Original Article

Age differences in ocular demodicosis: Demodex profiles and clinical manifestations

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Background: *Demodex* infestation is highly age-dependent. Intriguingly, our previous studies that focused on children and young adult patients suggested that the clinical features of young patients were different from those studies enrolling mainly elderly patients. Whether age plays a role between young and elderly patients with ocular demodicosis remains unclear.

Methods: This prospective comparative study included 91 patients younger than 35 years and 92 older than 45 years with ocular demodicosis. *Demodex* mite count, symptoms, tear film, and ocular changes were compared between the two groups. Risk factors of meibomian gland loss (MGL) and corneal changes were analysed in the two groups.

Results: *Demodex* counts were comparable between the two groups. Young patients had higher *D. brevis* counts and overall percentage of *D. brevis*, while elderly patients had more *D. folliculorum* (all P<0.05). Irritation and blurred vision were more common in young patients, while eye fatigue and photophobia were more common in elderly patients (both P<0.05). The two groups had comparable tear volume and tear break-up time. Meibomian gland dysfunction was the most common sign in both groups but MGL was significantly more severe in young patients. More prevalent corneal changes and more eyelash disorders were found in young patients (both P<0.05). Female sex, a higher *D. brevis* percentage, lid margin anomalies, and MGL were associated with corneal change, while a higher *D. brevis* percentage and lid margin anomalies were related to MGL in young patients. MGL was associated with corneal change, but age was the only predictor of MGL in the elderly group.

Conclusions: Young patients with ocular demodicosis tend to have more *D. brevis* infestation, more MGL, and more corneal involvement.

Keywords: *Demodex* mite; meibomian gland; age

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Introduction

Demodex folliculorum (*D. folliculorum*) and *Demodex brevis* (*D. brevis*) are the only two species of mites that affect humans (1,2). *D. folliculorum* infests the hair follicle, while *D. brevis* resides in the sebaceous and meibomian glands (2-4). Ocular demodicosis has been implicated in ocular surface inflammation, including blepharitis, eyelash disorders, meibomian gland dysfunction (MGD), chalazia, and blepharoconjunctivitis (BKC) (5-10). The incidence of *Demodex* infestation increases with age: it is observed in 84% of the general population aged over 60 years and

100% of the general population over 70 years old but is reported to be very rare in healthy children under 16 years of age (11-13). However, we previously reported ocular *Demodex* infestation in 12 paediatric patients who were diagnosed with BKC but failed to respond to conventional treatments (8). To the best of our knowledge, this was the first time that *Demodex* infestation was detected in children without systemically immunocompromised status. Recently, we conducted an epidemiological survey and revealed a low *Demodex* mite count in 12.0% of healthy Chinese children aged between 3 and 14 years (14).

To mitigate the concern that the demodex infestation is age-related and much more prevalent in the elders, our previous studies focussed on young patients and found a high prevalence of keratitis (14,15). Ahmad also reported 6 cases of keratopathy in patients with *Demodex* infestation, 2 of whom were under 35 years (9). We wondered whether young patients are more susceptible to corneal involvement than elderly patients. However, other studies that mostly included elderly patients have shown that the most common clinical features are MGD and eye dryness with predominantly *D. folliculorum* (15-20).

Whether age plays a role between young and elderly patients with ocular demodicosis remains unclear. Herein, for the first time, we conducted a prospective observational comparative study to investigate the differences in clinical features between young and elderly patients with ocular demodicosis.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7715).

Methods

This study followed the principles of the Declaration of Helsinki (as revised in 2013) for the protection of human subjects in medical research and was approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University (No. 2017KYPJ042). All participants were given a full explanation of the study, and written informed consent was obtained.

Patients

A total of 183 patients with a confirmed diagnosis of ocular demodicosis were enrolled at the cornea outpatient department of Zhongshan Ophthalmic Center between March 2018 and July 2019. Patients were divided into two groups according to age: patients aged ≤35 years were included in the young group, and patients aged ≥45 years were included in the older group. All subjects were Chinese. Both eyes underwent examination, and the worse eye with more severe corneal fluorescein staining or more severe conjunctival injection was selected for comparison. If severity was equal in both eyes, the right eye was designated as the study eye. Patient with ocular diseases other than ocular demodicosis and senile cataract, prior ocular surgery history, and contact-lens wearers were excluded in our study. Any systemic disease was also excluded.

