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The effect of the duration of diabetes on dry eye and corneal nerves

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ABSTRACT

Purpose: To investigate the relationship between the duration of type 2 diabetes mellitus (DM) and the ocular surface, and to address the question of why some people with lengthy DM duration are asymptomatic, whereas some people with shorter DM duration have pain or discomfort in their eyes.

Methods: Eighty-seven eyes of 87 subjects with different durations of DM and 49 eyes of 49 subjects without DM underwent Schirmer I test, tear film break-up time, sodium fluorescein staining and tear meniscus height (TMH) measurement, and completed the Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire. Corneal structure and function were assessed with in vivo confocal corneal microscopy and with a corneal sensitivity esthesiometer. Both corneal nerve fiber length and inferior whorl length (IWL) were assessed as indices for neural structure. Age and gender were matched between groups. HbA1c levels > 7.8% and proliferative diabetic retinopathy were exclusion criteria.

Results: In the DM group, compared with the non-DM group, the SPEED score was significantly higher ($p = 0.013$), and corneal sensitivity and IWL were lower ($p < 0.001$). Schirmer I test, corneal sensitivity and IWL differed significantly between the group with DM duration > 10 years and the non-DM (control) group ($p = 0.021$, $p < 0.001$, $p < 0.001$, respectively). Schirmer I test and IWL were significantly lower in the group with DM > 10 years than in the group with DM ≤10 years ($p = 0.023$, $p < 0.001$, respectively). Corneal sensitivity was positively correlated with IWL regardless of diabetes status.

Conclusions: The lower SPEED score and asymptomatic feeling in people with a longer DM duration may be explained by the decreased IWL and reduced sensitivity.

1. Introduction

According to the World Health Organization's Diabetes Country Profiles 2016, the total prevalence of type 2 diabetes mellitus (DM) was 9.4% of the 1376 million people in China (10.5% of males, 8.3% of females) [1]. Peripheral neuropathy is one of the long-term complications of diabetes. The cornea is the most-innervated tissue in the body, and a large body of literature has demonstrated that differences exist on the ocular surface and with the corneal nerves between non-diabetic and diabetic individuals [2–5]. In the Tear Film and Ocular Surface Society's Dry Eye Workshop II report [6], corneal neural changes were described as contributing to the pathophysiology of dry eye. More severe symptoms and signs of dry eye have been reported in diabetics, as compared with non-diabetics [7], but some diabetics have marked dry eye signs and yet minimal complaints; this is presumably is related to changes in the corneal nerves in diabetics. This discordance between the symptoms and signs of dry eyes in diabetics has been a puzzle for ophthalmologists for years. It was investigated in 2017 by Ong et al. [8]: they showed that the discordance was associated with comorbidities related to clinical pain and hyperalgesia. This is the same situation that ophthalmologists will encounter when treating people with diabetes, and is the incentive for this new research.

It is possible that the discordant signs and symptoms, as well as the decreased symptoms with longer duration of diabetes, result from changes in corneal nerve structure and function. There are multiple reports that diabetics have lower corneal sensitivity and decreased corneal nerve density [9–12], but whether the nerves change across the course of DM remains to be clarified. Therefore, corneal sensitivity and the corneal nerves were assessed in this study.

Participant age was controlled in this study because older adults have lower corneal nerve density than do young people [13]. In addition, diabetics without proliferative diabetic retinopathy (PDR) were

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recruited, because, as De Cilla et al. [14] reported, corneal nerve density is lower in diabetics with PDR than in those with non-proliferative diabetic retinopathy (NPDR). Thus, this study excluded diabetics with PDR, although it was difficult to recruit enough participants with NPDR. Recent studies have shown that corneal nerve fiber length (CNFL) has the closest association with neuropathy, and, thus, CNFL has recently been recommended as the most important corneal nerve parameter for the diagnosis of diabetic neuropathy [15–17]. The whorl-like pattern (a radiating pattern of nerve fiber bundles converging toward an area that is 1–2 mm inferior to the corneal apex) can be easily tracked during follow-up [18], thus increasing the credibility for ongoing research. Herein, the sensitivity of the corneal nerves, representing corneal nerve function, and CNFL and inferior whorl length (IWL), representing the neural structure, were analyzed, to explore the discordance between symptoms and signs of dry eye, especially in people with long-standing diabetes.

