The association between skin disorders and Demodex species mite including their causes, prevention, and treatment options.

Microbiology is the branch of science for microorganisms, this is a very important area of study as all areas of life are affected by the micro-biotic world. Economically microbes are very important for food production and preservation, all the way to engineering antibiotics that improve quality of and extend our life expectancy. On the flip side they also pose huge problems for the health care system. One way is we continuously find ways to suppress and remove microbes from ourselves. An equally important fact to know, microbes continuously change into forms that are becoming resistant to our health care methods. This creates limits to our current options of antibiotic treatments. Only through investigations and increased knowledge of them will we know; how they work, their needs, invasion tactics and evolutionary stages. By accomplishing this will we be able to rise above the perpetual challenges of being at the top of the food chain into participating in the web of life. We will be able to protect organisms by comprehending their true value to us. For my area of research, I am looking into the *Demodex* mite Sp. and despite *Demodex* being the most common human and canine microscopic ectoparasite found on the skin. The *Demodex* species is not considered a significant source of global concern with the spread of disease and has often been overlooked in the human population. With new findings are able to indicate that *Demodex* can also play a pathogenic role as vectors in more localized groups and can have a; mutualistic, commercial, or parasitic association with its host pending the hosts' skin composition(1). *Demodex* mites have been colonizing and living in hair follicles and sebaceous gland on most of the mammalian species for millions of years (7). Due to this very specific niche, they have remained relativity unchanged due to the protection they receive from the host (7).

Demodex species are in the family *Demodicidae* the super family *Cheyletoidea*(3), the class *Arachnida* and subclass or order *Acarina* (8). Their 15 day life cycle is short and includes; eggs, larval, protonymph, deutonymph and then finally an adult that can reproduce (3). Interestingly the adult population is generally larger than the

juvenile stages (3). These two species can be found worldwide in all races investigated, and the infection rate seems to be related to age, with the very young and old having the smallest inhabitation numbers and the 20-30 age range having the highest numbers (8). This is because during this time is when the body produces the most amounts of sebum, a food source for the mites (8). *Demodex* mites are most commonly found on the face and less commonly on other parts of the body (3). *D folliculoruom* is generally found in the follicular openings while *D brevis* is in the sebaceous glands and generally found only singly (3). *Demodex* Sp are suspected of being Vectors of pathogenic organisms, especially in the past with diseases like *leprosy bacillus* (3). Today scientists can see through electron-microscopy that *Demodex* has bacteria on its surface as well as in its gastro-intestinal tract (3). Also it has been found that eyelashes without mites have less amounts of *Staphylococcus aureus* when cultured than lashes with mites at a rate of 69% more in mite infected skin (3). *D. folliculorum* causes anterior blepharitis of the eye lid, specifically where the hair follicle grows and *D. brevis* causes posterior blepharitis with meibomian gland dysfunction and keratoconjunctivis (3). This is because *D. folliculorum* effects the follicular and *D. brevis* effects the glands (3). Both types are effectively treated with either a 50% lid scrub or 5% lid massage of tea tree oil (4). Studies on alcohol, tea tree oil, caraway oil and dill weed oil in 100% solutions have shown mites maximum survival time, for 100% death rate of mites at 15 min. (5). However the glands and follicles protect them, so only mites that were at least 1/2 exposed were observed (5). The conclusion of the study indicated that tea tree oil was most effective and daily treatment for 4 weeks brought the ocular mite count down to zero in 7 out of 9 cases (5).

The first *Demodex* mite was discovered by Gustav Simon, a German dermatologist. Gustav one day discovered a worm like object in some skin he was examining (1). Upon further investigation under the microscope he could see a head, legs, anterior and posterior body parts and it moved (1)! The name *Demodex* was given by Richard Owen in 1843 from the words ‘demo’ meaning lard and ‘dex’ meaning boring worm’(1). The life cycle of the mite is 14.5 days long and they only come out of their hair follicle at night as they are negatively phototaxic, plus they

move up to 16mm per hour(1). The mites can carry bacteria on their surface as they contain lipase enzymes, they also have endobacteria (1). In normal presentation the host immune system detects and tolerates the presences of the mite. While scientists do see an immune linkage to predisposition of developing generalized demodicosis, the primary leading defect to the disease is still unknown. As only a percent of all dogs that display generalized demodicosis also have an immunodeficiency (7). Despite not fully understanding the complicated nature of the mite and the skins relationship, we do understand the mechanisms for the immune response (7). First a "toll-like receptor-2 of keratinocytes" demonstrate recognition of the mites chitin and will elicit an innate immune response (7). This part of the response process is still poorly understood, but evidence is pointing to this being the key mechanism regarding the control of mite proliferation (7). The mouse model ($STAT^{-/-}/CD28^{-/-}$) was used for testing and early results are showing a complicated interaction most likely involving humeral and cellular mechanisms as well as requiring co-stimulatory molecules (CD28) (7). In advanced stages generalized demodicosis canines show a phenotype similar to that of T-cell exhaustion (7). This is characterized by low interleukin 2 production, high interleukin-10 as well as the transforming growth factor-^{beta} production, which is done by the lymphocytes (7). Treatment with Acaricidal medication like macrocyclic lactones will decrease the mite load and reverse T-cell exhaustion which leads to a clinical cure (7).