Diagnosis of ocular demodicosis

Symptomatic patents with ocular surface discomfort and clinical signs of cylindrical dandruff (CD) at eyelash roots were subjected to lash sampling and microscopic counting of *Demodex* as previously described (8,16,17) by a masked technician who had no idea of patients' clinical information. In brief, two lashes were epilated from each eyelid under a slit-lamp microscope and placed on a glass slide. One drop of saline or fluorescein solution was applied to dissolve the CD and to allow embedded *Demodex* to migrate out (17). *Demodex* species and counts for each patient were recorded and whose total counts greater than or equal to 3 in 8 lashes were recorded as *Demodex*-positive (21). Those symptomatic patients with positive *demodex* count were diagnosed as ocular demodicosis (20,21).

Evaluation of ocular surface parameters

The ocular surface examinations were as follows. Eyelid margin abnormalities were determined according to previously reported scoring criteria (22,23). The shape of the palpebral margin was observed under a slit lamp and checked for congestion of the palpebral margin, blockage of the meibomian gland opening, irregular shape of the palpebral margin, and backward displacement of the meibomian gland orifice opening. The score was 0 for normal and 1 point for the presence of any one of the above findings. The accumulated scores were recorded as the palpebral margin morphology score (range, 0–4) (22,23). Eyelash disorders were defined as trichiasis, CD, or scaly discharge at the roots of lashes.

Tear break-up time (TBUT) was measured using fluorescein solution under slit-lamp (24). The severity of MGD was graded by meibography using a Keratograph 5 M (Oculus; Wetzlar, Germany) as previously reported;

that is, 0 for no meibomian gland loss (MGL), 1–2 for less than one-third total MGL and considered as 'mild', 3–4 for one-third to two-thirds total MGL and considered as 'moderate', and 5–6 for more than two-thirds total MGL and considered as 'severe' (25). Tear meniscus height (TMH) was also evaluated under a Keratograph 5 M. According to a published corneal grading scale, corneal pathologies were graded by slit-lamp photographs as '0' for no abnormal finding, '1' for superficial punctate keratopathy (SPK) only or limbitis only, or '2' for stromal involvement such as infiltration or ulceration (7).

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY). Two investigators performed grading of MGD and corneal changes. Any inconsistent grading between the two was arbitrated by a third investigator who did not know the other clinical information. Continuous variables are reported as means ± standard deviation. Categorical variables were recorded as presence (yes) or absence (no) and reported as the number (percentage) of subjects. Variables were compared between groups using Student's *t*-test, the Kruskal-Wallis test, Pearson's χ^2 test, and Fisher's exact test, as appropriate. Those with probable statistical significance (P<0.15) were subjected to multiple logistic regression to determine factors associated with corneal changes and MGL. In all analyses, P<0.05 was considered statistically significant.

Results

Demographic data

Among 183 patients (73 males, 110 females) with ocular demodicosis, there were 91 patients (17.7±6.9 years, range: 6 to 30 years, 40 males and 51 females) in the young group and 92 patients (55.5±9.3 years, range: 45 to 81 years, 33 males and 59 females) in the elderly group. Sex was matched between the two groups (P=0.293, *Table 1*). Details of patient demographics and clinical data are provided in *Table 1*.

Prevalence of Demodex infestation and Demodex mite profiles

The total *Demodex* count was comparable between young and elder patients [6 (4, 8) *vs.* 7 (4, 13), P=0.176]. However, the *D. brevis* counts and the percentage of *D. brevis to* total *Demodex* (*D. brevis* %) of the young group was significantly higher than that of the elderly group [2 (1, 3) *vs.* 0 (0, 2), 43% (25%, 100%) *vs.* 4% (0, 21%), both P<0.001, *Table 1*]. In contrast, *D. folliculorum* was more dominant in the older group [6 (3, 10) *vs.* 3 (2, 6), P<0.001, 96% (73%, 100%) *vs.* 57% (40%, 82%), both P<0.001, *Table 1*]. Mixed infestation, i.e., both *D. folliculorum* and *D. brevis* were detected in 48.9% (45/92) and 78.0% (71/91) of elder and younger groups respectively.