2. Materials and methods

2.1. Study design and population

This was a prospective, cross-sectional, observational study that enrolled 49 individuals without type II DM and 87 individuals with type II DM but no PDR. Ages and genders were matched between these two groups. In Cornea practices, 50- to 75-years-old individuals were questioned about their history of diabetes. The eligibility criteria for the study were: either no diabetes (non-DM group) or DM with an HbA1c level ≤7.8% and no PDR (DM group); no history of eye disease in the past year (y); no use of ocular surface medication, except artificial-tear eye drops, in the past 3 months; no use of contact lenses in the past 3 months; no confirmed peripheral neural diseases; and no severe systemic diseases.

At an examination one week after a volunteer's initial evaluation, corneal sensitivity was tested first, to prevent interference from the anesthetics used in some other tests. Conversely, in vivo confocal corneal microscopy (IVCCM) was carried out at the end of the examination, in case it might influence the other outcome measures. The Standardized Patient Evaluation of Eye Dryness (SPEED) questionnaire [18], tear film break-up time (TFBUT), sodium fluorescein staining (NaFl staining) and Schirmer I test were performed in the order listed, after corneal sensitivity testing. This well-designed sequence was chosen to maximize the accuracy of the test outcomes. All examinations were conducted according to the tenets of the Declaration of Helsinki and approved by the ethics committee of hospital. Informed consent was obtained from all participants.

2.2. Diabetes and diabetic retinopathy assessment

Before performing the ocular surface examinations, the HbA1c level of the prospective DM participants was recorded, to document their blood glucose level in the past 3 months, and indirect ophthalmoscopy exams were performed, to exclude individuals with HbA1c > 7.8% or PDR.

2.3. Dry eye test

2.3.1. SPEED questionnaire

The SPEED questionnaire [18] was used to quickly assess dry eye symptoms. At the start of the questionnaire, subjects were asked if they had any of the four major symptoms in their eyes. Symptoms that occurred in either eye were recorded. The symptoms considered in the SPEED questionnaire are dryness or scratchiness, soreness or irritation, burning or watering and eye fatigue. Ifany of the symptoms in the DM group were reported, the patient would be asked about the frequency and severity of their symptoms. The questionnaire has four and five grades for frequency and severity, respectively. For frequency, the grades are: 0 = never, 1 = sometimes, 2 = often and 3 = constant. For severity: 0 = no problem, 1 = tolerable, 2 = uncomfortable, 3 = bothersome and 4 = intolerable. The outcome measure from the questionnaire is the sum of the numerical symptom responses: 0 = asymptomatic, 1–9 = mild dry eye symptoms, ≥10 = severe dry eye symptoms.

2.3.2. TMH

After assessing the dry eye symptoms, all subjects underwent TMH measurement using the Keratograph 5 M (Oculus GmbH, Wetzlar, Germany) equipped with a modified tear-film scanning function. The height from the lowest edge of the lid margin to the highest tear meniscus was measured.

2.3.3. TFBUT

To determine the TFBUT, the fluorescein strip was dipped into 0.9% sterile saline and then touched against the inferior bulbar conjunctiva. After three normal blinks, the time from the last blink to the first dark spot appearing was timed.

2.3.4. Sodium fluorescein staining

Immediately following the TFBUT measurement, corneal-surface damage was evaluated by NaFl staining. Staining area and density were each scored from 0 to 3. For the area, a score of 0 indicates no punctate staining; scores of 1, 2 and 3 correspond to staining of < 1/3, 1/3 – 2/3, and ≥ 2/3 of the corneal surface area, respectively. For density, scores of 0 to 3 indicate no punctate staining, sparse density, moderate density and high density with overlapping lesions, respectively. These two scores were summed to assess the damage to the corneal surface.

