al. (2005): Under a slit lamp microscope at a magnification of 25 times, two lashes preferably with cylindrical dandruff, one from each half of each lid, have to be removed slowly by fine forceps and placed separately on each end of glass slides. In the conventional method, a drop of oil or saline is added to the lash before a cover slip is mounted. A gentle and slow removal of the lashes is necessary to prevent Demodex mites at the root of the lash from falling off and staying on the shaft of the meibomian gland.
For the detection of mite infestation with ocular Demodex, epilation of lashes with cylindrical dandruff yields better results than random epilated lashes (Kheirkhah, 2007).

The density of Demodex varies with the methods used (Hsu, 2009).

The invasive method has been in use for more than 40 years and many studies have confirmed the effectiveness of this method (See for example Coston, 1967, Hom, Mastrota and Schachter, 2013). In the invasive Coston method described by Coston (1967) 16 randomly epilated eye lashes are mounted on a glass slide with a peanut oil base and viewed under a microscope. In the 'modified Coston' method described by Gao et al. (2005) only 8 lashes with cylindrical dandruff are selected and after mounting the coverslip saline is added. Under a microscope the number of Demodex are counted. Then 100% alcohol is added to the eye lash samples.
The alcohol stimulates the embedded Demodex to migrate out of the cylindrical dandruff After 20 minutes Demodex numbers are counted.
Gao et al.(2005) concluded that using the modified method, and a selection of two, rather than four, lashes per lid is sufficient to achieve a meaningful sampling for detecting Demodex.

Kheirkhah et al. (2007) described the 'modified Coston method with fluorescein' where fluorescein is added to a 0.9 % saline solution applied on the glass slide after mounting the coverslip. They compared counting of Demodex with and without fluorescein dye microscopic evaluation, and concluded that the addition of fluorescein enhanced the visualization of the Demodex mites in the lashes. The benefits of using fluorescein comes from two factors:

1. The watery component of the fluorescein leads to rapid swelling and dissolution of the cylindrical dandruff.
2. The yellowish contrast helped to detect the semitransparent mites embedded in the opaque cylindrical dandruff, which resulted in a significantly higher Demodex count in the same person.

A non-invasive method to identify Demodex mites is described by Mastrota (2013). She demonstrated that, when an eyelash is rotated by applying gentle tension, the mites inside the eyelash follicle move out of the follicle orifice and become visible on the eye lid margin with a high magnification slit lamp. This method was earlier described by Lacey et al. (2009) and was shown to be useful when the waxy debris at the base of the lashes are removed by scrubbing with tea tree oil or baby shampoo.

In vivo confocal laser scanning microscopy (CLSM) examination is another non-invasive method to identify Demodex mites in patients with cylindrical eyelash dandruff. CLSM is a useful instrument which can be used to detect, image and quantify Demodex mites noninvasively in the facial skin of patients with Rosacea (Maier, 2012).
Kojima et al. (2010) found it to be an efficient non-invasive tool and fast in vivo technique for the immediate diagnosis of Demodex mites and follow-up of the eyelid disease in patients with blepharitis associated with cylindrical dandruff. Kojima et al. (2011) concluded that although the mean mite count per lash was higher in confocal microscopy examinations when compared with the Demodex counts in direct light microscopy, no statistically significant differences were found in mean mite counts between the two methods of investigation.

Confocal laser scanning microscopy is easily reproducible on different test sites and the result can be directly evaluated.

The non-invasive eyelash rotating method for detecting Demodex is beneficial in the optometric practice as it is easy and can be done routinely. The practitioner normally starts

with a lid scrub with 50% tea tree oil to clean the lashes and free them of cylindrical dandruff. A high magnification slit lamp is used and the lash is and rotated with forceps. The mites are normally observed migrating along the lash trunk, and are then placed on a glass side for microscopic inspection.

The lashes are inspected under the microscope and are used for locating and counting the Demodex mites.

To find Demodex on the skin, cheek and forehead areas, standardized skin surface biopsy (SSSB) method and direct microscopic examination (DME) of fresh secretions from sebaceous glands are commonly used.

The standardized skin surface biopsy method is performed with a drop of adhesive cyanoacrylic (fast-acting adhesive) that is placed on a slide (1 cm^2) and applied to the demodicosis of the suspected skin, then gently removed after one minute and covered with a coverslip after the addition of a few drops of immersion oil.
Forton et al. (1998) investigated the standardized skin surface biopsy (SSSB) technique and reported some limitations. They indicated that in the SSSB method only mites on the superficial parts of the skin are collected. This suggests that only Demodex Folliculorum mites, located on the upper part of the infundibulum of the hair follicle, are collected. Demodex Brevis mites that live in deeper parts of the skin are not collected thereby underestimating the Demodex count.
In the direct microscopic examination (DME) technique the affected skin is squeezed between the finger and thumb and the expressed material is transferred to a microscopic slide.
Aşkin et al. (2010) compared the SSSB and DME techniques in the measurement of Demodex in patients (n= 37) with suspected demodicosis. The results of both samples from the same person on the same affected area was compared, in all the patients, the mean Demodex count measured with SSSB was higher than that with DME. Therefore their recommendation was that more patients with demodicosis can be diagnosed with SSSB method compared with the DME method.

Su et al. (2012) screened 612 medical students for Demodex with the transparent adhesive tape method (ATM), scraping method and extrusion method.
In the ATM pieces of cellophane tape are applied to forehead, cheeks, nose and chin, just before sleeping at night. In the morning the tape is removed and pressed over a glass slide to be examined with a microscope.
The skin can be squeezed to promote extrusion of Demodex mites from the hair follicles and then scraped with the blunt end of a metal spatula. The sample/smear is collected on a glass slide for microscopic examination.

The infection rates detected by adhesive tape method (ATM), scraping and squeezing methods were 21.73%, 14.71% and 15.35%, respectively.
The difference between these methods can be explained by the fact that ATM examines a greater skin surface therefore, the sensitivity of the ATM on Demodex prevalence is greater.

3.5 Slit lamp examination

Slit lamp examination covers tear film breakup time (BUT), signs of meibomian gland disease and (mixed) blepharitis. Foamy tear film on slit-lamp evaluation, significant lissamine green staining and significant corneal staining indicates an excessive dry eye and the possibility of Demodex.