In the Mutualistic relationship the mites live inside the hair follicle and feed on the hosts sebum, in return, they keep the hair follicle free from other bacteria and organisms, possibly by ingesting them (1). Another idea is that they, like other bacterial flora, also have immune-reactive lipase (8). These produce free fatty acids from the sebum triglycerides and could be a defense against other skin pathogenic bacteria, esp. staphylococcus aureus and streptococcus pyogenes (8). The author indicated that is it possible that the hosts' tolerance of the mite may be down regulated by the mite its self, but it does still have a regulating effect on the total numbers of mites living on the host (1). Only when the mites numbers increase to excessively high or critical numbers can they develop a pathogenic role (1). When this happens the cytokine/chemokine will be released and you will see an

inflammatory response and visible changes to the skin as it causes distension of the follicles through keratinocyte disruption (1). Then once the follicle ruptures, a 'granulomatous foreign-body type of reaction' results (1). The triggering agents in this chain reaction may be initiated by several different factors like natural physical barriers in the skin that may be absent(1). The authors propose that their findings suggest that epidermal growth factor receptor inhibitors may reduce/impair cutaneous defense mechanisms resulting in increased *Demodex* proliferation (1). Other preliminary studies show that the mites proliferate when the PH is higher, reducing the hydration level of the skin which could also be a contributing factor (1). People with papulopustular rosacea who show higher levels of mites, have not only the higher PH but also a different composition of the fatty acid layer of their skin (1). Their skin has increased levels of myristic and linoleic acid as well as reduced levels of specific saturated fatty acids (1). Knowing this, the author theorizes that this micro environment may be conducive to the overgrowth of the mite (1).

There are many types of mites in the genus *Demodex*, and while they all will have skin issues in the host when overpopulating, where the mite live also plays a role in the specific types of symptoms the host will show (2). Some live and infest the outer or superficial layer of the skins while others will infest and live inside of the hair follicles (2). This means that their adaptive strategies will differ and that there method of host nutrient uptake is also different (2). These differences will mean that they will also have differing treatment methods for maximum results with their removal (2). The Canine *Demodex Sp. Cornei* lives in the outer skin layers while *Demodex canis* lives inside the hair follicle (2). In humans *D. folliculorum* is found in the follicle and *D. brevis* is found in the skin (8). There are about 65 species of *Demodex* total (8). The adult mite is .3-.4mm long with brevis being shorter at .15-.2mm (8). This is one species that the females are smaller than the males, being shorter and rounder (8). Invisible to the naked eye they can be seen under a microscope displaying a semitransparent body that is elongated, consisting of two fused segments and eight legs attached to the first segment (8). Its body is covered in scales to help it anchor its self in place and has pin like mouth parts (8).

Canine Demodicosis is a common skin issue in veterinary medicine, and the mites are extracted from a deep skin scraping (2).The symptoms vary widely from dermatitis, pustules, crusts, follicular hyperkeratosis, seborrhea, alopecia, hyperanimia and erythema (2). While the exact cause is still unknown, research does indicate that immunosuppressive therapy (like hormones and cytotoxic therapy) as well as any immunosuppressive diseases do cause a pre-disposition to it, studies have also shown that just stress can also cause demodicosis with no immunosuppressive issues, this is commonly true in puppies (2). Canines have two forms of presentation of demodicosis called generalized and localized (3). The localized form is normally found on the face, only in small patched and normally spontaneously heal (3). Sometimes the localized form progresses to the generalized form which is generally accompanied by a super infection of *S. aureus* that can lead to pyoderma(3). Small number of cases can be so sever as to warrant euthanasia (3). In very heavy infestation the mites can even be found in the internal organs (3). While studies show that the majority of healthy dogs have the mites and the can be considered part of their normal cutaneous flora (6). The mites are transmitted to the puppies in the first few days after birth (6).

Humans are not spared where *Demodex* mites are concerned, the two species found on the human epidermis are *D. folliculorum* and *D. brevis* (3). The most common age range for infection in humans is 20-30 years old when sebum secretion is at the highest levels (8). Sebum is a type of oil AKA a fat, and coincidentally topical lotions and creams that contain fats will also encourage overpopulation of the mites (8). In younger children and older adults there is still a population of mites, but due to low oil levels in the skin during these ages, the mites do not have enough nutrients to over colonize easily (8). Also interestingly males have a higher rate of infestation than that of females at a rate of 23% to 12% introspectively, as-well-as harboring more of the *Sp. Brevis* than female counterparts (8). Transmission occurs through contact of hair, or sebaceous glands (8).

In conclusion we find that with *Demodex*, like most things in life, needs a balance to be maintained for any mutualistic effects to happen. They have a very well-defined niche and they are good at occupying it. Up to recent days, when

investigations have led to identifying them so that we can understand how to eradicate them or just gain better control over them, they have stayed relatively unchanged. As we move forward with treatment options it will be interesting to see the impact that we will have and how they will evolve to survive. In the end understanding the sensitive relationship between the host and the mite will be the best treatment option, as they have lived in relative harmony for millions of years with many species of hosts. So, learning what is the limiting factor that a healthy normal presentation host provides and being able to then re-create it or to support the hosts immune response to be able to better provide it will be the best option. If we take the track of eradicating them entirely, we may just open up the host to a variety of other parasites. At the same time because the mites do carry bacteria inside and on them, they could be vectors of horizontal transmission, which could be problematic on an even larger scale. So additional studies are definitively needed to further assess the intricate nature of the relationship, because, unfortunately when the balance is thrown off, the outcome can be painful and unsightly on the host. In extreme cases in the animal world it can even lead to their death, this is not an outcome that will be tolerated for long in the quickly advancing sciences of the check and mate dance between the micro and the macro worlds.

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