2.3.5. Schirmer I test

Five minutes were allowed to elapse, for participants to recover following the NaFl studies, before doing the Schirmer test. The standard Schirmer test strip was put behind the lateral 1/3 of the lower eyelid at the inferior conjunctival fornix without anesthesia. After closing the eyes for 5 min, the length of the wet strip was recorded.

2.4. Corneal neural parameters

2.4.1. Corneal sensitivity

The Cochet-Bonnet esthesiometer (Luneau, Paris, France) was used to assess the sensation of the corneal nerves before the examinations described in Section 2.3. Individuals were asked to sit in a still, quiet room. A 0.08-mm monofilament was used to gently touch the inferior portion of the cornea in the vertical direction. The filament length was sequentially reduced in 5-mm steps, starting from 60 mm, until a positive response (verbal or a blink) occurred. The length of the monofilament at the time of response was recorded as the corneal sensitivity threshold.

2.4.2. Corneal confocal microscopy

To assess the corneal neural structure, IVCCM was performed as the final examination. A Heidelberg Retinal Tomograph (HRTIII, Heidelberg, Germany) with Rostock Corneal Module was used. The participants' eyes were anesthetized with a drop of 0.4% oxybuprocaine (Santen Pharmaceutical Co., Ltd., Shiga, Japan) and the lens was covered by a sterile cap (Tomocap, Heidelberg Engineering, Heidelberg, Germany) that was coated with a layer of 0.2% carbomer eye gel (Dr. Gerhard Mann Chem-Pharm, Berlin Germany). The lens was adjusted to touch the cornea appropriately with the eye held open by an eye speculum. "Sequence" mode was used to record the inferior whorl of the subbasal nerve layer at 10 frames/s consecutively, and three clear images were selected. "Section" mode was used to record central corneal nerve images and three focused, non-overlapping images of the subbasal nerve plexus were used for analysis. Images were captured from only one eye, and the test duration was less than 3 min. Then an

experienced operator, who was masked regarding the patient's diabetes status, used NeuronJ (a semi-automated tracing plugin ImageJ) to calculate the CNFL and IWL within each image (384 pixel × 384 pixel). The CNFL is the total length of all nerve fibers and branches that were traced and counted within the area of corneal tissue (mm/mm^2). IWL is the length within the area of corneal tissue (mm/mm^2) that was counted. Pixel × 1.042 = μm; CNFL or IWL (mm/mm^2) = $\frac{(totalpixels \times 1.042)\mu m}{400\mu\,m \times 400\mu m} \times 1000$

2.5. Statistical analysis

Statistical analysis was performed with GraphPad Prism (version 6.00 for Mac OS X, www.graphpad.com). *P*-values of < 0.05 were considered statistically significant. The Kolmogorov-Smirnov test was used to assess all data for normal distributions. Student's *t*-test and one-way analysis of variance (ANOVA), followed by *Tukey post-hoc* analysis, were applied to test for differences between two groups and among three groups, respectively, if the data had a normal distribution. For non-normal distributions, the Mann-Whitney *U* test was utilized for two groups. Kruskal-Wallis tests and post-hoc analysis with Dunn's multiple comparison tests were used for non-parametric data. Descriptive statistics were specified as the mean ± standard deviation for normal distributions and median (min–max) for non-normal distributions; $\chi 2$ test was used in gender analysis.