It is difficult to observe mites on slit lamp examination even with high magnification without alcohol cleaning. The presence of cylindrical dandruff suggests that Demodex may be present (Braulio, 2011). However with prior removing of the dandruff and, with a high magnification on the slit lamp, the translucent mites might be visible.
In a study of 55 patients Gao et al. (2005) found that Demodex was 10 times higher in epilated lashes with cylindrical dandruff when compared to subjects who did not have cylindrical dandruff. They concluded that the clinical severity judged by the amount of cylindrical dandruff on the affected lashes, correlates well with the Demodex infestation.

To visualize the mites with a slit lamp, all debris and dandruff like material have to be first cleaned with an alcohol swab. The mites sit head down and tails up, with the along the lash at the root.
Then, pulling lightly on the lashes causes the Demodex tails to poke out of the follicular opening and further twirling the lash will stimulate the mites to come out and crawl on the skin surface (Mastrota, 2013).

4.0 Diagnosis of Demodex

Taking history is the first step in the potential diagnosis of Demodex, before the clinical examination. The anamnesis should consider epidemiologic data e.g. age, hygiene, eating habits (e.g. spicy food or alcohol intake), smoking, . and way of life (e.g. living closely together under poor sanitary conditions).

Information regarding previous medical conditions, treatments or presence of aggravating factors are also important (e.g. immunosuppression due local corticosteroid).

1. History: e.g. itchy eyebrows and eyelashes, especially in the morning, unilateral or bilateral.
2. Clinical history: high index of suspicion when blepharitis, conjunctivitis or keratitis in adult patients or blepharo conjunctivitis and recurrent chalazion in young patients are refractory to conventional treatments, or when there is madarosis or recurrent trichiasis.
3. Slit lamp examinations and lash sampling.
4. Microscopic confirmation: detection and counting of Demodex eggs, larvae and adult mites in epilated lashes.

The clinical examination is done with the use of a slit lamp. Direct examination of the eye and eyelids frequently provides the most rapid indication of microbial infection**.** Many of the potential diagnoses can be ruled out based on characteristic and clinical appearance. For example sudden onset after food consumption or use of facial creams or make-up, rather indicates an allergic reaction than Demodex infestations.

TABLE 3: SLIT LAMP EXAMINATION.

Adnexa: Association with rosacea, acne vulgaris, blepharitis, erythema, telangiectasia, papules, pustules, and hypertrophic sebaceous glands.
Eye lids: Abnormal eyelid position (i.e., ectropion and entropion), eyelid closure (i.e., lagophthalmos), or blink response. Chalazion or hordeolum, blepharitis and meibomian gland disease. Basal cell carcinomas, ulceration, neovascularization, thickening and keratinization.
Eye lashes: Special attention for the typical cylindrical dandruff and collarettes at the root of eyelashes. Misdirection, malposition, loss or breakage, erythema, telangiectasia, papules, pustules, hypertrophic sebaceous glands.
Conjunctiva: Conjunctival inflammation, blepharo-conjunctivitis.
Cornea: Superficial corneal vascularization, marginal corneal infiltration, superficial opacity and nodular corneal scar, phlyctenule-like lesion

Mites can be visualized under high magnifications with a slit lamp, using de Mastrota rotation technique (Mastrota, 2013), which has been described earlier.

Direct microscopic examination includes counting of eggs, larvae, nymphs and adults is used for the confirmation of diagnosis which is established by the laboratory examination of the eyelash samples.

TABLE 4: PATHOGENIC CONDITION BY DEMODEX COUNT.

Researcher	Condition:	Pathogenic Demodex findings:
Coston, 1967		6 or more mites per 16 lashes, or more than 5 mites per lash.
Gao et al (2005) Group with CD	Pipetted with 20 µl of 100% alcohol	4.1 ± 1.0 and 2.0 ± 1.2 per epilated lash in the group with retained cylindrical dandruff (CD)
Gao et al (2005) Group without CD	Pipetted with 20 µl of 100% alcohol	0.2 ± 0.5 and 0.2 ± 0.4 per lash in the group without retained CD
Kheirkhah et al (2007)	Demodex count without fluorescein.	3.1 ± 2.5 and 0.8 ± 0.7 on lashes without retained CD when using a drop of saline
Kheirkhah et al (2007)	Demodex count with fluorescein	4.4 ±2.8 and 1 ± 0.8 without retained CD with fluorescein dye.

4.1 Differential Diagnosis:

Because Demodex can be found in asymptomatic patients, one has to consider it in the differential diagnosis in recurrent or recalcitrant corneal and external disease. For example when a patient does not respond to traditional treatment of blepharitis and dry eye treatment, or worsens, the therapy should be directed to eradicate mites (Kheirkhah, 2007).
In cases of keratoconjunctivitis (atopic, epidemic, sicca and superior limbic) and dry eye syndrome as well as in limbal stem cell deficiency Demodex should be one of the differential diagnosis.
Rebound of itching after discontinuation of medication (e.g. corticosteroids), keratitis in adult patients or blepharo conjunctivitis or recurrent styes/chalazia in young patients, or in case of conjunctivitis (bacterial, viral and allergic), especially when it is severe and the patient is suspected of a long-standing demodicosis, could be a sign of Demodex infestation.

TABLE 5: DIFFERENTIAL DIAGNOSIS OF DEMODEX.

Acne vulgaris
Contact dermatitis
Cutaneous lymphoma
Favus
Perioral dermatitis
Rosacea
Seborrheic dermatitis
Tinai faciai

Demodex can mimic eyelid sebaceous gland carcinoma.(Galea et al., 2013.
Correct diagnosis can be facilitated by the finding of follicular Demodex mites in eye lash samples.

5.0 Treatment options:

Various treatments have been used to control Demodex mites. Most of them involve eyelid margin hygiene and pharmacological treatment.
In general the treatment goal is to reduce the presence of Demodex, prevent Demodex copulation and re-infestation. Spreading an ointment at the base of the eyelashes at night may trap mites as they come out of from their burrow and move from one follicle to another for mating.