Symptom profiles

Eye dryness, itching, fatigue, pain, blurred vision, photophobia, and redness were complaints common to all patients. Among these symptoms, itching and eye dryness were the two most common in both groups. Young patients had more blurred vision (40.7% *vs.* 9.8%, P<0.001), more redness (36.3% *vs.* 21.7%, P=0.030), and more eye pain (24.2% *vs.* 2.2%, P<0.001), while older patients had more eye fatigue (67.4% *vs.* 13.2%, P<0.001) and more photophobia (54.3% *vs.* 30.8%, P=0.002).

Ocular surface parameters

Lid margin abnormalities were comparable between the two groups [2 (1, 3) *vs.* 2 (2, 3), P=0.998]. More severe MGL was found in the young group (score ≥5, 34/ 91, 37.4 % *vs.* 14/92, 15.2%, P<0.001, *Table 1*).

MGD, blepharitis, and corneal change were the most common pathologies in the young group, while MGD and eye dryness were more common in the elderly group. TBUT and TMH were similar between groups (both P>0.05). The incidence of chalazia was higher in the young group than in the older group [12.1% (11/91) *vs.* 2.2% (2/92), P=0.009].

Prevalence and potential risk factors of corneal changes

Corneal changes were detected in 67 out of 91 (73.7%) patients in the young group, which was significantly higher than that in the elderly group (36/92, 39.1%, P<0.001, *Table 1*). Corneal findings included SPK or limbitis in 31.9% of patients and corneal stromal infiltration in 41.8% of young patients. In contrast, in the elderly group, SPK was the only corneal pathology in the 36 cases (39.1%) with corneal complications (*Table 1*). None of the patients developed stromal infiltration or ulceration.

Table 1 Demographics and clinical manifestations in young and elderly patients with ocular demodicosis

	Young patients (n=91)	Elderly patients (n=92)	P
Demographics			
Age (years), mean ± SD	17.7±6.9	55.5±9.3	<0.001†
Gender, female, n (%)	51 (56.0)	59 (64.1)	0.293
Demodex count			
Total *Demodex*, median [IQR]	6 [4, 8]	7 [4, 13]	0.176‡
D. folliculorum, median [IQR]	3 [2, 6]	6 [3, 10]	<0.001‡
D. brevis, median [IQR]	2 [1, 3]	0 [0, 2]	<0.001‡
D. folliculorum, %, median [IQR]	57 [40, 82]	96 [73, 100]	<0.001†
D. brevis, %, median [IQR]	43 [25, 100]	4 [0, 21]	<0.001†
Symptoms, n (%)			
Dryness	58 (63.7)	54 (58.7)	0.545
Itching	66 (72.5)	55 (59.8)	0.086
Eye fatigue	12 (13.2)	62 (67.4)	<0.001
Pain	22 (24.2)	2 (2.2)	<0.001
Blurred vison	37 (40.7)	9 (9.8)	<0.001
Photophobia	28 (30.8)	50 (54.3)	0.002
Redness	33 (36.3)	20 (21.7)	0.030
Ocular surface parameters			
TBUT (second)	5.46±5.19	6.45±5.57	0.257†
TMH (mm)	0.21±0.14	0.21±0.13	0.873†
Eyelash disorder, n (%)	40 (44.0)	25 (27.2)	0.021
Lid margin abnormalities	2 [1, 3]	2 [2, 3]	0.998‡
Meiboscore, mean ± SD	3.54±1.95	3.01±1.31	0.032§
Normal-mild [0–2], n (%)	34 (37.4)	38 (41.3)	0.547
Moderate [3–4], n (%)	23 (25.3)	40 (43.5)	0.010
Severe [5–6], n (%)	34 (37.4)	14 (15.2)	<0.001
Keratitis grading, n (%)			<0.001§
Grade 0	24 (26.3)	56 (60.9)	<0.001
Grade 1	29 (31.9)	36 (39.1)	0.305
Grade 2	38 (41.8)	0	<0.05
Chalazia	11 (12.1)	2 (2.2)	0.009

†, Student *t* test; ‡, Kruskal-Wallis Test; §, Fisher exact test. Pearson chi-squared test was used was used in the table except additional mentioned. TBUT, tear break-up time; TMH, tear meniscus height; *D. folliculorum*, *Demodex folliculorum, Demodex brevis*, *D. brevis; D. folliculorum %*, *D. folliculorum/total Demodex; D. brevis %*, *D. brevis/total Demodex*.