3. Results

3.1. Demographics

A total of 136 individuals participated in this study. Tables 1 and 2 display the demographics of the 49 individuals without DM, and the 87 individuals with DM (32 individuals with DM duration ≤10 y), and 55 individuals with DM duration > 10 y). In Tables 2 and 4, these three groups are referred to as groups A, B and C, respectively ("the DM group" comprises groups B and C combined). There were no differences in the gender distributions between the non-DM and DM groups ($\chi 2 = 0.305$), or between the non-DM group and the two groups with different durations of DM ($\chi^2 = 0.195$). Furthermore, there were no significant differences in age between the non-DM and DM groups (64 ± 5 y versus 65 ± 6 y, $p = 0.314$) or between the non-DM group and the groups with short or long durations of DM (64 ± 5, 64 ± 6, 65 ± 6 y, respectively, $p = 0.338$). As the level of HbA1c was not recorded for participants in the non-DM group, there was no HbA1c comparison between the non-DM and DM groups. There was no difference in HbA1c levels between the groups of DM duration ≤10 y and > 10 y (6.9 ± 0.5% and 7.0 ± 0.5%, respectively, $p = 0.196$) although the duration of DM in the DM > 10 y group (19 ± 6 y) was significantly longer than that in the DM ≤10 y group (5 ± 3 y), was would be expected.

Table 1
Demographics of study participants with and without DM.

Demographics	Non-DM	DM	*p*-value
Subjects/eyes(n)	49 (49)	87 (87)	
Gender (F/M)	32/17	49/38	.305
Age (y)			
Mean ± SD	64 ± 5	65 ± 6	.314
Range	53 ˜ 75	54 ˜ 79	
HbA_{1c} (%)	–	6.9 ± 0.5	–
Duration of DM (y)	0	14 ± 8	< **.001**

SD, standard deviation; Mean ± SD was for normal distributions; $\chi 2$ test was used in comparing groups by gender. *P*-values in bold indicate statistically significant differences.

Table 2
Demographics of non-DM study participants and study participants with different durations of DM.

Demographics	Non-DM (A)	DM ≤ 10y (B)	DM > 10 y (C)	*p*-value
Subjects/eyes (n)	49 (49)	32 (32)	55 (55)	
Gender (F/M)	32/17	22/10	27/28	.195
Age (y)				
Mean ± SD	64 ± 5	64 ± 6	65 ± 6	.338
Range	53 ˜ 75	54 ˜ 75	54 ˜ 78	
HbA_{1c} (%)	–	6.9 ± 0.5	7.0 ± 0.5	.196
Duration of DM (y)	0	5 ± 3	19 ± 6	< **.001**

SD, standard deviation; Mean ± SD was for normal distributions; $\chi 2$ test was used in comparing groups by gender. *P*-values in bold indicate statistically significant differences.

Table 3
Ocular surface parameters of study participants with and without DM (medians and ranges).

Parameter	Non-DM	DM	*p* value
SPEED score	5 (1 - 13)	6 (1 - 15)	**.013**
Schirmer I test (mm)	5 (1 - 30)	5 (0 - 28)	.083
TFBUT (sec)	5.6 (1.4 - 23.6)	6.5 (1.8 - 22.2)	.471
NaFl staining	0 (0 - 2)	0 (0 - 4)	.295
TMH (mm)	0.2 (0.1 - 0.5)	0.2 (0.1 - 0.6)	.348
Sensitivity (mm)	60 (45 - 60)	60 (35 - 60)	< **.001**
IWL (mm/mm^2)	30.2 (21.9 - 43.7)	27.6 (13.7 - 39.8)	< **.001**
CNFL (mm/mm^2)	24.7 (14.5 - 40.7)	23.9 (14.7 - 33.3)	.277

SPEED, Standard Patient Evaluation of Eye Dryness; TFBUT, Tear film break-up time; NaFl, Sodium fluorescein staining; TMH, Tear meniscus height; Sensitivity, Corneal sensitivity; IWL, Inferior whorl length; CNFL, Corneal nerve fiber length.
P-values for non-normal distribution, Mann-Whitney test. *P*-values in bold indicate statistically significant differences.