As Demodex mites also serves as a vector for skin organisms, the comorbidity based on a symbiotic relationship of bacterium Oleronius in Demodex mites also justifies the therapeutic strategy directed to killing the symbiotic bacterium via oral antibiotics such as tetracycline and at the same time preventing re-infestation by performing intensive eyelid hygiene.

Another way of controlling the Demodex infestation is to treat the underlying cause e.g. diabetic (Clifford et al.,1990), or to stop medication (e.g. topical corticosteroids).

5.1 Treatment methods:

In patients with altered fatty acids as produced in papulopustular Rosacea Demodex numbers are increased (Ní Raghallaigh, 2012). Therefore Jarmuda et al. (2012) suggested that non-antibiotic therapies could restore the normal fatty acid value of the sebum and improve the skin integrity and normalize the abundant Demodex infestation.

Patients with erythemato-telangiectatic rosacea or papulopustular Rosacea can benefit from moisturizers that contain adequate hydrating ingredients, promote stratum corneum barrier repair, and incorporate emulsifiers that are least damaging to stratum corneum integrity. However, it is also important that Rosacea patients use moisturizers that do not contain potential irritants that could exacerbate their symptoms (Del Rosso, 2005; Bikowski, 2007).

Tea tree oil

Demodex is susceptible to tea tree oil (TTO). Tea tree oil is a natural oil distilled from the leaf of Melaleuca alternifolia.

Gao et al. (2005) introduced a weekly lid scrubbing treatment with 50% tea tree oil; and a daily lid scrub with tea tree shampoo for effective eradication of ocular Demodex in vitro and in vivo. They noted a survival time of 15 minutes with 100% tea tree oil, and 150 minutes with baby shampoo (figure 3).

FIGURE 4. SURVIVAL TIME OF DEMODEX FOLLICULORUM (GAO ET AL., 2005)

Solution	**50% BS**	**10% PI**	**75% Alc**	**MO**	**4%Pilo**	**Mix 1**	**Mix 2**	**Mix 3**
ST (minutes)	150	150	150	150	150	150	150	150
DN	9	4	8	5	3	6	5	6
Solution	**100% Alc**	**10% TTO**	**25% TTO**	**50% TTO**	**100% TTO**	**100% CWO**	**100% DWO**	
ST (minutes)	3.9 (1.2)	150	34.7 (4.3)	14.8 (9.5)	3.7 (0.8)	4.4 (2.3)	14.0 (8.3)	
DN	7	5	5	11	21	16	5	

ST = SURVIVAL TIME; DN= NUMBER OF DEMODEX TESTED; BS = BABY SHAMPOO; MO = MINERAL OIL; PI = POVIDON IODINE; ALC = ALCOHOL; MIX 1 = 50% IN H2O FOR 30 MINUTES FOLLOWED BY 10% PI; MIX 2 = 10% SDS IN H2O FOR 30 MINUTES FOLLOWED BY 10% PI; MIX 3 = 10% PI FOR 30 MINUTES FOLLOWED BY 75% ALC; TTO = TEA TREE OIL; CWO = CARAWAY OIL; DWO = DILL WEED OIL; PILO = PILOCARPINE.

Conservative treatment starts in the office; a drop of 0.5% Oxybuprocaine is added. The next step is to scrub the eyelid margins with a cotton tip wetted in 50% tea tree oil, to remove the crust and collarets around the hair lashes. This treatment is repeated 3 times at a 10-minute interval. The office lid scrub is repeated weekly until the Demodex count reaches zero for two consecutive visits (Gao et al.,2005).

Research by Gao et al. (2005) as well as several other studies (e.g. Raju, 2011) confirmed the positive effects of this conservative treatment, showing that the Demodex counts dropped to zero in three weeks.

At home, a twice daily lid scrub with 5 % tea tree oil is followed by a massage of the eyelids in order to resolve the ocular Demodex infestation. After one month the home treatment is performed once a day. If the routine is not followed properly cylindrical dandruff returns within 1 week.

Gao et al. (2005) compared the killing effects of Demodex by scrubbing the lid margins in one eye of a patient 50 % tea tree oil and in the other eye with comparable dandruff with 50% diluted baby shampoo. After 5 minutes of cleaning in office, several mites where detected along the lash trunk and on the eyelid margins at the tea tree oil treating side. On rotating the eyelash on this site, Gao et al. (2005) found Demodex mites migrate out of the gland, while Demodex mites were not seen on the side that was treated with baby shampoo.
Demodex count was zero after 4 weeks weekly in office lid scrub with 50% tea tree oil and a daily home scrub with tea tree oil, without recurrence.

Gao et al. (2007) claimed that daily, at home, lid massage with 5% tea tree oil ointment was effective and a safe way of treating ocular demodicosis (see figure 5).
Kheirkhah et al. (2007) reported that it takes a minimum of seven weeks to show a significant reduction of Demodex count and resolution of ocular irritation, conjunctival inflammation, and all inflammatory signs. This was seen after treatment consisting of weekly lid scrubs with 50% tea tree oil and a daily lid scrubs with tea tree shampoo, He also noted a positive change of symptoms and corneal and conjunctival signs.

Koo et al. (2012) compared the results of lid scrubs with and without tea tree oil in patients with ocular Demodex infestation. The results show that the severity of ocular surface discomfort has a strong positive correlation with the number of Demodex and tea tree oil eyelid scrub treatment is an effective method for eliminating Demodex when frequently applied.

Gao et al. (2012) also recently reported that there is a strong correlation between symptomatic resolution and reduction of Demodex counts by daily massage with 5% tea tree oil ointment. The 50% tea tree oil has direct killing effect on the mites, whereas the 5% may interrupt their life cycle by preventing mating. In addition to tea tree oil, Gao et al.(2012) found that Caraway Oil and Dill Weed Oil could each kill Demodex within 25 minutes; a remark was made about the dose dependent killing effect of tea tree oil.
Lid scrubs with 50% tea tree oil do not eradicate mites hidden deep in the skin, therefore home daily lid scrub with 5% tea tree oil, or tea tree oil containing shampoo and repeated weekly scrubs for 3-4 weeks is indicated.

