

# Advances in Research on Diabetes and Ocular Surface Demodex

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## Article Info

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## Abstract

Demodex infection on ocular surface is a common ocular parasitic disease, which harms patients' physical and mental health and quality of life. Studies show that the incidence of ocular Demodex in diabetic patients is higher than that in normal people, and as the incidence of diabetes increases year by year, the ocular Demodex infection also increases, making it a disease that impairs the normal function of the eye of diabetic patients. However, the mechanism of diabetic ocular surface Demodex infection is still unclear and the treatment method is single and lacking. And there is no unified standard and lack of clinical data on the prognosis of patients. It needs more concern of patients and even endocrinologists and ophthalmologists. This article summarizes and analyzes the recent studies on diabetes and ocular surface Demodex infection in order to provide reference for clinical diagnosis and treatment.

The infection rate of ocular surface Demodex in diabetic patients is higher than that in normal people according to previous studies<sup>1</sup>. This indicates that there may be a correlation between ocular mite infection and diabetes. Based on the IDF Diabetes Atlas, global estimate of diabetes prevalence over 18 years old was 8.8%. These numbers are expected to increase to 9.9% in 2045<sup>2</sup>. Diabetes mellitus has become one of the top chronic diseases that threaten the health of our citizens. With the increase of diabetes, the associated ocular surface Demodex infection rate may also increase, which further increases the difficulty in treating ocular surface Demodex and threaten the eye health of diabetic patients.

As the relevant studies are rare and the mechanism of ocular epidemic Demodex infection in diabetes mellitus is unclear, this article summarizes and analyzes the recent studies on diabetes mellitus and ocular surface Demodex infection, in order to provide a reference for clinical diagnosis and treatment and further mechanism exploration.

## Overview of Ocular Surface Demodex Infection

### Demodex and ocular infection

Demodex is a small permanent parasitic mite parasitizing in human and mammalian hair follicles and sebaceous glands<sup>3</sup>. There are two types of Demodex that can reside in the human body, namely Demodex folliculorum and Demodex brevis<sup>4,5</sup>. In the eyes, Demodex folliculorum usually accumulate in clusters in the roots of the eyelashes and follicles, causing frontal blepharitis. Demodex brevis live alone in sebaceous glands and tarsal glands, causing posterior blepharitis<sup>6</sup>.

According to recent studies, Demodex infection is associated

with many common ocular surface diseases, such as adult blepharitis<sup>7,8</sup> and allergic conjunctivitis<sup>9</sup>. Patients with ocular surface Demodex infection often have clinical symptoms such as dryness, burning, grittiness, photophobia and trichiasis. Blurred vision and decreased vision may occur when the cornea is involved. Demodex infection can occur in all ages. The onset of Demodex infection is usually slow and eyes are generally both affected.

### Diagnosis of ocular surface demodex

1. Chronic or subacute course of disease in both eyes, with ocular symptoms such as redness, itching and foreign body sensation, or accompanied by repeated attacks and refractory chalazal swelling.
2. Abnormal eyelashes, lipid sleeve secretions at the root of eyelashes (with diagnostic value), and hyperemia and hypertrophy at the edge of eyelid.
3. Positive for Demodex mite test. (1) Demodex mites in all stages were counted; (2) in adult patients, the count of Demodex in any one of the four eyelids reached 3 /3 eyelashes; (3) if it is less than the above criteria, it is suspicious and positive, and it should be combined with clinical manifestations. If necessary, it can also be checked for other pathogenic microorganisms, such as bacteria and fungi.

At the same time in line with the above 3, it can confirm the Demodex palpebrachitis. In line with the first two, it can be repeatedly taken and examined with the help of laser confocal microscope in vivo in who Demodex mites were detected in eyelashes but the count was not up to the standard. If the count is still not up to the standard, it can be diagnosed as suspected Demodex palpebrachitis. Demodex palpebrachitis was not diagnosed if only Demodex was positive without clinical signs and symptoms<sup>10</sup>.

### Treatment of ocular surface demodex infection

At present, the clinical treatment of ocular surface Demodex infection is not multiple. 2% mercuric chloride can be used to alleviate the infection of ocular surface Demodex, while some patients have been reported to have toxic effects after application<sup>11</sup>. Demodex can be eradicated in 4 weeks after the use of tea tree essential oil<sup>12</sup>. However, contact dermatitis is prone to occur when using low concentration tea tree essential oil locally<sup>13</sup>. Besides it has high cost and long treatment cycle. In addition, tobramycin dexamethasone eye ointment also has a good therapeutic effect on ocular surface Demodex<sup>14</sup>. After Junk et al. used eyelid wash solution combined with topical 2% metronidazole gel for a month, chronic otitis parenchyma was relieved and the number of ocular surface Demodex was reduced by half<sup>15</sup>. Oral ivermectin can also treat and alleviate ocular surface Demodex

infection<sup>16</sup>, and combination therapy between ivermectin and metronidazole(71.6% complete remission) was better than ivermectin alone(45% complete remission )<sup>17</sup>. At present, there is no clinical data on the recurrence and prognosis of ocular surface Demodex infection around the world.