3.2. Ocular surface parameters

As shown in Table 3, SPEED scores were higher in the DM group than in the non-DM group (median values of 6 and 5, respectively, $p = 0.013$). When the DM group was subdivided by DM duration, the SPEED scores from the shorter-duration (B) group were higher than those of the non-DM group (medians of 8 and 5, respectively, $p = 0.008$, see Table 4). However, the SPEED scores of the two DM subgroups were not significantly different (medians of 8 and 6, respectively, p = 0.180). The median on the Schirmer I test in the non-DM group was 5 mm (range: 1–30 mm); the median was not statistically different in the DM group (range: 0–28 mm, $p = 0.083$, Table 3). The median NaFl staining scores were low in both the non-DM (range: 0–2) and DM groups (range: 0–4) ($p = 0.295$, Table 3). When subdivided further, there were still no differences (Table 4).

Compared with the non-DM group, the sensitivity of the DM group was lower ($p < 0.001$, Table 3). However, when group B (short duration) and group C (long duration) were compared with group A (non-DM), the sensitivity of group C (median value of 55 mm, $p < 0.001$), but not of group B (median value of 60 mm, $p = 0.141$), was significantly lower. The CNFL of the DM group showed no difference compared with the non-DM group (Table 3). The IWL was significantly lower in the DM group than in the non-DM group ($p = 0.277$; $p < 0.001$). Further, after subdividing the DM group, it was found that the median IWL of group B was a bit higher than in group A (33.0 mm/mm^2 versus 30.7 mm/mm^2, $p > 0.999$, Table 4 and Fig. 1) whereas the IWL of group C was much lower than that of group A (24.4 versus 30.7 mm/mm^2, $p < 0.001$).

Table 4
Ocular surface parameters of study participants with different durations of DM (medians and ranges).

Parameter	Non-DM (A)	DM ≤ 10 y (B)	DM > 10 y (C)	*p* value			
				Total	A vs. B	A vs. C	B vs. C
SPEED score	5 (1 - 13) ±	8 (3 - 13)	6 (1 - 15)	**.008**	**.006**	.418	.180
Schirmer I test (mm)	5 (1 - 30)	7 (1 - 28)	4 (0 - 12)	**.006**	> .999	**.021**	**.023**
TFBUT (sec)	5.6 (1.4 - 23.6)	6.5 (1.8 - 22.2)	6.3 (1.9 – 21.2)	.402	.604	> .999	.764
NaFl staining	0 (0-2)	0 (0-4)	0 (0-3)	.397	.523	> .999	> .999
TMH (mm)	0.2 (0.1 - 0.5)	0.2 (0.1 - 0.5)	0.2 (0.1 - 0.6)	.424	.578	> .999	> .999
Sensitivity (mm)	60 (45 - 60)	60 (35 - 60)	55 (25 - 60)	< **.001**	.141	< **.001**	.620
IWL (mm/mm^2)	30.7 (21.9 - 43.7)	34.0 (21.9-42.9)	24.4 (13.1-36.1)	< **.001**	> .999	< **.001**	< **.001**
CNFL (mm/mm^2)	24.8 (14.5-40.7)	26.8 (14.7-33.3)	23.1 (15.1-31.2)	**.005**	.865	.067	**.006**

SPEED, Standard Patient Evaluation of Eye Dryness; TFBUT, Tear film break-up time; NaFl, Sodium fluorescein staining; TMH, Tear meniscus height; Sensitivity, Corneal sensitivity; IWL, Inferior whorl length; CNFL, Corneal nerve fiber length.
P values calculated with Kruskal-Wallis tests and post-hoc analysis with Dunn's multiple comparison tests. *P*-values in bold indicate statistically significant differences.