Eyelid margin hygiene using eye pads is a very effective method in anterior blepharitis and meibomian gland disease. Guillon et al.(2012) presented the results of a study of three months duration with 40 subjects performing a twice daily management for three weeks with special eyelid wipes (Blephaclean™), followed by a maintenance cleaning once daily during the remaining six weeks.
The management involved two steps:

1. Massage of the eye lid margins at the root of the eye lashes during closed eyes.
2. Massage of the lower eye lid margin separately.

Guillon et al. (2012) observed good compliance and a marked improvement of the eyelid margin status. Maintenance of the eyelid margins with eyelid wipes is an important step in prevention of eyelash contamination and meibomian gland blockage.

Lid warming + massage

Lee et al. (2010) found a strong positive relation between ocular surface comfort and Demodex counts despite age. They concluded that good eyelid hygiene decreases the prevalence of Demodex and helps to improve ocular discomfort in all ages.
Eye lid cleaning procedures and a warm compress and vertical eyelid massage works to both melt the thick wax in the meibum and loosen any debris on the eyelid margin and eyelashes. There are several devices which can be used to warm the eye lids, these include an Eyebag™, a Blephasteam™ goggle or a Lipiflow™ device. The success of this treatment appears to be multifactorial and includes thickening and stabilization of the meibomian lipid layer as well as the reducing bacterial colonization, which has been proven to be effective in diminishing the symptoms (Dry Eye WorkShop, 2007).

Permethrin and Ivermectin:

Permethrin is effective because of its anti-parasitic nature which targets Demodex mites (Nally, Berson, 2006). Permethrin, leaves a long lasting effect on the skin and hair for several days after use and is the preferred treatment for Demodex. Its residual effect on the skin discourages re-infestation and lasts up to a week.

Ivermectin, a broad-spectrum antiparasitic agent is the chemical name of a drug called Stromectol. It works by paralyzing and killing the mites that are responsible for the symptoms associated with a scabies infection. Alternatively, topical Ivermectin compounded to a 2% concentration by weight in a cream, lotion, or gel carrier vehicle is administered as an effective treatment for all clinical stages and signs of inflammatory Rosacea, where Demodex Folliculorum is often present. González et al. (2008) found Ivermectin excreted into human milk in low concentrations, which implies that Ivermectine is contra-indicated for breast feeding mothers.

There are several clinical reports about the use of Ivermetcine with or without adjuvant for the elimination of Demodex. Holzchuh et al. (2011) noted significant reduction in the count of Demodex with oral Ivermectine, especially in cases of unsuccessful treatment related to patient compliance. Forstinger et al. (1999) described a patient who was successfully treated with a single dose of oral Ivermetrin followed by a once weekly 5% Permethrin cream to prevent re-infestation.

To summarise, Oral Ivermectin, in combination with topical Permethrin, can be a safe and effective treatment for severe demodicosis. Common side effects of Ivermectine can include fever, itchiness of the skin, rash, headache, dizziness, and swelling of the feet. More severe side effects can include seizures, a rapid heart rate, and a severe skin reaction (Stevens-

Johnson syndrome. These drugs are not recommended for use in pregnant women, infants, and in breastfeeding women.

Sodium sulfacetamide 10% + sulphur 5%

Sodium sulfacetamide has antibacterial properties. Sulphur treatment (sulphur is an insecticide) has been mentioned by several researchers (see for example Sauder et al., 1997; Liu et al. 2010.) as an effective treatment in Demodicosis.
Sulphurs are available in lotions, creams, pledgets, short-contact preparations, and cleansers. Forton et al. (1998) noted a significant decrease in Demodex count with sulphur treatment but also observed irritating effects like irritation in the eye and on the skin which may limit its use.

Ayres (1963) used sulphur containing ointment to treat demodicosis and noted a gradual disappearence of Demodex on the skin. Sulphur ointment is considered an inexpensive, and safe treatment for scabies and also for pregnant woman, very young children and breast-feeding mothers. The disadvantages of sulphur ointment is that it is very messy, stains clothing and bedding, has a bad odor and dries the skin.

Crotamiton

Crotamiton is a topical drug used in the treatment of scabies and pruritus.
In a retrospective case review Bikowsky and Del Rosso (2009) showed that the use of topical Crotamiton 10% twice daily was beneficial in treating patients with facial Demodex. They concluded that their results were similar to those described by Ayres and Ayres (1961).

Pourhasan et al. (2013) compared the efficacy of Permethrin 5% cream versus Crotamiton 10% cream in the treatment of scabies among 350 patients.
To perform this study, they selected patients with typical alterations of the skin (e.g. facial Rosacea), and patients with complaints of nocturnal itching on the face and a history of similar symptoms in the patient's families or close contacts.
They concluded that Permethrin is more effective than Crotamiton for the treatment of Demodex. It is a fast and safe cure through simple administration without serious adverse reactions. Crotamiton should be used with caution in pregnant and breast-feeding mothers. Worsening skin irritation (such as itching, redness) may occur.

Metronidazole

Metronidazole is an antibiotic effective against anaerobic bacteria and Demodex, but topical Metronidazole is not effective in disrupting Demodex Brevis because it cannot penetrate deep down in to the sebaceous glands (Hsu et al.,2009)
Metronidazole is available in tablets and capsules, creams, lotions, gels and for injection.
Metronidazole is extremely effective against Rosacea, Barnhorst et al. (1996) successfully used topical Metronidazole in treating eyelid infections related to ocular Rosacea.
Oral Metronidazole is effective in the management of chronic mite infestation. (Schaller; Sander; Plewig, 2003)

Salem et al. (2013) combined Metronidazole with Ivermectine and concluded that this combination of medications is more effective than Ivermectine alone in Demodex therapy. Nursing mothers, because of potential adverse effects on the new-borns, should not use metronidazole.

Petroleum Jelly:

Petroleum jelly is a translucent, semi-solid mixture of hydrocarbons that often serves as the vehicle or base of creams and ointments, including those which are used for the eyes. Tiuseco et al(2012) studied thirteen patients with anterior blepharitis and meibomian gland dysfunction, eight patients were instructed to use petroleum jelly scrubs and compared with five patients who used tea tree oil lid scrubs and tea tree facial wash for six weeks.
At 2-week intervals, petroleum jelly, available as Vaseline, was administered at the clinic to scrub the lashes for a total of 6 strokes. After waiting for 5 minutes excess petroleum jelly and any crusts and debris around eyelashes was removed. A second lid scrub in the same way was performed after 10 minutes.
The patients were instructed to do lid scrub with petroleum jelly, three times a day for six weeks, after using warm eyelid compresses.