### Clinical Study on Diabetes Mellitus and Ocular Surface Demodex Infection

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia caused by multiple causes which caused by the deficiency of insulin secretion and/or action. With the increasing prevalence of diabetes, the incidence of eye diseases related to diabetes is also increasing year by year.

According to relevant studies, the infection rate of ocular surface Demodex in diabetic patients is much higher than that in normal people. As early as 1990, Clifford CW et al. reported that diabetic patients had an increased risk of ocular surface Demodex infection compared with normal people<sup>18</sup>. In 2017, Zeynep Tas Cengiz et al. analyzed the potential pathogenic factors of ocular surface Demodex infection and found that in diabetic patients, ocular surface Demodex infection rate was higher than that in healthy controls<sup>19</sup>. Poor glycemic control in diabetic patients also increases the risk of ocular surface Demodex infection. In Gökçe Cumali et al. 's study, people with poor glycemic control (HbA1c>7%) had a higher infection rate of ocular surface Demodex than those with good glycemic control (HbA1c≤7%)<sup>20</sup>. This suggests that poor glycemic control may increase the susceptibility of diabetic patients to Demodex. The study also pointed out that the higher the blood sugar level of diabetic patients, the higher the risk of ocular surface Demodex infection<sup>20</sup>. It suggests that the infection of eye Demodex may be related to the blood glucose concentration in diabetic patients, and diabetic patients with eye diseases will further increase the incidence of eye Demodex infection. In a 2011 study of 84 samples (42 normal subjects and 42 diabetic retinopathy patients), the odds of detecting ocular surface Demodex were greater in the diabetic retinopathy group than in the control group<sup>21</sup>. The above studies indicate that diabetic patients have a greater susceptibility to ocular surface Demodex and are more likely to cause the infection of ocular surface Demodex, which not only further increases the difficulty of treating ocular surface Demodex, but also further poses a threat to the physical and mental health of diabetic patients.

Ocular Demodex infection, a common complication of diabetes, will further threaten the eye health and normal eye function of these patients and endanger the physical and mental health of patients. Some cross-sectional studies on diabetes mellitus and ocular surface Demodex infection indicate that diabetes mellitus can increase

the infection rate of ocular surface Demodex. However, prospective studies on diabetes mellitus complicated with ocular surface Demodex are still insufficient. There are not enough studies on the clinical diagnosis, clinical treatment, pathogenic mechanism and patient prognosis of diabetes associated with ocular Demodex. More prospective clinical studies are needed to provide evidence-based evidence for the causal relationship between the two, so as to provide a reference for the prevention and clinical treatment of diabetes associated with ocular Demodex.

## **Pathogenic Factors of Increased Ocular Surface Demodex Infection Caused by Diabetes Mellitus**

### **Decreased immunity**

Studies have shown that the infection rate of Demodex increases in patients with chronic renal failure<sup>19</sup>, HIV, undergoing hemodialysis<sup>22</sup>, cancer chemotherapy<sup>23</sup> and other weakened immunity. In patients with diabetes, many studies have shown that the body immunity of patients with diabetes will be reduced to different degrees due to various reasons, such as neutrophil chemotaxis<sup>24</sup>, mast cell function<sup>25</sup>, the interaction between white blood cells and endothelial cells<sup>26</sup>, lymph node clearance of pathogens<sup>27</sup> decreased, TNF, IL and prostaglandin release decreased<sup>28</sup>. The physiological dysfunction of these cells or cytokines will lead to the decrease of immune function of the body and increase the susceptibility to ocular Demodex. In normal healthy people, when the Demodex is in excessive proliferation, the strong immunity will cause a series of immune reactions in the body and inhibit the proliferation of the Demodex in order to resist the damage of the Demodex to the ocular surface. However, when the immunity of the body is decreased and the immune function is low, it can not effectively resist the infection of eye Demodex and cause a series of related inflammatory reactions. Therefore, the decrease of immunity may be an important reason for the increase of ocular Demodex infection rate in diabetic patients.