3.3. The correlations of parameters related to corneal nerves

In the DM group, the SPEED scores were positively correlated with IWL ($r = 0.231$, $p = 0.031$) and barely correlated with CNFL ($r = 0.149$, $p = 0.167$). There were also positive correlations between sensitivity and CNFL ($r = 0.602$, $p = 0.024$) as well as sensitivity and IWL ($r = 0.527$, $p < 0.001$) in the DM group (Table 5). In the non-DM group, sensitivity was positively correlated with IWL ($r = 0.474$, $p < 0.001$). For all participants combined, sensitivity was positively correlated with both CNFL and IWL ($r = 0.487$, $p < 0.001$; $r = 0.528$, $p < 0.001$, respectively).

Table 5
Correlations of parameters related to corneal nerves. (Spearman's CC).

	Non-DM		DM		All	
	CNFL	IWL	CNFL	IWL	CNFL	IWL
Sensitivity	0.163	0.474*	0.602*	0.527*	0.487*	0.528*
SPEED score	−0.125	−0.108	0.149	0.231*	0.023	0.032

CC: correlation coefficient.
* $p < 0.05$.

4. Discussion

The demographic factors considered here (age, female gender, HbA1c and PDR) are all widely reported risk factors influencing the ocular surface [3,14,19–21]. With increasing age or HbA1c, and with PDR, the corneal nerve density decreases and corneal sensitivity is compromised. It has also been reported that females have a higher prevalence of dry eyes than do males. The DM participants in this study were screened, so they were all at the early stage of DR without PDR, which excluded the potential role of PDR, although Murat Dogru et al. reported no differences in tear function and ocular surface condition based on the severity of DR [3]. The present research found that the SPEED score, corneal sensitivity and IWL differed between people with and without DM, and that the SPEED score, Schirmer I test, corneal sensitivity and IWL differed between the DM subgroups with different disease durations. The SPEED score was used as the criterion to assess dry eye symptoms, and higher scores were found in the DM group than the non-DM group. That finding is consistent with the retrospective study by Aljarousha et al. [7], who reported that the percentage of diabetics with dry eye symptoms was higher than the percentage of nondiabetic subjects with dry eyes.

However, many researchers have shown a poor correlation between the results of clinical examinations and symptom severity. In this study, there were no differences in dry eye signs, such as TMH, between the DM and non-DM groups. It is expected that, in diabetics, tear secretion would decrease [22], due to the diabetic peripheral neuropathy. The DM group showed higher SPEED scores than did the non-DM group, but when the DM group was subdivided according to the duration of participants' DM, the diabetics with more than 10 y of DM showed only a