Table 2 Probable risk factors of corneal changes in young and elderly patients

Variables	Young patients (n=91)[a]				Elderly patients (n=92)[b]			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Gender								
Male	Reference		Reference		Reference			
Female	4.52 (1.99–10.2)	<0.001	0.29 (0.08–1.07)	0.064	0.98 (0.41–2.35)	0.969		
Age	0.95 (0.89–1.00)	0.051	0.93 (0.86–1.01)	0.097	1.02 (0.98–1.07)	0.320		
Total *Demodex*	1.03 (0.97,1.09)	0.317	–	–	0.98 (0.93–1.04)	0.501		
D. brevis %	5.67 (1.27–25.2)	0.023	22.6 (2.15–236)	0.009	1.98 (0.31–12.6)	0.472		
BUT	0.95 (0.87–1.03)	0.227	–	–	0.97 (0.89–1.05)	0.385		
TMH	0.11 (0.01–2.23)	0.150	1.74 (0.04–77.3)	0.774	0.38 (0.01–10.4)	0.565		
Lid margin abnormalities	3.27 (2.06–5.20)	<0.001	3.00 (1.44–6.27)	0.003	1.15 (0.76–1.75)	0.513		
Meiboscore								
Normal-Mild	Reference		Reference		Reference		Reference	
Moderate	8.17 (2.60–25.7)	<0.001	3.44 (0.80–14.8)	0.096	0.93 (0.36–2.38)	0.873	0.93 (0.36–2.38)	0.873
Severe	62.7 (16.8–233)	<0.001	18.9 (3.61–98.6)	0.001	4.81 (1.26–18.3)	0.022	4.81 (1.26–18.3)	0.022
Eyelash disorders	2.07 (0.95,4.5)	0.069	0.88 (0.28–2.77)	0.823	1.65 (0.65–4.19)	0.289		

Variables which P<0.15 were included in the multivariate ordinal logistic regression analysis. [a], Ordinal logistic regression; [b], binary logistic regression. CI, confidence interval; OR, odds ratio; BUT, tear break-up time; TMH, tear meniscus height. *D. brevis*, *Demodex brevis; D. brevis %*, *D. brevis/Total Demodex.*

Univariate analysis indicated that severity of corneal changes was significantly correlated with sex, lid margin abnormalities, *D. brevis* %, and meiboscore (all P<0.05) in the young group. However, the severity of corneal changes was not correlated with any of these factors except for meiboscore in the elderly group (*Table 2*). Multivariate ordinal logistic regression revealed that higher *D. brevis* %, more lid margin abnormalities, and severe MGL were predictors of corneal changes severity in the young group (*Table 2*). However, severe MGL was a predictor of the presence of SPK in the elderly group (*Table 2*).

Prevalence and potential risk factors of MGL

Severe MGL was detected in 34 out of 91 (37.4%) patients in the young group, which was higher than that in the elderly (15.2%, P<0.001, *Table 1*). In univariate analysis, the severity of MGL was correlated with female sex, *D. brevis* %, *TBUT*, TMH, lid margin abnormalities, and eyelash disorder in the young group, but only age in the elderly group (*Table 3*). Multivariate ordinal logistic regression revealed that female sex, *D. brevis* %, and severer lid margin abnormalities were significantly correlated with more severe MGL. However, age was the only predictor of MGL in the elderly group (*Table 3*).