### **Changes of ocular surface flora**

There is normal bacterial flora on the ocular surface constituting a stable microbial community on the ocular surface and participating in regulating the normal micro-environment of the ocular surface in the normal ocular surface. Y. Huang et al. used 16s-rDNA gene sequencing to detect that the core flora of conjunctival microbial community consisted of *Corynebacterium*, *Pseudomonas*, *Staphylococcus*, *Acinetobacter*, *Streptococcus*, *Micrococcus*, *Anaerobic bacteria*, ciliates, *Siemens* and *Micrococcus*<sup>29</sup>. In patients with diabetes mellitus, normal ocular flora changes due to elevated blood sugar, decreased immunity, microvascular changes and so on. In patients with diabetes, the numbers of *staphylococcus epidermidis*<sup>30</sup>,

*staphylococcus aureus*, *Acinetobacter* and *Pseudomonas* at the genus level<sup>31</sup> were higher than normal, and the numbers of gram-negative cocci, *Escherichia coli*, *Klebsiella pneumoniae*<sup>32</sup> and *Bacteroidetes*<sup>31</sup> were also slightly higher than normal. Proteobacteria were at a lower abundance<sup>31</sup>. Changes in normal flora of ocular surface in diabetic patients lead to disturbance of ocular surface microecology.

In a normal organism, ocular Demodex are commonly found in the head and face<sup>33</sup>, which can regulate the activities of ocular surface bacteria and participate in maintaining the balance of ocular surface microecology. Relevant studies have shown that the symptoms of the eyes become worse after anti-mite treatment and then combined anti-bacterial treatment can make the disease relieve, which indicates that there is a balance between Demodex and ocular surface bacteria<sup>34</sup>. R Wolf et al. showed that Demodex could carry large amounts of bacteria on their surfaces, such as *Streptococcus* and *Staphylococcus*. The increase of Demodex proliferation makes the normal flora of ocular surface change, which causes the change of ocular surface microenvironment<sup>35</sup>. The increase of *Staphylococcus epidermidis* and *Staphylococcus aureus* in the ocular surface of diabetic patients may lead to the corresponding increase in the number of bacteria on the surface of eye Demodex, thereby increasing the probability of bacteria causing ocular surface diseases and increasing the occurrence of an inflammation on the ocular surface.

### **Changes of hair follicles and sebaceous glands**

The hyperglycemia environment in the blood of patients with diabetes will damage the endothelial cells of blood vessels in the whole body, leading to different degrees of lesions of blood vessels in the whole body, especially the small arteries in the whole body are prone to lesions<sup>36</sup>. The supply of oxygen and nutrients to cells in normal tissues and organs is completed by the corresponding arteries. However, due to the pathological changes in the blood vessels of patients with diabetes, tissues and organs supplied will be damaged to varying degrees, eventually leading to complications of diabetes<sup>37</sup>. Hair follicles are divided into terminal hair follicles, sebaceous glands, and hair follicles<sup>38,39</sup>. Most of the terminal hair follicles and sebaceous glands are located on the ocular surface. Hair follicles are active organs in the body, which need a special microenvironment, such as sufficient oxygen and nutrition. They are easy to be damaged during the process of diabetes, leading to hairless, fragile and slow growth<sup>40,41</sup>. Hair follicles remain empty for a period of time after hair loss and microorganisms are prone to invade hair follicles resulting in an infection of the hair follicles<sup>42,43</sup>. Also, in diabetes, it causes follicular dilation and changes in lipid synthesis<sup>44</sup>. The Demodex infection will lead to sebaceous gland secretion disorder, leading to increased sebum secretion<sup>45</sup>. Sebum increase will accelerate the proliferation

of Demodex as Demodex habit to feed on sebum<sup>46</sup>. The infection of ocular Demodex in diabetic patients may increase due to the damage of hair follicles, the change of the physiological state of hair follicle sebaceous glands, the increase of lipid synthesis, the hair follicle emptiness caused by hair loss and other factors.

At present, the mechanism of the increase of diabetic ocular Demodex infection is not clear, and further research is needed.

## Summary and Prospect

With the increasing number of diabetic patients, the incidence of ocular surface diseases in diabetic patients increases year by year. It is indicated above that there is a correlation between ocular Demodex infection and diabetes. It is important to prevent and control ocular surface Demodex infection in diabetic patients, improve the symptoms of ocular surface Demodex infection, and effectively treat ocular surface Demodex infection, so as to improve the quality of life of diabetic patients.

When patients with diabetes experience redness, itching and foreign body sensation, or are accompanied by recurrent attacks and chalazal swelling, doctors should consider whether there is ocular Demodex infection and improve relevant examinations if other diseases cannot be ruled out. Now ocular Demodex can be treated with 2% mercuric chloride, tea tree essential oil, tobramycin dexamethasone eye ointment, topical 2% metronidazole gel, Oral ivermectin and so on. Because of the change of ocular surface flora in diabetic patients, the treatment of ocular surface Demodex should be combined with antibacterial treatment to relieve symptoms.

At present, due to the single treatment means, the majority of medical workers are still required to further clinical and basic research on ocular surface Demodex infection. It is not clear why Ocular surface caused by diabetes Demodex infection rate increased and how to treat the patients. We still need more prospective clinical study of the causal relationship between them to provide evidence-based study and more basic research based on both the pathophysiology of correlation for further elaboration, in order to provide a reference for clinical treatment.

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