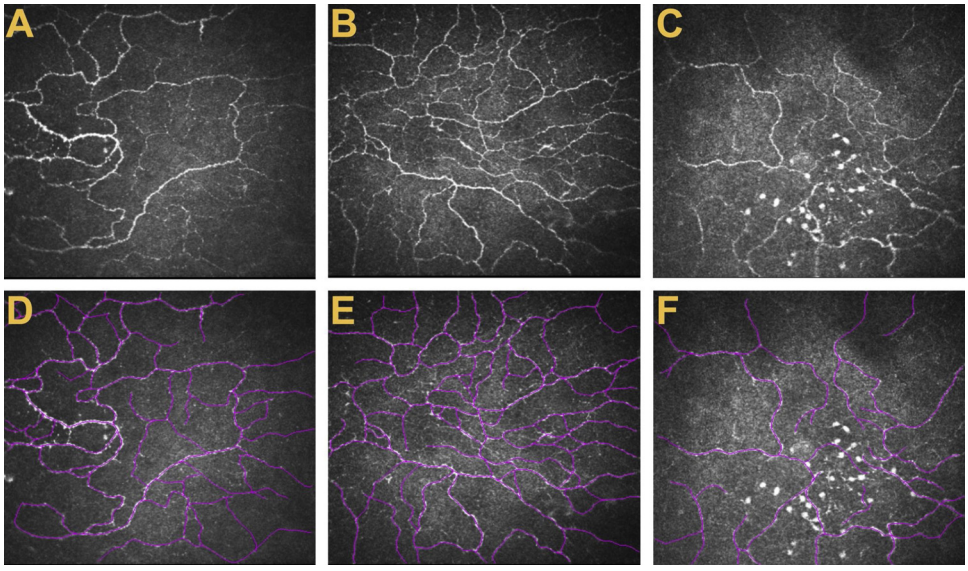

Fig. 1. Representative images of IVCCM from the non-DM group and the groups of different DM duration.
The whorl-like patterns of subbasal corneal nerves were captured by IVCCM in sequence mode at 10 frames/s and 1 representative picture was selected for display. Panel A, from a participant in the non-DM group; B, from a participant with DM duration ≤10 years; C, from a participant with DM duration > 10 years; D, E, F are the pictures corresponding to A, B, C, after those were traced and saved with NeuronJ software.

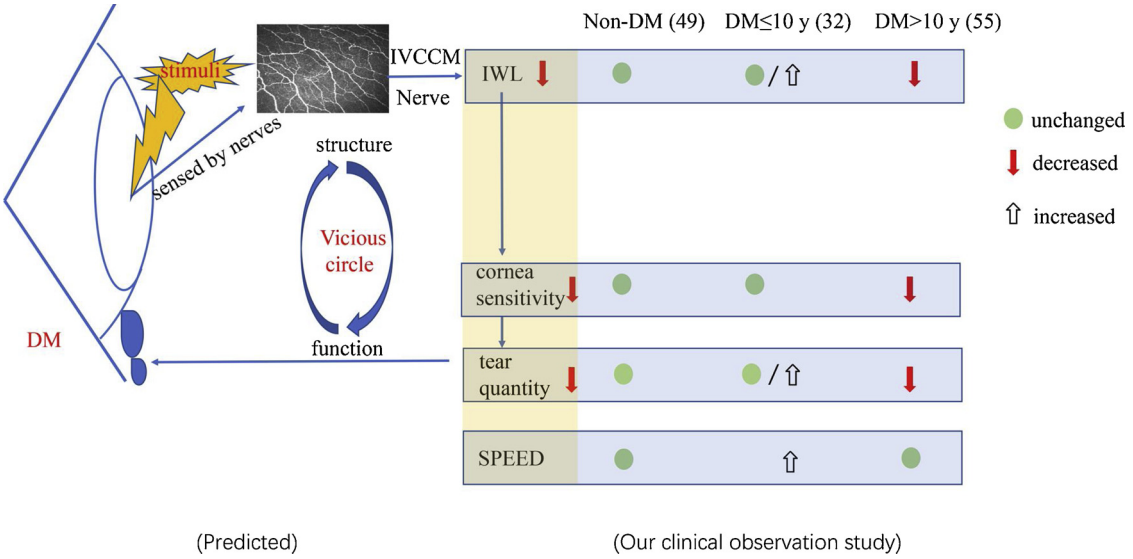

Fig. 2. Corneal neural changes in people without DM and those with different durations of DM.
The left panel shows the predicted changes in corneal nerves of people with diabetes mellitus. In the normal micro-environment of the ocular surface, exotic environmental stimuli can be sensed instantly by the corneal nerves, and lead to corresponding blinks, as a protective reflex, causing tears to flow. However, in people with diabetes, the nerves are not only structurally shorter, and more tortuous than in non-diabetics, as demonstrated by IVCCM, but also have functional changes including: (1) compromised corneal sensitivity, (2) decreased tear quantity and (3) altered tear components. Sensitivity decreases and tear alterations damage the nerves further, in a vicious cycle. The right panel shows the results from the present experiment. The group of DM duration > 10 y patients showed the predicted tendencies, but the group of DM duration ≤10 y patients showed no change, or even went in the opposite direction. DM: diabetes mellitus; IVCCM: in vivo corneal confocal microscopy.