Representative case 1: young patient with ocular demodicosis

A 12-year-old girl complained of redness and decreased vision in both eyes for two years. She was previously treated for herpes simplex keratitis and allergic conjunctivitis but failed to respond to antiviral and anti-allergy therapies. On examination, her visual acuity was 20/20 and 20/40, respectively. Lash sampling revealed four *D. brevis* and two *D. folliculorum* mites. The right eye had milder blepharitis with inferior corneal SPK (*Figure 1A*). The left eye had more blepharitis, especially in the upper lid in contact with the corneal epithelial defect associated with stromal infiltrate and neovascularisation (*Figure 1B*). Both eyes had a meiboscore of four (*Figure 1C,D*).

Table 3 Probable risk factors of meibomian gland loss in young and elderly patients.

Variables	Young patients (n=91)[a]				Elderly patients (n=92)[b]			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Gender								
Male	Reference		Reference		Reference			
Female	3.00 (1.36–6.63)	0.007	0.27 (0.08–0.93)	0.038	1.06 (0.47–2.36)	0.893		
Age	0.97 (0.91–1.02)	0.227	–	–	1.06 (1.01–1.10)	0.010	1.06 (1.01–1.11)	0.011
Total *Demodex*	1.01 (0.96–1.06)	0.826	–	–	1.02 (0.97–1.07)	0.471		
D. brevis %	6.67 (1.48–30.1)	0.014	28.6 (3.37–243)	0.002	4.11 (0.71–23.7)	0.113	4.02 (0.68–23.8)	0.125
BUT	0.89 (0.81–0.98)	0.019	0.91 (0.81–1.01)	0.106	1.00 (0.93–1.07)	0.935		
TMH	0.02 (0.00–0.57)	0.023	0.07 (0.00–4.49)	0.208	0.46 (0.02–8.92)	0.608		
Lid margin abnormalities	2.88 (1.85–4.49)	<0.001	2.86 (1.47–5.57)	0.002	0.99 (0.68–1.46)	0.965		
Eyelash disorder	2.39 (1.10–5.22)	0.029	1.28 (0.44–3.70)	0.653	1.08 (0.45–2.57)	0.863		

Variables which P<0.15 were included in the multivariate ordinal logistic regression analysis. CI, confidence interval; OR, odds ratio; BUT, tear break-up time; TMH, tear meniscus height. *D. brevis*, *Demodex brevis; D. brevis %*, *D. brevis/total Demodex.*