For the tea tree oil group a lid scrub in clinic was performed every two weeks for a period of six weeks. The lashes were scrubbed with 50 % tea tree oil, after 5 minutes excess tea tree and any left debris and dandruff was removed. After another 5 minutes this treatment was repeated in the same manner. Patients were instructed to use 5 % tea tree oil facial wash twice daily for six weeks.

Tiuseco et al.(2012) concluded that lid scrub with petroleum jelly caused a significant reduction in Demodex counts compared to lid scrub with tea tree oil and tea tree facial wash, without significant adverse reactions. Petroleum jelly is safe in pregnancy and for breast-feeding mothers.
The outcomes of the study of Tiuseco et al.(2012) compared with the study of Gao et al. (2007) raises questions about the effectiveness of tea tree oil (TTO). Tiuseco et al.(2012) gave no information about the percentage of the TTO preparation used. In their study. Furthermore they used a two weekly lid scrub with TTO compared to Gao et al (2007) who used a more intensive weekly regimen leading them to conclude ‘our empirical dosage or scheduling of application may have resulted in inadequate treatment’- this may have been why they did not find a significant effect of TTO whereas other studies have found a positive effect.

Tetracyclines

The cornerstone of the oral treatment of Rosacea involves the use of tetracyclines. In particular, minocycline and systemic doxycycline are the most commonly used oral antibiotics and have been the mainstay of Rosacea therapy for more than 50 years. Combinations of topical and oral therapy may provide satisfactory results for individuals with mild-to-moderate Rosacea (Culp and Scheinfield, 2009).

The comorbidity based on a symbiotic relationship of bacillus Oleronius in Demodex mites justifies the consideration of a therapeutic strategy directed to killing the symbiotic bacterium via oral antibiotics such as tetracycline or doxocycline and to killing and preventing mating/re-infestation of Demodex mites, by lid scrub with tea tree oil.

An advantage of taking this drug is the ability to combine it with topical treatments, Culp and Scheinfield (2009) found the combination of doxycycline and metronidazole gel 1% the best therapy in Demodex treatment.
Pregnant women and Breastfeeding mothers should avoid taking tetracycline as it can be passed on to the nursing baby through the breast milk.

Pilocarpine

Fulk et al. (1996) demonstrated that treatment with 4% pilocarpine HCl gel decreased the number of parasites, and diminished itching.
Participants were examined for Demodex and subjects with abundant mites were invited to the study. 4% pilocarpine gel treatment was given to one eye and the other eye was untreated. After two week of treatment with 4% pilocarpine gel the mite counts in the treated eye where reduced significantly.
The results of the study of Fulk et al. (1996) did not indicate that pilocarpine gel was more effective than other ointment. Gao et al. (2005) found that 4% pilocarpine could not kill Demodex in 150 minutes (figure 3).

Patient instructions:

In general, patients with Rosacea should avoid skin care regimens that contain toners, astringents, abrasives, and sensory stimulants (Bikowski, 2001; Draelos, 2002).
Soaps and cleansers that are based on alcohol and harsh chemicals could aggravate the condition and should be avoided (Ayres, 1961). Lid margin hygiene can influence Demodex counts and improve the condition, but miciliare solutions and shampoo does not eradicate the mites. (Gao, 2005)
Patients should be encouraged to purchase a supply of Ocusoft Plus Lid Scrub pads (Cynacon/Ocusoft). The lid scrubs pads make it easier to thoroughly scrub the lash margins, eyelids and eyebrows.

Besides the daily eye lid hygiene and lid scrubs and the instruction on how to use their medication, patients should be informed about the regular use of sun-creams and how to prevent aggravation of the Demodex infestation (see for example table 1).
To prevent re-infestation the patient should wash the entire bedding and pillows with hot water or a warm dryer immediately after the first in-office treatment, and then wash them regularly no less than once every week.
Makeup should not be used for at least 1 week and all old makeup should be discarded.
Patients should consider using tea tree soap for their face and tea tree oil hair shampoo as well as there is growing evidence to suggest this works (see for example Gao et al (2005); Lacey et al. (2007)).
Patient's relatives should be encouraged to have an evaluation, as they are frequently also infested.

Diet:

Even though there is no special diet to prevent Demodex, there are factors that may change the environment to encourage mites' proliferation for example sunlight exposure and abrupt changes in temperature (Liu, 2010).

In a randomized placebo controlled trial Mascai (2008) investigated the effects of omega 3 fatty acids in patients who suffered from meibomian gland disease and blepharitis. Supplementing omega-3 fatty acids encourages the production of anti-inflammatory prostaglandins and modifies the composition of meibomian lipids. The results demonstrated an improvement in their overall Ocular Surface Disease Index (OSDI) score, tear break-up time (TBUT), and meibum score. They concluded that when the intake of unprocessed oils, cold-water fish and natural oils is low, omega-3 fatty acids can help to improve the tear film.