non-significant trend to higher SPEED scores than in the non-DM group. Dry eye symptoms are sensed by the corneal nerves, so, from this perspective, some clues regarding the SPEED scores can be found by review of the corneal nerves, as demonstrated in an earlier paper [23] and in Fig. 2. The corneal sensitivity in the DM duration ≤10 y group was unchanged (median = 60 mm) from normal, so the changed micro-environment in DM may stimulate the ocular surface in those diabetics differently from the ocular surface stimulation in a normal micro-environment, which could increase the ocular discomfort in the diabetics with short disease duration. Conversely, when the corneal sensation has decreased because of constant, *long-term* stimulation from the diabetic micro-environment, afferent stimuli likely do not evoke as much of a response as before. The results of the IWL measurements support this speculation. The IWL in the group of participants with short DM duration (group B) was a little more than that in the non-DM group (group A) (although not significantly so), or, in other words, the IWL was not abnormally short, as has often been demonstrated in the literature. However, the median IWL in the group of participants with a long DM duration (group C) (24.4 mm/mm^2) was sharply decreased compared to the median IWLs in both groups A (30.7 mm) and B (34.0 mm). Normal neural function requires normal nerve structure: normal and decreased corneal sensation can be explained by unchanged and decreased nerve quantities, respectively. In previous studies, the authors did not divide patients based on their DM duration and many participants with DM duration > 20 y were included [22,24], but in the present study, there were 24 participants with duration > 20 y, and 31 with duration < 20 y. The relatively short durations of DM here may account for the lack of significant decreases in CNFL when comparing the non-DM and DM groups, but the IWL showed a more obvious decrease, from non-DM to DM, than did the CNFL. The lack of significant change in CNFL was unexpected, as other researchers have shown [5,25,26] that CNFL and IWL are generally correlated [10,27,28]. The possible reasons for the different finding here are the controlled HbA1c levels and early DR stages in these recruited individuals, as corneal fiber length was related to the HbA1c levels in Mehra's study and in their study, diabetic subjects who had an improvement in HbA1c, either from well-controlled medical therapy or from pancreas and kidney transplantation, showed corneal nerve repair [29]. IWL in the inferior part of the cornea and the corneal sensation of that part of the cornea were measured in this study, the IWL and corresponding measured sensitivity may show a greater sensitivity for the diagnosis of diabetic corneal neuropathy as results indicated.

Besides corneal sensitivity, tear volume and altered tear composition are associated with corneal function. The absence of tear-composition tests was one of the shortcomings of this study, as a relationship between dry eyes and tear protein factors has been shown [30,31], indicating that dry eye symptoms were correlated with the changed tear components. It is another limitation of this study that the eyelids and lid margins were not examined, as they should be, to confirm meibomian gland dysfunction. In further research, a larger sample size is needed to verify the present findings, and analysis of tear samples is needed to detect the neural trophic factors. To further support the hypothesis of this study, an animal model with diabetes and dry eye will be tested in the future.

5. Conclusion

Altogether, the change in corneal neural function in these diabetic individuals was not a linear decrease. With up to 10 y of DM, the corneal sensitivity was not greatly compromised, due to the compensatory effect of the unchanged, or even increased, number of corneal subbasal nerves (reflected in the IWL). When the duration of DM was more than 10 y, the corneal sensitivity was reduced, following the decreasing IWL. Meanwhile, the dry eye symptoms (SPEED score) showed a similar tendency, due to the altered neural function, although with a lack of dry eye signs. The changed micro-environment of the ocular surface (such as the chronic inflammation status, and hyperosmolarity due to the hyperglycemia) is sensed by the uncompromised nerves and gives people in the DM duration ≤10 y group burning eyes and a foreign body sensation. As the decreased inferior whorl cannot sense abnormal environmental stimuli very well, diabetics with DM duration > 10 y feel the same as non-diabetics or experience even less discomfort from their ocular surface.

Author disclosure statement

No competing financial interests exist.

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Conflict of interest

No competing financial interests exist.

Ethical NO

2018KY(L)-06.

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