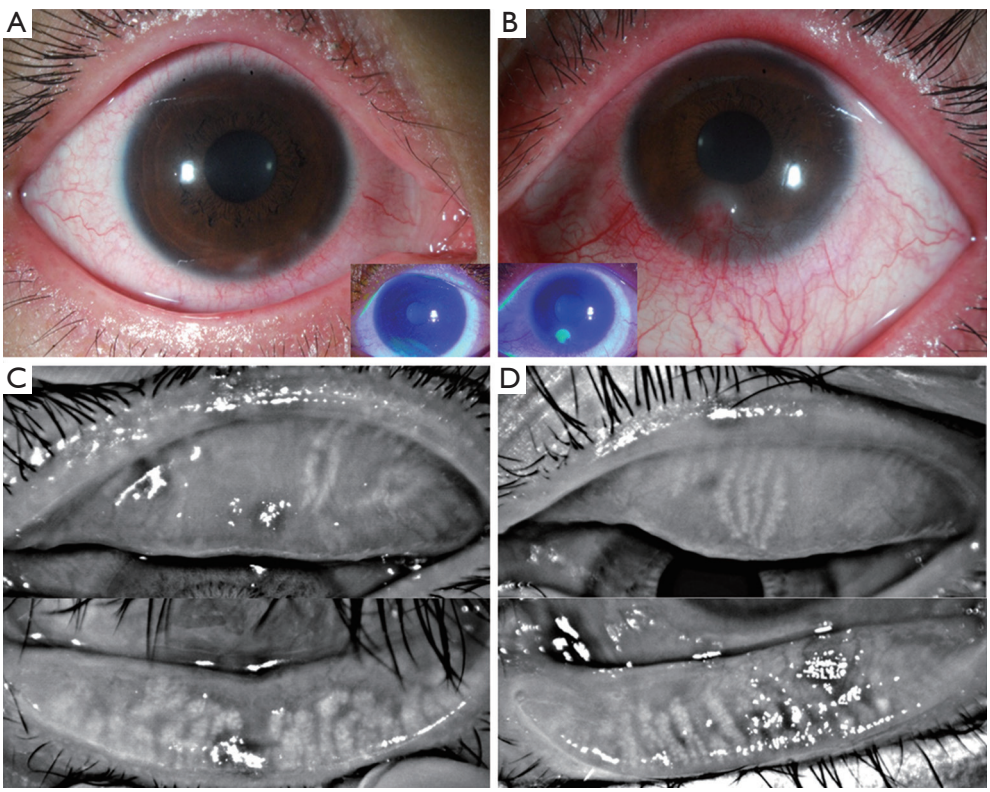

Figure 1 Representative case 1. The left eye presented with grade-2 corneal change with an epithelium defect associated with stromal infiltration and vascularisation and lid/conjunctival inflammation (A,B). Blepharitis appeared to be worse in the upper lid and the neovascularisation grows into the cornea from below. Meibography showed that meibomian gland loss was severe in the upper lids (C,D).

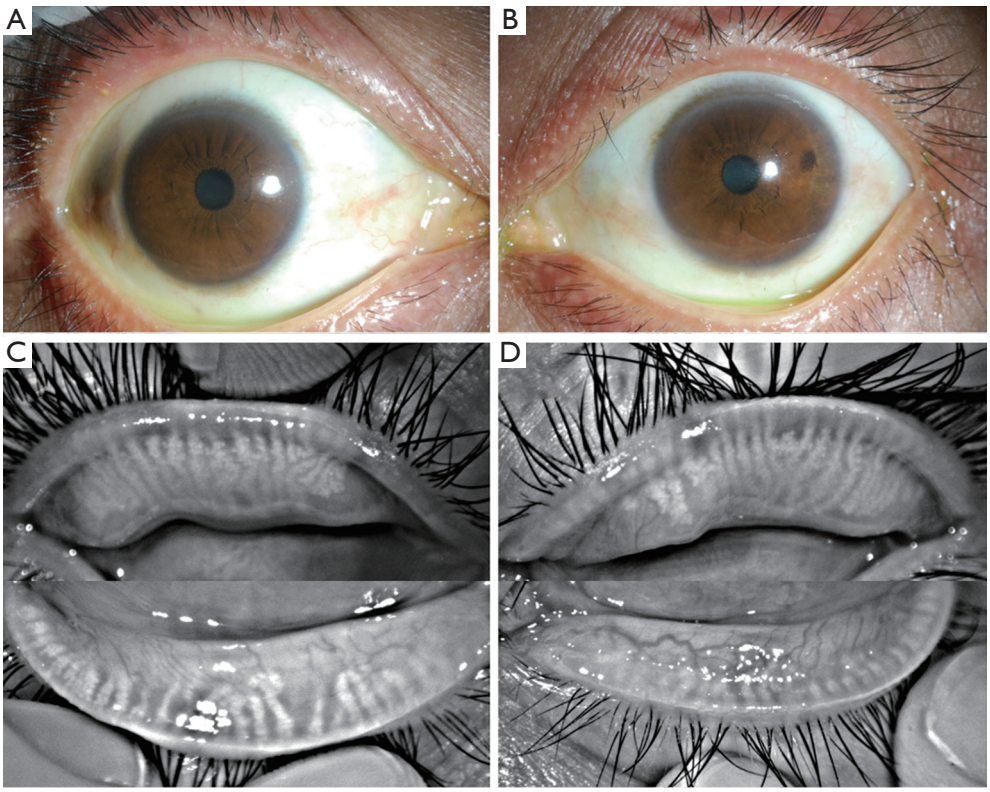

Figure 2 Representative case 2. Both eyes presented with meibomian gland orifice plugging, irregular lid margin, mild conjunctival hyperaemia and normal cornea of both eyes (A,B). Meibography showed that meibomian gland loss was mild in the upper and lower lids (C,D).

Representative case 2: elderly patient with ocular demodicosis

A 52-year-old woman complained of irritation and dryness for four years. She was previously diagnosed with MGD and was treated with artificial tears. On examination, her vision was 20/20 and 20/25 respectively. Lash sampling detected nine *D. folliculorum*. Both eyes had meibomian gland orifice plugging, irregular lid margin, and mild conjunctival hyperaemia (*Figure 2A,B*). Meibography showed mild MGL in both eyes (*Figure 2C,D*).