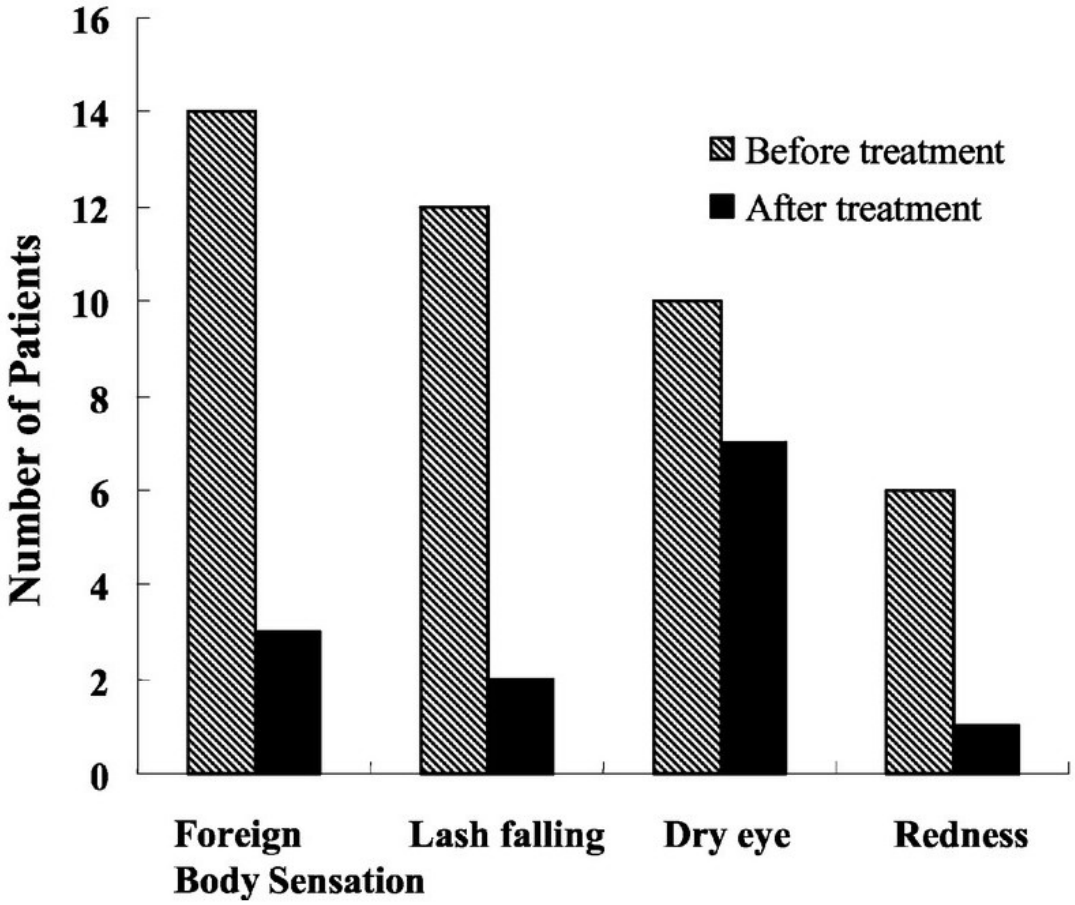

FIGURE 4. 2ILLUSTRATIVE BAR SHOWING THE INCIDENCE OF SYMPTOMS AMONG DEMODECOSIS PATIENTS BEFORE AND AFTER TREATMENT WITH AN OINTMENT CONTAINING 5% (W/W) TEA TREE OIL OINTMENT.(HTTP://WWW.GOOGLE.COM/PATENTS/US8455015)

Counselling and referral:

The American Academy of Ophthalmology (AAO) (2011) emphasize that an important aspect of caring for patients with demodectic blepharitis is to educate them about the chronicity and recurrence of the disease process. Patients should be informed that the results of the treatment frequently improve the symptoms but are rarely eliminated.

Another recommended AAO guideline is the prompt referral to an ophthalmologist when a patient, visiting a non-ophthalmologist health care provider, indicates one of the following:

- Visual loss
- Moderate or severe pain
- Severe or chronic redness
- Corneal involvement
- Recurrent episodes
- Lack of response to therapy

6.0 Demodex in the optometric practice

As mentioned earlier, Demodex infestation is a common cause of chronic and non-responsive blepharitis (Liu, 2010). In an optometric practice many patients with dry eyes, and blepharitis are managed. In the clinical management guidelines from the College of Optometrists, the pharmacological and non-pharmacological treatment options in the optometric practice are fully described. Also possible management by an Ophthalmologist and evidence based research are mentioned (College of Optometrists, 2014).

Special attention should be paid to complaints of itching of the eyelids (especially in the morning), itching eyebrows, loss of eye lashes, foreign body feeling and burning sensation. Slit lamp evaluation can indicate the possibility of Demodex as cylindrical dandruff while oilier eyelids gives the punch line; a non-invasive Demodex identifying method will confirm the suspicion.
The most important part is to inform the patient about this condition and give detailed instructions for eyelid care regime, risk factors for re-infestation and follow up appointments.

Work flow chart:

To help visualize what happens if a patient has a Demodex infestation a flow chart is included which has been created by the author (see figure 6, and appendix-1).
This chart gives step by step information how to detect Demodex, and helps in the decisions making for detecting and treatment of Demodex in an optometric practice.

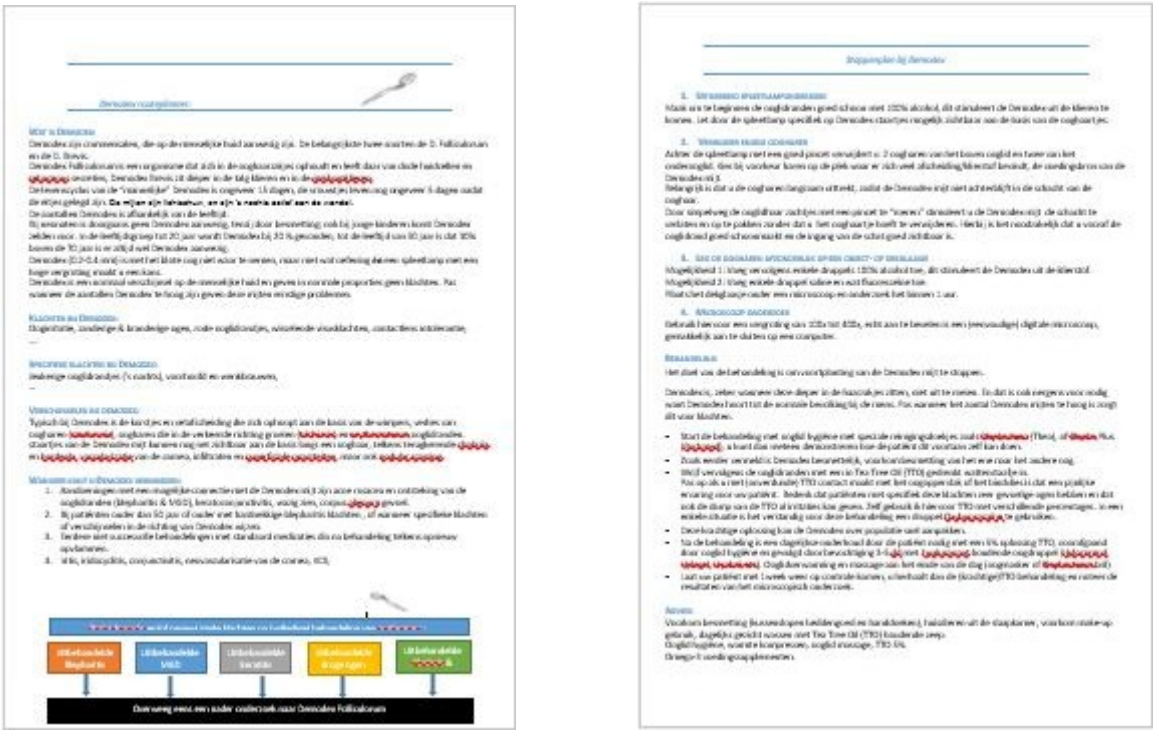

Figure 5: Flow chart for detecting and treatment of Demodex in the optometric practice (Jan de Groot, 2014)

7.0 Results/Discussion

Demodex can be considered as an normal inhabitant of the human skin. In the majority of cases symptoms of Demodex are not detected and there are no adverse symptoms.

Demodex Folliculorum is a condition that is often related to the patient's age and skin condition and is more common amongst patients with immunodeficiency.
Demodex Folliculorum is more frequent in patients with Rosacea and the mite count is also higher in patients with blepharitis. Both conditions are related to complaints of ocular irritation, dry eyes and visual complains (Hsu et al., 2009), and are possible triggers for carcinogenesis in basal cell carcinomas of the eyelid (Erbagci et al., 2003).
The main ocular complains are: itching eyelids and eyebrows especially during the night and in the morning, dry eyes, redness and blurry vision (see table 2).

The first step in the detection and diagnosis of Demodex is history taking, followed by a slit lamp examination.

Cylindrical dandruff, misdirected eye lashes and loss of lashes can indicate above normal Demodex counts. Several invasive methods of lash sampling for observations of Demodex under a microscope such as epilation of eyelashes and non-invasive methods such as confocal laser scanning microscopy and standardized skin surface biopsy (SSSB) are used to detect and count the Demodex (Lacey et al., 2013). The non-invasive technique of sampling Demodex by rotating the eyelash, (Mastrota, 2013) is very useful in a optometric practice where a slit lamp is routinely used. The diagnosis of Demodex is based on clinical findings of blepharitis, recurrent chalazae, madarosis and trichiasis after slit lamp findings.

A definitive diagnosis of Demodex can be made by microscopic conformation after taking lash samples. Above 6 or more mites per 16 lashes or more than five mites per lash (Coston, 1967) indicates significant Demodex invasion. The use of fluorescein dye makes the detection, evaluation and counting of Demodex in practice under a microscope easier.

The mainstay of treatment is to lower the density of the Demodex mites. Eyelid hygiene as described in the work flow chart (appendix 1) is the first step in fight against Demodex. The conclusion that the Demodex mites are a vector of the bacillius Oleronius bacteria, which functions as a co-pathogen in the development of severe forms of blepharitis, is an important step in the treatment (Szkaradkiewicz et al., 2012). The bacterium Oleronius is sensitive to different antibiotics as doxycycline and ivermectin (Lacey et al., 2007).

Tea tree oil is an effective and safe treatment for Demodex (see for example Koo et al.,2012). Weekly in-practice lid scrubs with 50% tea tree oil combined with a daily in-house lid cleaning of the eyelid margins with 5 % tea tree shampoo, has been shown to be a very effective method for eliminating Demodex resulting in a significant reduction of inflammatory signs and visual improvement (Gao et al., 2012). The flow chart (appendix 1) can be used as a guidance for treatment Demodex Folliculorum in the optometric practice. Ivermectine administered orally or topically and combined with permethrin can also be used to eliminate Demodex. However some side effect are reported (diarrhea and nausea) although it is particularly useful in case of unsuccessful treatment due patient compliance (Holzchuh et al., 2011).

Treatment with Petroleum jelly appears to be promising although there is still a lack of evidence about how beneficial it is, and there is no evidence to suggest that Petroleum jelly eradicates Demodex mites. Dietary supplements may also help. For example supplementation with Omega-3 fatty acid dietary has been found to improve both ocular health and patient dry eye symptoms (College of Optometrists, 2014)).

Regardless of the treatment method patients should be encouraged to change bedding and towels at regular intervals and not to share hair combs etcetera in order to prevent re-infestation. Good hygiene is thought to reduce the chances of Demodex infestation and demodicosis.

Demodex are greatly underdiagnosed, under treated and underappreciated. (Hom et al., 2013) That makes the treatment a challenge for the daily optometric practice to help patients with non-responsive dry eyes and blepharitis (Kheirkhah et al., 2007).

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APPENDIX-1

Demodex Flow chart

What is Demodex:

Demodex are commensals, they are present on the human skin. The two most important species are D. Folliculorum and D. Brevis. Demodex Folliculorum lives in the hair follicles and feeds on dead skin cells and sebaceous secretions. Demodex Brevis lives in sebaceous- and meibomian glands.
The life cycle of the "male" Demodex is about 15 days, the females live about 5 days after laying its eggs. The mite are photophobic and active at night. The number of Demodex present are age dependent:
Neonates normally have no Demodex, only if contaminated; in young children it is also rare. In the age group till 20 Demodex is found in 20 % of the humans, in the age group till 50 it is 30% and for the group over 70 years of age Demodex is always present. Demodex (size 0.2-0.4 mm) is not visible by the naked eye but, with a good slit lamp and high magnification and some practice it is possible to see Demodex if present. As Demodex are commensals, there will not be any complaints if the number of Demodex is within normal limits. Only if the number are rising these mites can cause severe problems.

Problems caused by Demodex:

Eye irritation, gritty and burning eyes, dry eyes and red eyelid margins, changing visual complaints, contact lens intolerance, chalazae.

Specific complains in Demodex:

Itchy eyelid edges, forehead and eyebrows, tingling of the skin especially at night.