Discussion

In this study, we found that *D. brevis* infestation was significantly higher and corneal changes and MGL were more severe in young patients with ocular demodicosis than in elderly patients. The diagnostic criteria for ocular demodicosis are still controversial. This study showed that *Demodex* profiles differ between young and elderly patients with ocular demodicosis. Therefore, age might be considered when setting diagnostic criteria for ocular demodicosis.

Our results showed that there was no significant difference in *Demodex* counts between young and elderly patients, which was inconsistent with previous studies showing that demodicosis is highly age-dependent (8,13,26). We further discovered that the *D. brevis* counts and *D. brevis* % of the young group were higher than that of the elderly group. We speculate that this may be closely related to the parasitic environment of *D. brevis* and the more active meibum secretion in young individuals, which is beneficial to *D. brevis* parasitism (2,27). It should be noted that the mean demodex count in our study was different from other published studies (28,29). The plausible reasons include the different ages ranges and different numbers of epilated lashes in those studies.

It has been exhibited that *Demodex* plays an important role in blepharitis and ocular surface irritation (30-32). Herein, we noted that elderly patients with ocular demodicosis often complain of eye dryness, eye fatigue, and itching. On the contrary, blurred vision and eye pain are more common in young patients, perhaps because eye

dryness and MGD are the main manifestations in elderly patients, and mainly cause ocular surface discomfort. However, in young patients, severe MGL, corneal changes, and even visual impairment are the dominant manifestations.

Severe MGL was found in young patients, and multiple logistic analyses illustrated that the severity of MGL was significantly correlated with *D. brevis* %. Previous studies have indicated that ageing influences the structure and/or function of the meibomian gland by decreasing the density of acinar units and acinar diameter in meibomian glands (33-36). In our study, elderly patients mainly showed MGD, but their MGL was classified as mild to moderate. Multivariable logistic regression analysis demonstrated that age was the only risk factor for MGL. Therefore, ageing, but not *Demodex* infestation itself, may be the major cause of MGL in elderly patients with ocular demodicosis.

Moreover, we observed that the prevalence of severe MGL was higher in the young group. Further multivariable logistic regression analysis indicated that lid margin abnormalities and *D. brevis* % may be the main risk factors of MGL in young patients, suggesting that *D. brevis* may have a higher potential for triggering severe MGD in young patients. Further studies on the pathogenicity of *D. brevis* are warranted.

In the present study, it can be clearly seen that the young group had a higher prevalence of corneal changes involving the stroma, such as infiltration or ulceration, while SPK was the main corneal change in elderly people. Our previous research and the findings in this study provide strong support to *D. brevis* or *D. brevis* % as a risk factor for corneal changes in young patients with ocular demodicosis (13-15). This study revealed that there are relatively fewer *D. brevis* mites and milder corneal changes in elderly patients, which further supports our notions that *D. brevis* plays a more important role in the pathogenesis of ocular demodicosis. The question of why young people with ocular demodicosis were detected with more *D. brevis* mites needs to be further studied.

Several limitations of our study should also be mentioned. Although lash sampling and microscopic examination are commonly applied to identify mites in lashes, it may miss *Demodex* mites that accumulate in the follicles of eyelashes. *In vivo* confocal microscopy may provide a more complete examination of follicles. The age groups were chosen relatively arbitrary. The participants enrolled in our study are patients who come to the cornea department. Their conditions might be more severe than those went to the general ophthalmology department or family doctors. In conclusion, ocular demodicosis has different clinical features between young and elderly patients, and the predominance of *D. brevis* may be the potential cause. This may be related to the fact that active secretion by the meibomian gland in young people could be conducive to the life of *D. brevis*. Therefore, the pathological mechanism of *Demodex* needs to be further explored.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-7715). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University (No. 2017KYPJ042), and complied with the Declaration of Helsinki (as revised in 2013) for human research. All participants were given a full explanation of the study, and written informed consent was obtained.

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