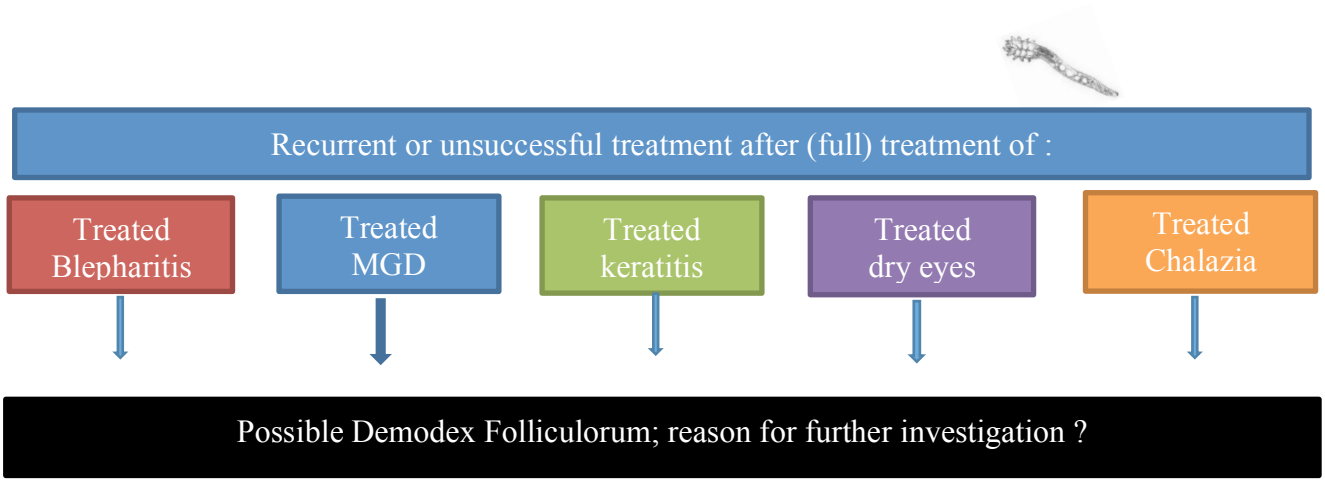
Symptoms in Demodex:

Typical for Demodex we see crusting and sebaceous discharge at the basis of the lashes, loss of lashes (madarosis), lashes growing towards the eye (trichiasis) en erythematic eyelid margins.
Sometimes the tail of the mite is only just seen at the basis along the lash, recurrent chalazae and hordeola, vascularization of the cornea, infiltrates and superficial opacities, as also nodular scarring.

When is a patient suspicious for Demodex::

Diseases which is strongly related to the Demodex mite are acne rosacea and inflammation of the lid margins (blepharitis & MGD), kerato-conjunctivitis, blurry vision, corpus alienism feeling.

1. Patients over 50 years of age with recurrent blepharitis, or when specific complaints point in the direction of Demodex.
2. Previous unsuccessful treatment with standard medication.
3. Iritis, iridocyclitis, conjunctivitis, corneal neovascularization and KCS,



Demodex Flow-chart

1. Slit lamp

Start with cleaning eyelid margins very carefully with 50 % or 100% alcohol, this stimulates Demodex to surface. Specifically look for the Demodex tales at basis of the lashes, or Demodex on the surface (high magnification).

2. Selection of the eye lashes:

Invasive: Behind the slit lamp with a good pair of tweezers , remove two lashes of the upper eyelid , and two of the lower eyelid Preferably choose hair at the place where there is a lot of separation / glandular substance is , the food of the Demodex mite . It is important to slowly pull the eyelashes so that the Demodex mite does not remain in the shaft of the eyelash .
Non-invasive: By simply gently rotating one eyelash with a tweezer, the Demodex mites are stimulated to leave the shaft, without removing the eyelash. It is important that prior to this stirring, the eyelid margins are properly cleaned, and the orifices are free of dandruff.

3. Examination of the sample lashes or selected material:

Place the selected epilated lashes or sampled dandruff on a glass slide.
Possibility 1: Add a few drops of 100% alcohol and saline , this will stimulate the Demodex from the dandruff (wait for 20 minutes).
Possibility 2: Add a few drops of saline and fluorescein (induces expansion and dissolution of the cylindrical dandruff).
Place the mounted coverslip under a microscope an make the observation within 60 minutes.

4. Microscoop detection

Demodex is visible under a microscope with a magnification 100x tot 400x, use a simple digital microscope, which is ease connected to a computer. It allows you to make fabulous pictures.

5. Treatment of Demodex:

The goal of treatment is 1. To eradicate the adult mites and prevention of further mating.
2. Avoiding re-infestation and alleviating the patient's symptoms.

Demodex, especially when bedded deep in the hair follicles, cannot be exterminated. Because it is a common commensals in humans, it is not necessary to eradicate them completely. Only when there are abundant of mites can exacerbate coexisting lid-margin disease and causes complaints.

- Start the treatment with eyelid hygiene. Use either Blephaclean (Thea), of Blepha Plus (Rockmed) and demonstrate how the patient needs to use these to remove dandruff and crust of the eyelid margins.
- Demodex is contagious, try to avoid contamination from one eye to the other eye, use separate cleaning tissues.
- Than rub the lids with Tea Tree Oil (TTO) on a cotton tip.
- Mind you that the (undiluted) TTO does not makes contact with the conjunctiva or cornea, this will be a painfully experience for your patient. If patients have very sensitive eyes even the damp of the TTO can irritate the eyes. I use TTO in various percentages. Sometimes sedation of the eye with Oxybuprocaïne is a good option for comfort of the patient.
- This powerful solution can solve the Demodex problem in a population fast.
- After the treatment one needs a daily continued treatment with a 5% solution TTO, and eyelid hygiene followed by 3-5 dd a hyaluronate containing eye drop (Hylocomod, Hylogel, Hyabak etc). Eyelid warming and massage at the end of the day (eye mask or Blephasteam goggle)
- Your patient has to return within one week for checkup; repeat the treatment with the in-office TTO treatment and write down all the outcomes of the microscopic findings.

6. ADVICE TO THE PATIENT:

Try to prevent contamination: daily changing pillowcase, towels, bedding), no pets in the bedroom, do not use make-up, wash your face daily with soap containing Tea Tree Oil (TTO). Omega-3 fat acids will improve the condition.
People living together with the same complains should be examined and treated to.